Silver State Scripts Board Meeting

September 26, 2019

OPTUMRx®

Table of Contents

Agenda	5
Silver State Scripts Board Summary	14
Current Preferred Drug List (PDL)	18
Previous Meeting minutes	45
Annual Review – Established Drug Classes Being Reviewed Due to the Release of New Drugs	68
Cardiovascular Agents, Antihypertensive Agents, Calcium-Channel Blockers	69
Cardiovascular Agents, Antilipemics, HMG-CoA Reductase Inhibitors (Statins)	87
Psychotropic Agents, ADHD Agents	117
Psychotropic Agents, Psychostimulants, Narcolepsy Agents	136
Analgesics, Opiate Agonists	146
Analgesics, Opiate Agonists - Abuse Deterrent	146
Anti-infective Agents, Aminoglycosides, Inhaled Aminoglycosides	175
Anti-infective Agents, Antivirals, Anti-hepatitis Agents, Polymerase Inhibitors/Combination Products	183
Anti-infective Agents, Antivirals, Influenza Agents	198
Anti-infective Agents, Macrolides	210
Biologic Response Modifiers, Immunomodulators, Targeted Immunomodulators	219
Cardiovascular Agents, Antihypertensive Agents, Angiotensin II Receptor Antagonists	282
Cardiovascular Agents, Antihypertensive Agents, Vasodilators, Oral	298
Cardiovascular Agents, Antilipemics, Omega-3 Fatty Acids	318
Dermatological Agents, Topical Anti-infectives, Topical Antivirals	326
Dermatological Agents, Topical Anti-infectives, Topical Scabicides	331
Dermatological Agents, Topical Anti-inflammatory Agents, Immunomodulators: Topical	340
Gastrointestinal Agents, Antiemetics, Miscellaneous	347
Gastrointestinal Agents, Antiulcer Agents, Proton Pump Inhibitors (PPIs)	366
Gastrointestinal Agents, Gastrointestinal Anti-inflammatory Agents	389
Hematological Agents, Erythropoiesis-Stimulating Agents	400
Hormones and Hormone Modifiers, Antidiabetic Agents, Biguanides	414
Hormones and Hormone Modifiers, Antidiabetic Agents, Dipeptidyl Peptidase-4 Inhibitors	421
Hormones and Hormone Modifiers, Antidiabetic Agents, Incretin Mimetics	442
Hormones and Hormone Modifiers, Antidiabetic Agents, Insulins (Vials, Pens and Inhaled)	457
Hormones and Hormone Modifiers, Antidiabetic Agents, Meglitinides	480
Hormones and Hormone Modifiers, Antidiabetic Agents, Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors	487
Hormones and Hormone Modifiers, Antidiabetic Agents, Sulfonylureas	509
Hormones and Hormone Modifiers, Antidiabetic Agents, Thiazolidinediones	522
Neurological Agents, Anti-Migraine Agents, Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists (NEW)	531

Table of Contents

Neurological Agents, Anti-Migraine Agents, Serotonin-Receptor Agonists	541
Psychotropic Agents, Antipsychotics, Atypical Antipsychotics - Oral	557
Respiratory Agents, Long-acting/Maintenance Therapy	594
Toxicology Agents, Substance Abuse Agents	613
RxOutlook	627

Agenda

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NOTICE OF PUBLIC MEETING – SILVER STATE SCRIPTS BOARD

AGENDA

Date of Publication:	**August 27, 2019**
Date and Time of Meeting:	**September 26, 2019 at 1:00 PM**
Name of Organization:	**The State of Nevada, Department of Health and Human Services (DHHS), Division of Health Care Financing and Policy (DHCFP)**
Place of Meeting:	Springs Preserve 333 S. Valley View Blvd. Las Vegas, Nevada 89107 **Please check with staff to verify room location.** **There will not be a North Location for this meeting.**
Webinar Registration:	https://optum.webex.com/optum/onstage/g.php?MTID=e92408862a87476dc413f27f0e9f41a5e OR www.webex.com, select "Join," enter Meeting Number 649 066 646, your name and email and then select, "Join." A Password should not be necessary, but if asked, enter, "Medicaid1!" OR Audio Only: (763) 957-6300 Event Number: 649 066 646

Follow the instructions that appear on your screen to join the teleconference. Audio will also be broadcast over the internet (VoIP).

Reasonable efforts will be made to assist and accommodate physically challenged persons desiring to attend the meeting. Please call Tanya Benitez at: (775) 684-3722 or email Tbenitez@dhcfp.nv.gov in advance, but no later than two working days prior to the meeting, so that arrangements may be conveniently made.

Items may be taken out of order.
Items may be combined for consideration by the public body.
Items may be pulled or removed from the agenda at any time.

Public comment is limited to five minutes per individual, organization or agency, but may be extended at the discretion of the Chairperson.

1:00 PM – 2:00 PM – Closed Executive Session

Pursuant to Nevada Revised Statues (NRS) 422.405(4), as amended by Senate Bill 378 during the 80th Legislative session, the Board intends to hold a closed session for discussions between the Division of Healthcare Financing and Policy (DHCFP), OptumRx and the Silver State Scripts Board regarding the methodology and selection of preferred agents on the Nevada Medicaid Preferred Drug List (PDL).

2:00 PM – 5:00 PM – Public Meeting (Open Session)

AGENDA

1. Call to Order and Roll Call

2. Public Comment

3. Old Business

a. **For Possible Action**: Review and Approve Meeting Minutes from June 27, 2019.

4. New Business

a. Status Update by the DHCFP.

b. **For Possible Action:** Board Discussion and Approval of Existing PDL as Established by the Nevada Medicaid Pharmacy and Therapeutics Committee.

c. **Annual Review – Established Drug Classes Being Reviewed Due to the Release of New Drugs**

1. Cardiovascular Agents: Antihypertensive Agents (Calcium-Channel Blockers), Antilipemics (HMG-CoA Reductase Inhibitors (Statins))

a. Public Comment
b. Drug Class Review Presentation – OptumRx
c. **For Possible Action**: Board Discussion and Action
    1. Approve Clinical/Therapeutic Equivalency of Agents in Class
d. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
e. **For Possible Action**: Board Discussion and Action
    1. Approval of drugs for Inclusion on the PDL

2. Psychotropic Agents: Attention Defict Hyperactivity Disorder (ADHD) Agents, Psychostimulants (Narcolepsy Agents)

a. Public Comment
b. Drug Class Review Presentation – OptumRx
c. **For Possible Action**: Board Discussion and Action
    1. Approve Clinical/Therapeutic Equivalency of Agents in Class
d. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
e. **For Possible Action**: Board Discussion and Action
    1. Approval of drugs for Inclusion on the PDL

d. **Annual Review – Established Drug Classes**

1. Analgesics: Opiate Agonists (Opiate Agonists - Abuse Deterrent)

a. Public Comment
b. Drug Class Review Presentation – OptumRx
c. **For Possible Action**: Board Discussion and Action
    1. Approve Clinical/Therapeutic Equivalency of Agents in Class
d. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
e. **For Possible Action**: Board Discussion and Action
    1. Approval of drugs for Inclusion on the PDL

2. Anti-infective Agents: Aminoglycosides (Inhaled Aminoglycosides), Antivirals, Anti-hepatitis Agents (Polymerase Inhibitors/Combination Products), Antivirals (Influenza Agents), Macrolides

a. Public Comment
b. Drug Class Review Presentation – OptumRx
c. **For Possible Action**: Board Discussion and Action
    1. Approve Clinical/Therapeutic Equivalency of Agents in Class
d. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
e. **For Possible Action**: Board Discussion and Action
    1. Approval of drugs for Inclusion on the PDL

3. Biologic Response Modifiers: Immunomodulators (Targeted Immunomodulators)

    a. Public Comment
    b. Drug Class Review Presentation – OptumRx
    c. **For Possible Action**: Board Discussion and Action
        1. Approve Clinical/Therapeutic Equivalency of Agents in Class
    d. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
    e. **For Possible Action**: Board Discussion and Action
        1. Approval of drugs for Inclusion on the PDL

4. Cardiovascular Agents: Antihypertensive Agents (Angiotensin II Receptor Antagonists), Vasodilators (Oral), Antilipemics (Omega-3 Fatty Acids)

    a. Public Comment
    b. Drug Class Review Presentation – OptumRx
    c. **For Possible Action**: Board Discussion and Action
        1. Approve Clinical/Therapeutic Equivalency of Agents in Class
    d. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
    e. **For Possible Action**: Board Discussion and Action
        1. Approval of drugs for Inclusion on the PDL

5. Dermatological Agents: Topical Anti-infectives (Topical Antivirals, Topical Scabicides), Topical Anti-inflammatory Agents (Immunomodulators: Topical)

    a. Public Comment
    b. Drug Class Review Presentation – OptumRx
    c. **For Possible Action**: Board Discussion and Action
        1. Approve Clinical/Therapeutic Equivalency of Agents in Class
    d. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
    e. **For Possible Action**: Board Discussion and Action
        1. Approval of drugs for Inclusion on the PDL

6. Gastrointestinal Agents: Antiemetics (Miscellaneous), Antiulcer Agents (Proton Pump Inhibitors [PPIs]), Gastrointestinal Anti-inflammatory Agents

    a. Public Comment
    b. Drug Class Review Presentation – OptumRx
    c. **For Possible Action**: Board Discussion and Action
        1. Approve Clinical/Therapeutic Equivalency of Agents in Class
    d. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP

e. **For Possible Action**: Board Discussion and Action
    1. Approval of drugs for Inclusion on the PDL

7. Hematological Agents: Erythropoiesis-Stimulating Agents

    a. Public Comment
    b. Drug Class Review Presentation – OptumRx
    c. **For Possible Action**: Board Discussion and Action
        1. Approve Clinical/Therapeutic Equivalency of Agents in Class
    d. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
    e. **For Possible Action**: Board Discussion and Action
        1. Approval of drugs for Inclusion on the PDL

8. Hormones and Hormone Modifiers: Antidiabetic Agents (Biguanides, Dipeptidyl Peptidase-4 Inhibitors, Incretin Mimetics, Insulins [Vials, Pens and Inhaled], Meglitinides, Sodium-Glucose Co-Transporter 2 [SGLT2] Inhibitors, Sulfonylureas, Thiazolidinediones)

    a. Public Comment
    b. Drug Class Review Presentation – OptumRx
    c. **For Possible Action**: Board Discussion and Action
        1. Approve Clinical/Therapeutic Equivalency of Agents in Class
    d. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
    e. **For Possible Action**: Board Discussion and Action
        1. Approval of drugs for Inclusion on the PDL

9. Neurological Agents: Anti-Migraine Agents (Calcitonin Gene-Related Peptide [CGRP] Receptor Antagonists, Serotonin-Receptor Agonists)

    a. Public Comment
    b. Drug Class Review Presentation – OptumRx
    c. **For Possible Action**: Board Discussion and Action
        1. Approve Clinical/Therapeutic Equivalency of Agents in Class
    d. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
    e. **For Possible Action**: Board Discussion and Action
        1. Approval of drugs for Inclusion on the PDL

10. Psychotropic Agents: Antipsychotics (Atypical Antipsychotics – Oral)

    a. Public Comment
    b. Drug Class Review Presentation – OptumRx

c. **For Possible Action**: Board Discussion and Action
    1. Approve Clinical/Therapeutic Equivalency of Agents in Class
d. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
e. **For Possible Action**: Board Discussion and Action
    1. Approval of drugs for Inclusion on the PDL

11. Respiratory Agents: Long-Acting/Maintenance Therapy

    a. Public Comment
    b. Drug Class Review Presentation – OptumRx
    c. **For Possible Action**: Board Discussion and Action
        1. Approve Clinical/Therapeutic Equivalency of Agents in Class
    d. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
    e. **For Possible Action**: Board Discussion and Action
        1. Approval of drugs for Inclusion on the PDL

12. Toxicology Agents: Substance Abuse Agents

    a. Public Comment
    b. Drug Class Review Presentation – OptumRx
    c. **For Possible Action**: Board Discussion and Action
        1. Approve Clinical/Therapeutic Equivalency of Agents in Class
    d. Presentation of Recommendations for PDL Inclusion by OptumRx and the DHCFP
    e. **For Possible Action**: Board Discussion and Action
        1. Approval of drugs for Inclusion on the PDL

e. **Annual Review – Drug Classes Without Proposed Changes, For Possible Action**

1. Public Comment

2. Presentation of Recommendation for PDL Inclusion by OptumRx and the DHCFP without Changes.

    a. Analgesics: Analgesic/Miscellaneous (Neuropathic Pain/Fibromyalgia Agents, Tramadol and Related Drugs), Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) – Oral,
    b. Antihistamines: H1 blockers (Non-Sedating H1 Blockers)
    c. Anti-Infective Agents: Antivirals (Alpha Interferons), Anti-Hepatitis Agents (Ribavirins), Anti-Herpetic Agents, Cephalosporins (Second-Generation Cephalosporins, Third-Generation Cephalosporins), Quinolones (Quinolones - 2nd Generation, Quinolones - 3rd Generation)
    d. Autonomic Agents: Sympathomimetics (Self-Injectable Epinephrine)

e. Biologic Response Modifiers: Multiple Sclerosis Agents (Injectable, Oral, Specific Symptomatic Treatment)
f. Cardiovascular Agents: Antihypertensive Agents (Angiotensin-Converting Enzyme Inhibitors [ACE Inhibitors], Beta-Blockers, Vasodilators [Inhaled], Antilipemics (Bile Acid Sequestrants, Absorption Inhibitors, Fibric Acid Derivatives, Niacin Agents)
g. Dermatological Agents: Antipsoriatic Agents (Topical Vitamin D Analogs, Topical Analgesics, Topical Anti-infectives [Acne Agents: Topical, Benzoyl Peroxide, Antibiotics and Combination Products]), Topical Anti-infectives (Impetigo Agents: Topical), Topical Antineoplastics (Topical Retinoids)
h. Electrolytic and Renal Agents: Phosphate Binding Agents
i. Gastrointestinal Agents: Antiemetics (Serotonin-receptor antagonists/Combo), Antiulcer Agents (H2 blockers), Functional Gastrointestinal Disorder Drugs, Gastrointestinal Enzymes
j. Genitourinary Agents: Benign Prostatic Hyperplasia (BPH) Agents (5-Alpha Reductase Inhibitors, Alpha-Blockers), Bladder Antispasmodics
k. Hematological Agents: Anticoagulants (Injectable, Oral), Platelet Inhibitors
l. Hormones and Hormone Modifiers: Androgens, Antidiabetic Agents (Alpha-Glucosidase Inhibitors/Amylin Analogs/Misc.), Pituitary Hormones (Growth Hormone Modifiers)
m. Monoclonal Antibodies for the Treatment of Respiratory Conditions
n. Musculoskeletal Agents: Antigout Agents, Bone Resorption Inhibitors (Bisphosphonates, Nasal Calcitonins), Restless Leg Syndrome Agents, Skeletal Muscle Relaxants
o. Neurological Agents: Alzheimer's Agents, Anticonvulsants (Barbiturates, Benzodiazepines, Hydantoins), Antiparkinsonian Agents (Non-Ergot Dopamine Agonists)
p. Ophthalmic Agents: Antiglaucoma Agents, Ophthalmic Antihistamines, Ophthalmic Anti-Infectives (Ophthalmic Macrolides, Ophthalmic Quinolones), Ophthalmic Anti-Infective/Anti-Inflammatory Combinations, Ophthalmic Anti-Inflammatory Agents (Ophthalmic Corticosteroids, Ophthalmic Nonsteroidal Anti-inflammatory Drugs [NSAIDs], Ophthalmics for Dry Eye Disease
q. Otic Agents: Otic Anti-infectives (Otic Quinolones)
r. Psychotropic Agents: Antidepressants (Other, Selective Serotonin Reuptake Inhibitors [SSRIs]), Anxiolytics, Sedatives, and Hypnotics
s. Respiratory Agents: Nasal Antihistamines, Respiratory Anti-inflammatory Agents (Leukotriene Receptor Antagonists, Nasal Corticosteroids, Phosphodiesterase Type 4 Inhibitors), Short-Acting/Rescue Therapy
t. Toxicology Agents: Antidotes (Opiate Antagonists)

3. **For Possible Action**: Board Discussion and Action

a. Approval of drugs for Inclusion on the PDL

f. **Report by OptumRx on New Drugs to Market, New Generic Drugs to Market, and New Line Extensions**

g. **Presentation, Discussion and Possible Adoption of Updated Silver State Script Board Bylaws for Possible Action**

1. Public Comment on Bylaws
2. Presentation by DHCFP of updates to Bylaws
3. Discussion by Board and review of updates to Bylaws
4. Proposed adoption of updated Bylaws

h. **Closing Discussion**

1. Public comments on any subject
2. Date and location of the next meeting
3. Adjournment

Notice of this public meeting and draft copies of the changes will be available on or after the date of this notice at the DHCFP Web site at http://dhcfp.nv.gov and notice.nv.gov/. The agenda posting of this meeting can be viewed at the follow locations: Carson City Central Office; Las Vegas District Office; Reno District Office; Elko District Office; Nevada State Library; Carson City Library; Churchill County Library; Las Vegas Library; Douglas County Library; Elko County Library; Esmeralda County Library; Lincoln County Library; Lyon County Library; Mineral County Library; Tonopah Public Library; Pershing County Library; Goldfield Public Library; Eureka Branch Library; Lander County Library; Storey County Library; Washoe County Library; and White Pine County Library and may be reviewed during normal business hours.

If requested in writing, a copy of the proposal will be mailed to you. Requests and/or written comments on the proposed changes may be sent to the DHCFP, 1100 E. William Street, Suite 101, Carson City, Nevada 89701 at least three days prior to the public workshop.

All persons that have requested in writing to receive the public meeting agenda have been duly notified by mail or e-mail.

Note: We are pleased to make reasonable accommodations for members of the public who are physically challenged and wish to attend the meeting. If special arrangements for the meeting are necessary, please notify the DHCFP, in writing, at 1100 East William Street, Suite 101, Carson City, or call Tanya Benitez at (775) 684-3730, as soon as possible, or e-mail at tbenitez@dhcfp.nv.gov.

Summary of Silver State Scripts Board

Silver State Scripts Board

By statute (NRS 422.4025), the State of Nevada requires the DHCFP to develop and maintain a Preferred Drug List (PDL) to be used for the Medicaid program and CHIP, and each public or nonprofit health benefit plan that elects to use the PDL. The Silver State Scripts Board (formerly known as the Pharmacy & Therapeutics or P&T Committee) was established to identify prescription drugs to be included on the PDL.

A governing body of a county, school district, municipal corporation, political subdivision, public corporation or other local government agency of the State of Nevada that provides coverage of prescription drugs pursuant to NRS 287.010 or any issuer of a policy health insurance purchased pursuant to NRS 287.010 may use the PDL developed by DHHS as its PDL.

The PDL is not a restricted formulary. Drugs not on the PDL are still available to recipients if they meet the Standard Preferred Drug List Exception criteria.

The Silver State Scripts Board consists of members who are Director-appointed physicians and pharmacists. Members must be licensed to practice in the State of Nevada as either an actively practicing physician or an actively practicing pharmacist.

Meetings are held quarterly and are open to the public. Anyone wishing to address the Silver State Scripts Board may do so. Public comment is limited to 5 minutes per speaker/organization (due to time constraints). Anyone presenting documents for consideration must provide sufficient copies for each Board member and an electronic copy to the DHCFP Coordinator for official record.

For pharmacists and physicians wishing to serve on the Silver State Scripts Board, please email your contact information, NPI and current CV/Resume to rxinfo@dhcfp.nv.gov

Current Board Members:

Mark Decerbo, PharmD (Chairman)

Kate Ward, PharmD (Vice Chairman)

Joseph Adashek, MD

Sapandeep Khurana, MD

Brian Passalacqua, MD

Steven Zuchowski, MD

Michael Hautekeet, R.Ph

Evelyn Chu, Pharm.D.

Mark Crumby, Pharm.D.

Aditi Singh, MD

Silver State Scripts Board Meeting scheduled for 2019

Date	Time	South Nevada Location	North Nevada Location
September 26, 2019	1:00 PM	Springs Preserve – Las Vegas	None
December 5, 2019	1:00 PM	Springs Preserve – Las Vegas	None

Web References

Preferred Drug List:

https://www.medicaid.nv.gov/providers/rx/PDL.aspx

Medicaid Services Manual (MSM) Chapter 1200:

http://dhcfp.nv.gov/Resources/AdminSupport/Manuals/MSM/C1200/Chapter1200/

Silver State Scripts Board Bylaws:

http://dhcfp.nv.gov/uploadedFiles/dhcfpnvgov/content/Boards/CPT/PandT_Bylaws.pdf

The Division of Health Care Financing and Policy Public Notices:

http://dhcfp.nv.gov/Public/AdminSupport/PublicNotices/

Definition of "Therapeutic Alternative"

A "Therapeutic Alternative" is defined by the AMA as: "Drug products with different chemical structures but which are of the same pharmacological and/or therapeutic class and usually can be expected to have similar therapeutic effects and adverse reaction profiles when administered to patients in therapeutically equivalent doses."

Standard Preferred Drug List Exception Criteria

Drugs that have a "non-preferred" status are a covered benefit for recipients if they meet the coverage criteria.

a. Coverage and Limitations
    1. Allergy to all preferred medications within the same class;
    2. Contraindication to or drug-to-drug interaction with all preferred medications within the same class;
    3. History of unacceptable/toxic side effects to all preferred medications within the same class;
    4. Therapeutic failure of two preferred medications within the same class.
    5. If there are not two preferred medications within the same class therapeutic failure only needs to occur on the one preferred medication;
    6. An indication which is unique to a non-preferred agent and is supported by peer-reviewed literature or a FDA-approved indication;
    7. Antidepressant Medication – Continuity of Care. Recipients discharged from acute mental health facilities on a non-preferred antidepressant will be allowed to continue on that drug for up to 90 days following discharge. After 90 days, the recipient must meet one of the above five (5) PDL Exception Criteria; or
    8. For atypical or typical antipsychotic, anticonvulsant and antidiabetic medications the recipient demonstrated therapeutic failure on one preferred agent.
b. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms/aspx

Current Preferred Drug List

Analgesics 4
Analgesic/Miscellaneous 4
Opiate Agonists 4
Opiate Agonists - Abuse Deterrent 4
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) - Oral 4
Antihistamines 5
H1 blockers 5
Anti-infective Agents 5
Aminoglycosides 5
Antivirals 5
Cephalosporins 6
Macrolides 6
Quinolones 7
Autonomic Agents 7
Sympathomimetics 7
Biologic Response Modifiers 7
Immunomodulators 7
Multiple Sclerosis Agents 7
Cardiovascular Agents 8
Antihypertensive Agents 8
Antilipemics 9
Dermatological Agents 10
Antipsoriatic Agents 10
Topical Analgesics 11
Topical Anti-infectives 11
Topical Anti-inflammatory Agents 12
Topical Antineoplastics 12
Electrolytic and Renal Agents 12
Phosphate Binding Agents 12
Gastrointestinal Agents 12
Antiemetics 12
Antiulcer Agents 12
Gastrointestinal Anti-inflammatory Agents 13
Gastrointestinal Enzymes 13
Genitourinary Agents 13
Benign Prostatic Hyperplasia (BPH) Agents 13

Bladder Antispasmodics 14
Hematological Agents 14
Anticoagulants 14
Erythropoiesis-Stimulating Agents 14
Platelet Inhibitors 14
Hormones and Hormone Modifiers 15
Androgens 15
Antidiabetic Agents 15
Pituitary Hormones 17
Progestins for Cachexia 17
Monoclonal Antibodies for the treatment of Respiratory Conditions 17
Musculoskeletal Agents 17
Antigout Agents 17
Bone Resorption Inhibitors 17
Restless Leg Syndrome Agents 18
Skeletal Muscle Relaxants 18
Neurological Agents 18
Alzheimers Agents 18
Anticonvulsants 18
Anti-Migraine Agents 20
Antiparkinsonian Agents 21
Ophthalmic Agents 21
Antiglaucoma Agents 21
Ophthalmic Antihistamines 21
Ophthalmic Anti-infectives 21
Ophthalmic Anti-infective/Anti-inflammatory Combinations 22
Ophthalmic Anti-inflammatory Agents 22
Ophthalmics for Dry Eye Disease 22
Otic Agents 22
Otic Anti-infectives 22
Psychotropic Agents 23
ADHD Agents 23
Antidepressants 23
Antipsychotics 24
Anxiolytics, Sedatives, and Hypnotics 24
Psychostimulants 25

Respiratory Agents 25
Nasal Antihistamines 25
Respiratory Anti-inflammatory Agents 25
Long-acting/Maintenance Therapy 25
Short-Acting/Rescue Therapy 26
Toxicology Agents 26
Antidotes 26
Substance Abuse Agents 26

Preferred Products	PA Criteria	Non-Preferred Products
Analgesics		
Analgesic/Miscellaneous		
Neuropathic Pain/Fibromyalgia Agents		
DULOXETINE * GABAPENTIN LYRICA® * SAVELLA® * (Fibromyalgia only)	* PA required *No PA required for drugs in this class if ICD-10 - M79.1; M60.0-M60.9, M61.1.*	CYMBALTA® * GRALISE® LIDODERM® * LYRICA® CR (NEW) HORIZANT® QUTENZA® (NEW)
Tramadol and Related Drugs		
TRAMADOL TRAMADOL/APAP		CONZIPR® NUCYNTA® RYZOLT® RYBIX® ODT TRAMADOL ER ULTRACET® ULTRAM® ULTRAM® ER
Opiate Agonists		
MORPHINE SULFATE SA TABS (ALL GENERIC EXTENDED RELEASE) QL FENTANYL PATCH QL BUTRANS®	**PA required for Fentanyl Patch** **General PA Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-59.pdf	AVINZA® QL BUPRENORPHINE PATCH DOLOPHINE® DURAGESIC® PATCHES QL EXALGO® KADIAN® QL METHADONE METHADOSE® MS CONTIN® QL NUCYNTA® ER OPANA ER® OXYCODONE SR QL OXYMORPHONE SR XARTEMIS XR® QL ZOHYDRO ER® QL
Opiate Agonists - Abuse Deterrent		
EMBEDA® HYSINGLA ER® MORPHABOND®		ARYMO® ER OXYCONTIN® QL XTAMPZA ER®
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) - Oral		
DICLOFENAC POTASSIUM DICLOFENAC TAB DR FLURBIPROFEN TAB		CAMBIA ® POWDER CELECOXIB CAP DICLOFENAC SODIUM TAB ER

Preferred Products	PA Criteria	Non-Preferred Products
IBUPROFEN SUSP IBUPROFEN TAB INDOMETHACIN CAP KETOROLAC TAB MELOXICAM TAB NABUMETONE TAB NAPROXEN SUSP NAPROXEN TAB NAPROXEN DR TAB PIROXICAM CAP SULINDAC TAB		DICLOFENAC W/ MISOPROSTOL TAB DUEXIS TAB ETODOLAC CAP ETODOLAC TAB ETODOLAC ER TAB INDOMETHACIN CAP ER KETOPROFEN CAP MEFENAM CAP MELOXICAM SUSP NAPRELAN TAB CR NAPROXEN TAB CR OXAPROZIN TAB TIVORBEX CAP VIMOVO TAB ZIPSOR CAP ZORVOLEX CAP
Antihistamines		
H1 blockers		
Non-Sedating H1 Blockers		
CETIRIZINE D OTC CETIRIZINE OTC LORATADINE D OTC LORATADINE OTC	A two week trial of one of these drugs is required before a non-preferred drug will be authorized.	ALLEGRA® CLARITIN® CLARINEX® DESLORATADINE FEXOFENADINE LEVOCETIRIZINE SEMPREX® XYZAL®
Anti-infective Agents		
Aminoglycosides		
Inhaled Aminoglycosides		
BETHKIS® KITABIS® PAK TOBI PODHALER® TOBRAMYCIN NEBULIZER		
Antivirals		
Alpha Interferons		
PEGASYS® PEGASYS® CONVENIENT PACK PEG-INTRON® and REDIPEN		

Preferred Products	PA Criteria	Non-Preferred Products
Anti-hepatitis Agents		
Polymerase Inhibitors/Combination Products		
EPCLUSA® HARVONI® LEDIPASVIR/ SOFOSBUVIR (NEW) MAVYRET® SOFOSBUVIR/ VELPATASVIR (NEW) SOVALDI® ZEPATIER®	**PA required: (see below)** http://dhcfp.nv.gov/uploadedFiles/dhcfpnvgov/content/Resources/AdminSupport/Manuals/MSMCh1200Packet6-11-15(1).pdf https://www.medicaid.nv.gov/Downloads/provider/Pharmacy_Announcement_Viekira_2015-0721.pdf	DAKLINZA® OLYSIO® TECHNIVIE® VIEKIRA® PAK VOSEVI®
Ribavirins		
RIBAVIRIN		RIBASPHERE RIBAPAK® MODERIBA® REBETOL®
Anti-Herpetic Agents		
ACYCLOVIR FAMCICLOVIR VALCYCLOVIR		FAMVIR®
Influenza Agents		
AMANTADINE TAMIFLU® RIMANTADINE RELENZA® XOFLUZA® (NEW)		OSELTAMIVIR CAP OSELTAMIVIR SUSP RAPIVAB
Cephalosporins		
Second-Generation Cephalosporins		
CEFACLOR CAPS and SUSP CEFACLOR ER CEFUROXIME TABS and SUSP CEFPROZIL SUSP		CEFTIN® CECLOR® CECLOR CD® CEFZIL
Third-Generation Cephalosporins		
CEFDINIR CAPS / SUSP CEFPODOXIME TABS and SUSP		CEDAX® CAPS and SUSP CEFDITOREN OMNICEF® SPECTRACEF® SUPRAX® VANTIN®
Macrolides		
AZITHROMYCIN TABS/SUSP CLARITHROMYCIN TABS/SUSP ERYTHROMYCIN BASE		BIAXIN® DIFICID® ZITHROMAX®

Preferred Products	PA Criteria	Non-Preferred Products
ERYTHROMYCIN ESTOLATE ERYTHROMYCIN ETHYLSUCCINATE ERYTHROMYCIN STEARATE		ZMAX®
Quinolones		
Quinolones - 2nd Generation		
CIPROFLOXACIN TABS CIPRO® SUSP		FLOXIN® OFLOXACIN
Quinolones - 3rd Generation		
LEVOFLOXACIN MOXIFLOXACIN		AVELOX® LEVAQUIN®
Autonomic Agents		
Sympathomimetics		
Self-Injectable Epinephrine		
EPINEPHRINE AUTO INJ EPINEPHRINE®	* PA required	ADRENACLICK® QL AUVI-Q® * SYMJEPI® (NEW)
Biologic Response Modifiers		
Immunomodulators		
Targeted Immunomodulators		
ACTEMRA® CIMZIA® COSENTYX® ENBREL® HUMIRA® INFLECTRA® KEVZARA® KINERET® OLUMIANT® ORENCIA® OTEZLA® SIMPONI® XELJANZ®	Prior authorization is required for all drugs in this class https://www.medicaid.nv.gov/Downloads/provider/FA-61.pdf	DUPIXENT® ENTYVIO® ILARIS® ILUMYA® REMICADE® RENFLEXIS® SILIQ® STELARA® TALTZ® TREMFYA®
Multiple Sclerosis Agents		
Injectable		
AVONEX® AVONEX® ADMIN PACK BETASERON® COPAXONE® QL EXTAVIA® OCREVUS® REBIF® QL TYSABRI®	*Trial of only one agent is required before moving to a non-preferred agent*	GLATOPA® LEMTRADA® PLEGRIDY® ZINBRYTA®

Preferred Products	PA Criteria	Non-Preferred Products
Oral		
AUBAGIO® GILENYA® TECFIDERA®		
Specific Symptomatic Treatment		
DALFAMPRIDINE QL	PA required	AMPYRA® QL
Cardiovascular Agents		
Antihypertensive Agents		
Angiotensin II Receptor Antagonists		
DIOVAN® DIOVAN HCTZ® LOSARTAN LOSARTAN HCTZ		ATACAND® AVAPRO® BENICAR® CANDESARTAN COZAAR® EDARBI® EDARBYCLOR® EPROSARTAN HYZAAR® IRBESARTAN MICARDIS® TELMISARTAN TEVETEN® VALSARTAN
Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors)		
BENAZEPRIL BENAZEPRIL HCTZ CAPTOPRIL CAPTOPRIL HCTZ ENALAPRIL ENALAPRIL HCTZ EPANED® £ LISINOPRIL LISINOPRIL HCTZ RAMIPRIL	£ PREFERRED FOR AGES 10 AND UNDER ‡ NONPREFERRED FOR OVER 10 YEARS OLD	ACCURETIC® EPANED® ‡ FOSINOPRIL MAVIK® MOEXIPRIL QUINAPRIL QUINARETIC® QBRELIS® TRANDOLAPRIL UNIVASC®
Beta-Blockers		
ACEBUTOLOL ATENOLOL ATENOLOL/CHLORTH BETAXOLOL BISOPROLOL BISOPROLOL/HCTZ BYSTOLIC®* CARVEDILOL LABETALOL	*Restricted to ICD-10 codes J40-J48	KAPSPARGO® SOTYLIZE®

Preferred Products	PA Criteria	Non-Preferred Products
METOPROLOL (Reg Release) NADOLOL PINDOLOL PROPRANOLOL PROPRANOLOL/HCTZ SOTALOL TIMOLOL		
Calcium-Channel Blockers		
AFEDITAB CR® AMLODIPINE CARTIA XT® DILTIA XT® DILTIAZEM ER DILTIAZEM HCL DYNACIRC CR® EXFORGE® EXFORGE HCT® FELODIPINE ER ISRADIPINE LOTREL® NICARDIPINE NIFEDIAC CC NIFEDICAL XL NIFEDIPINE ER NISOLDIPINE ER TAZTIA XT® VERAPAMIL VERAPAMIL ER		
Vasodilators		
Inhaled		
VENTAVIS® TYVASO®		
Oral		
ADCIRCA® ORENITRAM® SILDENAFIL TRACLEER®		ADEMPAS® LETAIRIS® OPSUMIT® REVATIO ® TADALAFIL UPTRAVI®
Antilipemics		
Bile Acid Sequestrants		
COLESTIPOL CHOLESTYRAMINE WELCHOL®		QUESTRAN®

Preferred Products	PA Criteria	Non-Preferred Products
Cholesterol Absorption Inhibitors		
ZETIA®		EZETIMIBE
Fibric Acid Derivatives		
FENOFIBRATE FENOFIBRIC GEMFIBROZIL		ANTARA® FENOGLIDE® FIBRICOR® LIPOFEN® LOFIBRA® TRICOR® TRIGLIDE® TRILIPIX®
HMG-CoA Reductase Inhibitors (Statins)		
ATORVASTATIN CRESTOR® QL FLUVASTATIN LOVASTATIN PRAVASTATIN SIMVASTATIN		ADVICOR® ALTOPREV® AMLODIPINE/ATORVASTATIN CADUET® EZETIMIBE-SIMVASTATIN LESCOL® LESCOL XL® LIPITOR® LIPTRUZET® LIVALO® MEVACOR® PRAVACHOL® ROSUVASTATIN SIMCOR® VYTORIN® ZOCOR® ZYPITAMAG®
Niacin Agents		
NIASPAN® (Brand only) NIACIN ER (ALL GENERICS)		NIACOR®
Omega-3 Fatty Acids		
LOVAZA® VASCEPA®		OMEGA-3-ACID OMTRYG®
Dermatological Agents		
Antipsoriatic Agents		
Topical Vitamin D Analogs		
DOVONEX® CREAM SORILUX® (FOAM) TACLONEX® SUSP VECTICAL® (OINT)		CALCITENE® CALCIPOTRIENE CALCIPOTRIENE OINT/BETAMETHAZONE

Preferred Products	PA Criteria	Non-Preferred Products
		ENSTILAR ® (AER) TACLONEX OINT
Topical Analgesics		
CAPSAICIN FLECTOR® LIDOCAINE LIDOCAINE HC LIDOCAINE VISCOUS LIDOCAINE/PRILOCAINE PENNSAID® VOLTAREN® GEL		DICLOFENAC (gel/sol) EMLA® LIDODERM® QL LIDAMANTLE®
Topical Anti-infectives		
Acne Agents: Topical, Benzoyl Peroxide, Antibiotics and Combination Products		
ACANYA® AZELEX® 20% cream BENZACLIN® BENZOYL PEROXIDE (2.5, 5 and 10% only) CLINDAMYCIN ONEXTON GEL®	PA required if over 21 years old	ACZONE GEL® BENZOYL PER AEROSOL CLINDAMYCIN AEROSOL CLINDAMYCIN/BENZOYL PEROXIDE GEL DUAC CS® ERYTHROMYCIN ERYTHROMYCIN/BENZOYL PEROXIDE SODIUM SODIUM SULFACETAMIDE/SULFUR SULFACETAMIDE
Impetigo Agents: Topical		
MUPIROCIN OINT		ALTABAX® CENTANY® MUPIROCIN CREAM
Topical Antivirals		
ABREVA® XERESE® CREAM ZOVIRAX®, OINTMENT		ACYCLOVIR OINT DENAVIR®
Topical Scabicides		
NIX® PERMETHRIN RID® SKLICE® ULESFIA®	* PA required	EURAX® LINDANE MALATHION NATROBA® * OVIDE® SPINOSAD

Preferred Products	PA Criteria	Non-Preferred Products
Topical Anti-inflammatory Agents		
Immunomodulators: Topical		
ELIDEL® QL EUCRISA® PROTOPIC® QL	Prior authorization is required for all drugs in this class	TACROLIMUS
Topical Antineoplastics		
Topical Retinoids		
RETIN-A MICRO®(Pump and Tube) TAZORAC® ZIANA®	Payable only for recipients up to age 21.	ADAPALENE GEL AND CREAM ATRALIN® AVITA® DIFFERIN® EPIDUO® TRETINOIN TRETIN-X® VELTIN®
Electrolytic and Renal Agents		
Phosphate Binding Agents		
CALCIUM ACETATE CAP ELIPHOS® RENAGEL® RENVELA®		AURYXIA ® CALCIUM ACETATE TAB FOSRENOL® PHOSLO® PHOSLYRA® SEVELAMER CARBONATE VELPHORO®
Gastrointestinal Agents		
Antiemetics		
Miscellaneous		
Diclegis® OTC Doxylamine 25mg/Pyridoxine 10mg		BONJESTA®
Serotonin-receptor antagonists/Combo		
GRANISETRON QL ONDANSETRON QL	PA required for all medication in this class	AKYNZEO® ANZEMET® QL KYTRIL® QL SANCUSO® ZOFRAN® QL ZUPLENZ® QL
Antiulcer Agents		
H2 blockers		
FAMOTIDINE RANITIDINE RANITIDINE SYRUP*	*PA not required for < 12 years	

Preferred Products	PA Criteria	Non-Preferred Products
Proton Pump Inhibitors (PPIs)		
NEXIUM® CAPSULES NEXIUM® POWDER FOR SUSP* PANTOPRAZOLE	PA required if exceeding 1 per day *for children ≤ 12 yrs.	ACIPHEX® DEXILANT® ESOMEPRAZOLE LANSOPRAZOLE OMEPRAZOLE OTC TABS PREVACID® PRILOSEC® PRILOSEC® OTC TABS PROTONIX®
Functional Gastrointestinal Disorder Drugs		
AMITIZA® * LINZESS®	* PA required for Opioid Induced Constipation	MOVANTIK® * RELISTOR® * SYMPROIC® TRULANCE®
Gastrointestinal Anti-inflammatory Agents		
APRISO® ASACOL HD® ASACOL®SUPP BALSALAZIDE® CANASA® DELZICOL® LIALDA ® MESALAMINE ENEMA SUSP PENTASA® SULFASALAZINE DR SULFASALAZINE IR		COLAZAL® GIAZO® MESALAMINE (GEN LIALDA) MESALAMINE (GEN ASACOL HD)
Gastrointestinal Enzymes		
CREON® ZENPEP®		PANCREAZE® PANCRELIPASE PERTZYE® ULTRESA® VIOKACE®
Genitourinary Agents		
Benign Prostatic Hyperplasia (BPH) Agents		
5-Alpha Reductase Inhibitors		
DUTASTERIDE FINASTERIDE		AVODART® DUTASTERIDE/TAMSULOSIN JALYN® PROSCAR®
Alpha-Blockers		
DOXAZOSIN		ALFUZOSIN

Preferred Products	PA Criteria	Non-Preferred Products
TAMSULOSIN TERAZOSIN		CARDURA® FLOMAX® MINIPRESS® PRAZOSIN RAPAFLO® UROXATRAL®
Bladder Antispasmodics		
BETHANECHOL OXYBUTYNIN TABS/SYRUP/ER TOVIAZ® VESICARE®		DETROL® DETROL LA® DITROPAN XL® ENABLEX® FLAVOXATE GELNIQUE® MYRBETRIQ® OXYTROL® SANCTURA® TOLTERODINE TROSPIUM
Hematological Agents		
Anticoagulants		
Oral		
COUMADIN® ELIQUIS® * JANTOVEN® PRADAXA® * QL WARFARIN XARELTO ® *	* No PA required if approved diagnosis code transmitted on claim	SAVAYSA®*
Injectable		
FONDAPARINUX ENOXAPARIN FRAGMIN®		ARIXTRA® INNOHEP® LOVENOX®
Erythropoiesis-Stimulating Agents		
ARANESP® QL PROCRIT® QL	PA required Quantity Limit	EPOGEN® QL MIRCERA® QL RETACRIT®
Platelet Inhibitors		
AGGRENOX® ANAGRELIDE ASPIRIN BRILINTA® * QL CILOSTAZOL® CLOPIDOGREL DIPYRIDAMOLE	* PA required	ASPIRIN/DIPYRIDAMOLE DURLAZA® EFFIENT® * QL PLAVIX® PRASUGREL ZONTIVITY® YOSPRALA®

Preferred Products	PA Criteria	Non-Preferred Products
Hormones and Hormone Modifiers		
Androgens		
ANDRODERM®	**PA required** **PA Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-72.pdf	ANDROGEL® (NEW) AXIRON® FORTESTA® NATESTO® STRIANT® TESTIM® TESTOSTERONE GEL TESTOSTERONE SOL (NEW) VOGELXO®
Antidiabetic Agents		
Alpha-Glucosidase Inhibitors/Amylin analogs/Misc.		
ACARBOSE GLYSET® SYMLIN® (PA required)		CYCLOSET® PRECOSE®
Biguanides		
FORTAMET® GLUCOPHAGE® GLUCOPHAGE XR® METFORMIN EXT-REL (Glucophage XR®) GLUMETZA® METFORMIN (Glucophage®) RIOMET®		METFORMIN (GEN GLUMETZA)
Dipeptidyl Peptidase-4 Inhibitors		
JANUMET® JANUMET XR® JANUVIA® JENTADUETO® KOMBIGLYZE XR® ONGLYZA® TRADJENTA®		ALOGLIPTIN ALOGLIPTIN-METFORMIN ALOGLIPTIN-PIOGLITAZONE KAZANO® NESINA® OSENI®
Incretin Mimetics		
BYDUREON® * BYDUREON® PEN * BYETTA® * TRULICITY® VICTOZA® *	* PA required	ADLYXIN® BYDUREON® BCISE * OZEMPIC® SOLIQUA® TANZEUM® XULTOPHY®

Preferred Products	PA Criteria	Non-Preferred Products
Insulins (Vials, Pens and Inhaled)		
APIDRA® HUMALOG® HUMULIN® LANTUS® LEVEMIR ® NOVOLIN® NOVOLOG® TRESIBA FLEX INJ		ADMELOG® AFREZZA® BASAGLAR® FIASP® HUMALOG® U-200 TOUJEO SOLO® 300 IU/ML
Meglitinides		
NATEGLINIDE (Starlix®) PRANDIMET® PRANDIN® STARLIX®		
Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors		
FARXIGA® INVOKANA® JARDIANCE®		GLYXAMBI® INVOKAMET® INVOKAMET® XR QTERN® SEGLUROMET® STEGLATRO® STEGLUJAN™ SYNJARDY® SYNJARDY® XR XIGDUO XR®
Sulfonylureas		
AMARYL® CHLORPROPAMIDE DIABETA® GLIMEPIRIDE (Amaryl®) GLIPIZIDE (Glucotrol®) GLUCOTROL® GLUCOVANCE® GLIPIZIDE EXT-REL (Glucotrol XL®) GLIPIZIDE/METFORMIN (Metaglip®) GLYBURIDE MICRONIZED (Glynase®) GLYBURIDE/METFORMIN (Glucovance®) GLUCOTROL XL® GLYBURIDE (Diabeta®) GLYNASE®		

Preferred Products	PA Criteria	Non-Preferred Products
METAGLIP® TOLAZAMIDE TOLBUTAMIDE		
Thiazolidinediones		
ACTOPLUS MET XR® ACTOS® ACTOPLUS MET® AVANDAMET® AVANDARYL® AVANDIA® DUETACT®		
Pituitary Hormones		
Growth hormone modifiers		
GENOTROPIN® NORDITROPIN®	**PA required for entire class** https://www.medicaid.nv.gov/Downloads/provider/FA-67.pdf	HUMATROPE® NUTROPIN AQ® OMNITROPE® NUTROPIN® SAIZEN® SEROSTIM® SOMAVERT® TEV-TROPIN® ZORBTIVE®
Progestins for Cachexia		
MEGESTROL ACETATE, SUSP		MEGACE ES®
Monoclonal Antibodies for the treatment of Respiratory Conditions		
NUCALA® XOLAIR®		CINQAIR® FASENRA®
Musculoskeletal Agents		
Antigout Agents		
ALLOPURINOL COLCHICINE TAB/CAP PROBENECID PROBENECID/COLCHICINE ULORIC®		COLCRYS® TAB MITIGARE® CAP ZURAMPIC® ZYLOPRIM®
Bone Resorption Inhibitors		
Bisphosphonates		
ALENDRONATE TABS		ACTONEL® ALENDRONATE SOLUTION ATELVIA® BINOSTO® BONIVA® DIDRONEL® ETIDRONATE

Preferred Products	PA Criteria	Non-Preferred Products
		FOSAMAX PLUS D® IBANDRONATE SKELID®
Nasal Calcitonins		
CALCITONIN-SALMON		MIACALCIN®
Restless Leg Syndrome Agents		
PRAMIPEXOLE REQUIP XL ROPINIROLE		HORIZANT® MIRAPEX® MIRAPEX® ER REQUIP
Skeletal Muscle Relaxants		
BACLOFEN CHLORZOXAZONE CYCLOBENZAPRINE DANTROLENE METHOCARBAMOL METHOCARBAMOL/ASPIRIN ORPHENADRINE CITRATE ORPHENADRINE COMPOUND TIZANIDINE		
Neurological Agents		
Alzheimers Agents		
DONEPEZIL DONEPEZIL ODT EXELON® PATCH EXELON® SOLN MEMANTINE TABS		ARICEPT® 23mg ARICEPT® GALANTAMINE GALANTAMINE ER MEMANTINE SOL MEMANTINE XR NAMENDA® TABS NAMENDA® XR TABS NAMZARIC® RAZADYNE® RAZADYNE® ER RIVASTIGMINE CAPS RIVASTIGMINE TRANSDERMAL
Anticonvulsants		
APTIOM® BANZEL® BRIVIACT® CARBAMAZEPINE CARBAMAZEPINE XR CARBATROL ER®	PA required for members under 18 years old	OXTELLAR XR®

Preferred Products	PA Criteria	Non-Preferred Products
CELONTIN® DEPAKENE® DEPAKOTE ER® DEPAKOTE® DIVALPROEX SODIUM DIVALPROEX SODIUM ER EPIDIOLEX® EPITOL® ETHOSUXIMIDE FELBATOL® FYCOMPA® GABAPENTIN GABITRIL® KEPPRA® KEPPRA XR® LAMACTAL ODT® LAMACTAL XR® LAMICTAL® LAMOTRIGINE LEVETIRACETAM LYRICA® NEURONTIN® OXCARBAZEPINE SABRIL® STAVZOR® DR TEGRETOL® TEGRETOL XR® TOPAMAX® TOPIRAGEN® TOPIRAMATE (IR AND ER) TRILEPTAL® VALPROATE ACID VIMPAT® ZARONTIN® ZONEGRAN® ZONISAMIDE		POTIGA® QUDEXY XR® TROKENDI XR® SPRITAM®
Barbiturates		
LUMINAL® MEBARAL® MEPHOBARBITAL SOLFOTON® PHENOBARBITAL MYSOLINE® PRIMIDONE	PA required for members under 18 years old	

	Preferred Products	PA Criteria	Non-Preferred Products
Benzodiazepines			
	CLOBAZAM CLONAZEPAM CLORAZEPATE DIASTAT® DIAZEPAM DIAZEPAM rectal soln KLONOPIN® TRANXENE T-TAB® VALIUM®	PA required for members under 18 years old	ONFI®
Hydantoins			
	CEREBYX® DILANTIN® ETHOTOIN FOSPHENYTOIN PEGANONE® PHENYTEK® PHENYTOIN PRODUCTS	PA required for members under 18 years old	
Anti-Migraine Agents			
Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists (NEW)			
	AIMOVIG® (NEW) AJOVY® (NEW)	PA required for all products	EMGALITY® (NEW)
Serotonin-Receptor Agonists			
	RELPAX® RIZATRIPTAN ODT SUMATRIPTAN TABLET ZOLMITRIPTAN ODT	PA required for exceeding Quantity Limit	ALMOTRIPTAN AMERGE® AXERT® FROVA® ELETRIPTAN FROVATRIPTAN SUCCINATE IMITREX® MAXALT® TABS MAXALT® MLT NARATRIPTAN ONZETRA XSAIL® RIZATRIPTAN BENZOATE SUMATRIPTAN INJECTION SUMATRIPTAN/NAPROXEN SUMATRIPTAN NASAL SPRAY SUMAVEL® TREXIMET® ZEMBRACE SYMTOUCH ZOLMITRIPTAN ZOMIG® ZOMIG® ZMT

Preferred Products	PA Criteria	Non-Preferred Products
Antiparkinsonian Agents		
Non-ergot Dopamine Agonists		
PRAMIPEXOLE ROPINIROLE ROPINIROLE ER		MIRAPEX® MIRAPEX® ER NEUPRO® REQUIP® REQUIP XL®
Ophthalmic Agents		
Antiglaucoma Agents		
ALPHAGAN P® AZOPT® BETAXOLOL BETOPTIC S® BRIMONIDINE CARTEOLOL COMBIGAN® DORZOLAM DORZOLAM / TIMOLOL LATANOPROST LEVOBUNOLOL LUMIGAN® METIPRANOLOL RHOPRESSA® SIMBRINZA® TIMOLOL DROPS/ GEL SOLN TRAVATAN Z® TRAVATAN®		ALPHAGAN® BETAGAN® BETOPTIC ® BIMATOPROST COSOPT PF® COSOPT® DORZOL/TIMOL SOL PF (NEW) OCUPRESS® OPTIPRANOLOL® TIMOPTIC XE® TIMOPTIC® TRAVOPROST TRUSOPT® VYZULTA® XALATAN® XELPROS® (NEW) ZIOPTAN®
Ophthalmic Antihistamines		
BEPREVE® KETOTIFEN PAZEO® ZADITOR OTC®		ALAWAY® AZELASTINE ALOMIDE ALOCRIL ELESTAT® EMADINE® EPINASTINE LASTACRAFT® OLOPATADINE (drop/sol) OPTIVAR® PATADAY® PATANOL®
Ophthalmic Anti-infectives		
Ophthalmic Macrolides		
ERYTHROMYCIN OINTMENT		

Preferred Products	PA Criteria	Non-Preferred Products
Ophthalmic Quinolones		
BESIVANCE® CIPROFLOXACIN LEVOFLOXACIN MOXEZA® VIGAMOX®		CILOXAN® MOXIFLOXACIN OFLOXACIN® ZYMAXID®
Ophthalmic Anti-infective/Anti-inflammatory Combinations		
NEO/POLY/DEX PRED-G SULF/PRED NA SOL OP TOBRADEX OIN TOBRADEX SUS ZYLET SUS		BLEPHAMIDE MAXITROL NEO/POLY/BAC OIN /HC NEO/POLY/HC SUS OP TOBRA/DEXAME SUS TOBRADEX SUS TOBRADEX ST SUS
Ophthalmic Anti-inflammatory Agents		
Ophthalmic Corticosteroids		
ALREX® DEXAMETHASONE DUREZOL® FLUOROMETHOLONE LOTEMAX® PREDNISOLONE		FLAREX® FML® FML FORTE® MAXIDEX® OMNIPRED® PRED FORTE® PRED MILD® VEXOL®
Ophthalmic Nonsteroidal Anti-inflammatory Drugs (NSAIDs)		
DICLOFENAC FLURBIPROFEN ILEVRO® KETOROLAC NEVANAC®		ACULAR® ACULAR LS® ACUVAIL® BROMDAY® BROMFENAC® PROLENSA®
Ophthalmics for Dry Eye Disease		
ARTIFICIAL TEARS RESTASIS®		CEQUA® (NEW) RESTASIS® MULTIDOSE XIIDRA®
Otic Agents		
Otic Anti-infectives		
Otic Quinolones		
CIPRODEX® CIPRO HC® OTIC SUSP OFLOXACIN		CIPROFLOXACIN SOL 0.2% CETRAXAL® OTIPRIO® OTOVEL® SOLN

Preferred Products	PA Criteria	Non-Preferred Products
Psychotropic Agents		
ADHD Agents		
ADDERALL XR® AMPHETAMINE SALT COMBO IR ATOMOXETINE DEXMETHYLPHENIDATE DEXTROAMPHETAMINE SA TAB DEXTROAMPHETAMINE TAB DEXTROSTAT® DYANAVEL® FOCALIN XR® GUANFACINE ER METADATE CD® METHYLIN® METHYLIN ER® METHYLPHENIDATE METHYLPHENIDATE ER (All forms generic extended release) METHYLPHENIDATE SOL PROCENTRA® QUILLICHEW® QUILLIVANT® XR SUSP RITALIN LA® VYVANSE®	**PA required for entire class** **Children's Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-69.pdf **Adult Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-68.pdf	ADDERALL® ADZENYS® AMPHETAMINE SALT COMBO XR APTENSIO XR® CLONIDINE HCL ER CONCERTA® COTEMPLA XR®-ODT DAYTRANA® DESOXYN® DEXEDRINE® DEXTROAMPHETAMINE SOLUTION EVEKEO® FOCALIN® INTUNIV® KAPVAY® METADATE ER® MYDAYIS® RITALIN® STRATTERA® ZENZEDI®
Antidepressants		
Other		
BUPROPION BUPROPION SR BUPROPION XL DULOXETINE * MIRTAZAPINE MIRTAZAPINE RAPID TABS PRISTIQ® TRAZODONE VENLAFAXINE (ALL FORMS)	PA required for members under 18 years old * PA required *No PA required if ICD-10 - M79.1; M60.0-M60.9, M61.1.*	APLENZIN® BRINTELLIX® (Discontinued) CYMBALTA® * DESVENLAFAXINE FUMARATE EFFEXOR® (ALL FORMS) FETZIMA® FORFIVO XL® KHEDEZLA® TRINTELLIX®

Preferred Products	PA Criteria	Non-Preferred Products
		VIIBRYD® WELLBUTRIN®
Selective Serotonin Reuptake Inhibitors (SSRIs)		
CITALOPRAM ESCITALOPRAM FLUOXETINE PAROXETINE PEXEVA® SERTRALINE	PA required for members under 18 years old	CELEXA® FLUVOXAMINE QL LEXAPRO® LUVOX® PAXIL® PROZAC® SARAFEM® ZOLOFT®
Antipsychotics		
Atypical Antipsychotics - Oral		
ARIPIPRAZOLE CLOZAPINE FANAPT® LATUDA® NUPLAZID®* OLANZAPINE QUETIAPINE QUETIAPINE XR REXULTI® RISPERIDONE SAPHRIS® VRAYLAR® ZIPRASIDONE	**PA required for Ages under 18 years old** **PA Forms:** https://www.medicaid.nv.gov/Downloads/provider/FA-70A.pdf (ages 0-5) https://www.medicaid.nv.gov/Downloads/provider/FA-70B.pdf (ages 6-18) *(No PA required Parkinson's related psychosis ICD code on claim)	ABILIFY® CLOZARIL® FAZACLO® GEODON® INVEGA® PALIPERIDONE RISPERDAL® SEROQUEL® SEROQUEL XR® ZYPREXA®
Anxiolytics, Sedatives, and Hypnotics		
ESTAZOLAM FLURAZEPAM ROZEREM® TEMAZEPAM TRIAZOLAM ZALEPLON ZOLPIDEM	No PA required if approved diagnosis code transmitted on claim (All agents in this class)	AMBIEN® AMBIEN CR® BELSOMRA® DORAL® ESZOPICLONE EDLUAR® HETLIOZ® INTERMEZZO® LUNESTA® SILENOR®

Preferred Products	PA Criteria	Non-Preferred Products
		SOMNOTE®
	PA required for members under 18 years old	SONATA®
		ZOLPIDEM CR
		ZOLPIMIST®
Psychostimulants		
Narcolepsy Agents		
Provigil® *	* (No PA required for ICD-10 code G47.4)	MODAFINIL NUVIGIL® XYREM®
Respiratory Agents		
Nasal Antihistamines		
DYMISTA® PATANASE®		ASTEPRO® AZELASTINE OLOPATADINE
Respiratory Anti-inflammatory Agents		
Leukotriene Receptor Antagonists		
MONTELUKAST ZAFIRLUKAST ZYFLO® ZYFLO CR®		ACCOLATE® SINGULAIR® ZILEUTON ER
Nasal Corticosteroids		
FLUTICASONE TRIAMCINOLONE ACETONIDE		BECONASE AQ® FLONASE® FLUNISOLIDE NASACORT AQ® NASONEX® OMNARIS® QNASL® RHINOCORT AQUA® VERAMYST® XHANCE™ ZETONNA®
Phosphodiesterase Type 4 Inhibitors		
DALIRESP® QL	PA required	
Long-acting/Maintenance Therapy		
ADVAIR DISKUS® ADVAIR HFA® ANORO ELLIPTA® ARNUITY ELLIPTA® ASMANEX® BEVESPI® DULERA® FLOVENT DISKUS® QL		AEROSPAN HFA® AIRDUO® ALVESCO® ARCAPTA NEOHALER® ARMONAIR® BREO ELLIPTA® BROVANA® BUDESONIDE NEBS*

Preferred Products	PA Criteria	Non-Preferred Products
FLOVENT HFA® QL FORADIL® PULMICORT FLEXHALER® PULMICORT RESPULES®* QVAR® SEREVENT DISKUS® QL SPIRIVA® HANDIHALER STIOLTO RESPIMAT® STRIVERDI RESPIMAT® TUDORZA® SYMBICORT®		FLUTICASONE PROPIONATE/SALMETEROL INCRUSE ELLIPTA ® LONHALA MAGNAIR® PERFOROMIST NEBULIZER® QVAR® REDIHALER™ SEEBRI NEOHALER® SPIRIVA RESPIMAT® TRELEGY ELLIPTA® UTIBRON NEOHALER ®
Short-Acting/Rescue Therapy		
ALBUTEROL NEB/SOLN ATROVENT® COMBIVENT RESPIMAT® IPRATROPIUM NEBS IPRATROPIUM/ALBUTEROL NEBS QL LEVALBUTEROL* NEBS PROVENTIL® HFA XOPENEX® HFA* QL		LEVALBUTEROL* HFA PROAIR RESPICLICK® PROAIR® HFA VENTOLIN HFA® XOPENEX® Solution* QL
Toxicology Agents		
Antidotes		
Opiate Antagonists		
EVZIO ® NALOXONE NARCAN® NASAL SPRAY		
Substance Abuse Agents		
BUNAVAIL® SUBLOCADE® (NEW) SUBOXONE® VIVITROL® (NEW) ZUBSOLV®	PA required for class	BUPRENORPHINE / NALOXONE FILM/TAB (NEW)

Meeting Minutes

STEVE SISOLAK
Governor

RICHARD WHITLEY, MS
Director

SUZANNE BIERMAN, JD, MPH
Administrator

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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PHARMACY AND THERAPEUTICS COMMITTEE

Date and Time of Meeting: **Thursday, June 27, 2019 at 1:00 PM**

Name of Organization: **The State of Nevada, Department of Health and Human Services (DHHS), Division of Health Care Financing and Policy (DHCFP)**

Place of Meeting:

South Location:
Springs Preserve
333 S Valley View Blvd
Las Vegas, NV 89107

Please check with staff to verify room location

North Location:
Optum Office
9850 Double R Blvd
Ste 200
Reno, NV 89521

ATTENDEES

Board Members (Present – Las Vegas)
Shamim Nagy, MD, Chair
Evelyn Chu, Pharm.D.
Mark Decerbo, Pharm.D.
Sapandeep Khurana, MD

Board Members (Absent)
Joseph Adashek, MD

Board Members (Present – Reno)
Brian Passalacqua, MD
Kate Ward, Pharm.D.

Board Members (Absent)
Michael Hautekeet, RPh
Steven Zuchowski, MD
Mark Crumby, Pharm.D.

DHCFP:
Holly Long, Social Services Program Specialist III
Gabriel Lither, DAG
Beth Slamowitz, Pharm.D., DHHS Senior Advisor on Pharmacy

DXC:
Tiffany Kavales

OputmRx:
Carl Jeffery, Pharm.D.
Kevin Whittington, RPh

Public (Las Vegas)
Jinesh Patel, Acrie Pharma
Jennifer Lauper, BMS
David Freilich, Amneal
Lee Hochner, Amneal
Lee Staub, Chies
Lisa Wells, Greenwich Biosciences
Deron Grothe, Teva
Melissa Sommers, Novartis
Joana Colabianchi, Sunovion
Steven Burch, Sunovion
Randi Lewandowski, EMD Serono
Marc Rahmina, Astellas
Anthony Hoovler, Novo Nordisk
Elaine Morlock, UCB
Dave West, United Therapeutics
Chris Holtzer, Abbvie
Lovell Robinson, Abbvie
Amy Rodenburg, Allergan
Matt Royle, Pfizer
Nena Hartman, Neurocrine
Kaysen Bala, Biogen
Leon Ravin, DPBH
Kelvin Yamashita, Sanofi

Public (Reno)
None

AGENDA

1. Call to Order and Roll Call

The meeting was called to order at 1:00 PM.

Roll Call:
Las Vegas:
Sid Khurana
Shamim Nagy
Gabriel Lither
Mark Decerbo
Evelyn Chu
Holly Long
Kevin Whittington
Carl Jeffery
Reno:
Brian Passalacqua
Kate Ward
Tiffany Kavales

Beth Slamowitz

2. Public Comment

No public comment.

3. Administrative

a. **For Possible Action**: Review and Approve Meeting Minutes from March 28, 2019. Meeting minutes were reviewed by the board, a motion was made to approve as presented and seconded. Voting: Ayes across the board, the minutes were approved.

b. Status Update by DHCFP

Holly Long – I am going to do a little maintenance here for the meeting because there were some comments that were made after the last meeting because we're at split locations and if everybody can speak clearly and state your name before any voting, any comments, any questions (audio disruption), will make this a little bit easier and easier with the meeting minutes. Beth Slamowitz from DHCFP is going to give an update on Senate Bill 378 that was approved by the Governor.

Beth Slamowitz – I'm just going to give an update on Senate Bill 378. Senate Bill 378 makes changes does need some changing to both the P&T as well as our PDL and covered drug classes. So, I wanted to do a quick review of that as well as go over some of the implementation dates, so everybody is aware. If there are any questions, I can probably briefly answer some of them, otherwise, we'll most likely have to take those offline. From the aspect of the managing of the pharmacy benefits, SB 378 gives the Department of Health and Human Services the authority to manage that benefit as they see fit and enter in contract with PBM or a Health Maintenance Organization or what we refer to as a Managed Care Organization. It also went over some of the transparency in contracting under that same section of the bill as far as rebates and how they are passed through to the state, so if you are interested, I would suggest reading section 31.15 of SB 378 which is comprehensive in defining how those rebates are passed through. As far as the P&T committee, section 31.4 of the bill did make amendments to NRS 422.4025 which is where the provision for the PDL are held. It did finally put a sunset to the allowance of the preferred drug list to address antipsychotics, anticonvulsants, antidiabetic drugs. We have been addressing those on the PDL. If the provision had sunset, we would no longer be allowed to discuss these drugs or classes, but with the passage of this bill, we are allowed to continue doing that. So, we will probably be introducing some changes to the structure of what we report as well as drugs or classes to review. What this bill also did, it created the Silver State Scripts Board. The Silver State Scripts Board is what they are renaming the P&T Committee. The allowances of this bill also gives permission to nonprofit groups and outside organizations to join within that Silver State Scripts Board and be able to join in group purchasing and must follow the Medicaid PDL if that choice is made. With the development of the Silver State Scripts Board, the makeup of the P&T committee does change somewhat in that there is no longer a requirement for the members to be limited to 10. They still require a third of the members to be active licensed physicians and a third of the members to be active pharmacists. Instead of being governor appointed the board will now be director appointed. The Director of Health and Human Services will be given the authority to appoint the board. The terms of the chair and each member are limited and the member can be reappointed. After the initial term of the chair, the term of each member will be two years and the member can be reappointed. The frequency of when the board meets every three months will stay the same. The determination of what constitutes the quorum

will also stay the same. With that, just to give you some timelines, the term of the P&T Committee that are current will end as of 6/30/2019. We have already submitted paperwork to the director's office and the new board appointed will be announced probably within the next week or so. I'll let Holly add more details as far as that process is concerned. The majority of the provisions in the bill are and do become active once the governor signed the bill. He signed it on June 14, so the majority of the provisions are already active. There are a couple of sections within the bill mainly around the management of the pharmacy benefits for the State. These changes cannot be made until current contracts end or January 1, 2020, depending on which is later. So, with that I'm going to stop for a moment, and Holly I don't know if you want to add anything. It's a very comprehensive bill, so I would recommend that anyone who didn't, go back and read it and look at the details of it and if you have any questions please reach out to either Holly or I and we'll do our best to answer.

Holly Long – I think that was a great overview of everything. The major changes to the members are effective as of June 30, 2019. With the name change from the P&T Committee to the Silver State Scripts Board and the other caveat being that these are no longer Governor appointed positions they will be Director of DHHS appointed positions. Along with that, we will be working with all of the members to help provide communication around that. If you have any questions that are directly related to the changes that are happening, please feel free to email us. I believe what Beth provided is accurate. The Director should be making the appointment decisions, the letters should be going out with the new appointments within the next week or so. With the fourth of July coming up it may take two weeks. If there are any questions, please let us know.

Gabriel Lither – As far as you are all concerned, our big change in the future is that next iteration of this which will be called Silver State…

Holly Long – Silver States Scripts Board.

Gabriel Lither – They will be discussing costs, so cost will be something that will be discussed. We've tried our best to not discuss that in the past. One thing that we are trying to work on is the best way to go about that logistically without having a closed-door meeting for our portions of it in which we have proprietary information. If you have ideas on ways that perhaps they've done it in other states or ideas that would work for us here, we'll consider that and come up with the best ways to move that moving forward. Big changes.

i. Public Comment

There was no public comment.

4. Proposed New Drug Classes

a. Neurological Agents - Antiparkinsonian Agents - Dopamine Precursors

Opened for public comment.

David Freilich – From Amneal Pharmaceuticals a division of Impax. I'm here to talk about Rytary. For the last 50 years, the gold standard for treating Parkinson's disease has been levodopa and we have been using levodopa very effectively, but unfortunately it has a really short half-life and so for about 50 years, we've been trying to come up with ways to get around it. Dopamine agonists, enzyme inhibitors, or extended release preparations.

So, what we found is that as the disease progresses, people have a therapeutic window. When you're levodopa is in the window, you get good motor performance. When it's too high, you end up dyskinetic. When it's too low, you end up akinetic and rigid. And, so the trick is you want to keep people in this window. The problem is, the window gets smaller as the disease progresses. So, the loss of dopamine neurons lose the ability to buffer because you just don't have enough, and that's sort of what we tried to work around. So, we when developed Rytary and we came up with a four-bead formulation that's in a gelatin capsule. We have an instant-release part, and the reason we did that is people feel like they're wearing off, sometimes their medication's wearing off, so they need to be able to take the medication and know within 20-30 minutes, it's going to kick in. CR didn't do that, so we wanted to have an immediate release part of the preparation. Then we have two beads that have different controlled release elements. So, think of two more pharmacokinetic profiles on top of it. The other thing we did that's really creative, is we actually added the bead that's a time released tartaric acid. It turns out that tartaric acid, it actually changes the absorption of levodopa in the gut. This gave us an ability to monkey with the pharmacokinetic profile in ways that had not been done previously. Because of this, we actually did head-to-head trials against IR, so carbidopa-levodopa IR, and we also did it against entacapone plus IR, which you have both in your monogram. Against all of these, we actually saw that we increased on time. So, the way you do it, you have a diary and people fill it out. Are they off being very kinetic, are they asleep, or are they on and are they on with this, no dyskinesia's, non-troublesome or troublesome dyskinesia's. When we looked at this, what we found is that people have a reduction in off time against both products, with and without entacapone. They saw an improvement in the time. Then they also measured the quality of the on time using the unified Parkinson's disease rating scale and we saw dramatic improvements in both part two and in part three. We saw an improvement in the quality of on time against both of those. And, when we did this, we allowed all of the normal drugs one would use to treat Parkinson's. People were allowed to take amantadine. They were taking dopamine agonists. They were taking NAOBs. They had this sort of full repository of tools in the bag to manage the disease state and we still saw these improvements. So, what I'd like to respectfully suggest is that as a place in therapy, this should be something that people have access to after they're treated with immediate release, so probably something like preferred because I don't think that a step through CR makes sense. So, the Movement Disorder Society does an annual role-up of evidence-based medicine, VA ended one in 2006, and the popular views is also with that and they thought that Sinemet-CR is not effective in reducing off time or increasing on time so all three of them agreed about the same trials run by Merck. So, if you want something that is levodopa-based that's going to reduce off time and improve on time, this is a product that's been shown to be an improvement over IR. So I think a step-through CR would be inappropriate but a step-through IR is obviously appropriate, and I think in your guidelines that would put it either as preferred or maybe we can do a smart step or something like that so that people could have access to it, because it really I think should be something that folks have an opportunity to use. Any questions?

Chris Holtzer - I'm with Abbvie medical affairs and I'm here to talk to you about Prolopa. It's indicated for the treatment of motor fluctuations in patients with advanced Parkinson's disease. Please see the full prescribing information at RXmd.com. Oral carbidopa-levodopa is an effective drug for treatment of Parkinson's disease; however, as PD advances, efficacy of levodopa may diminish resulting in on-off periods when the medication suddenly and unpredictably stops respectively. Additionally, patients who require higher oral levodopa doses may experience dyskinesias which are spontaneous

and involuntary with this. Physicians may adjust the dose of levodopa and increase dosing intervals to minimize these unpredictable motor fluctuations, but they still occur when patients are taking their Parkinson's medications as prescribed. An educational program was established to provide recommendations on the management of Parkinson's disease refractory to oral therapy in which 103 experts from 13 countries participated, generating guidance that can assist healthcare providers in their treatment decision making. The group of experts included the patient's requiring levodopa greater than five times daily who have severe troublesome off periods more than one to two hours a day while awake despite optimal oral therapy, should be referred to a specialist for excessive disease duration of less than four years. Motor fluctuations accompanied by troublesome dyskinesias not controlled by amantadine are usually considered as an indication for referral for device-native therapy. In addition, another multicenter study created to obtain consensus on the definition of advanced Parkinson's disease. Investigators found that the development of severe motor fluctuations with disabling off periods was considered a definite factor for advanced Parkinson's disease. They also considered that recurrent falls, severe dysphasia and dementia were definite determinants in the diagnosis of advanced Parkinson's disease. Duopa, a carbidopa-levodopa interval suspension, is an option for the treatment of motor fluctuations in patients with advanced Parkinson's disease. Duopa as an oral suspension is administered daily every 16 hours via continuous infusion into the jejunum through a percutaneous endoscopic gastronomy, with a PICC J-tube. It's done using the CADD-Legacy 1400 portable infusion pump. At the end of the daily 16-hour infusion, patients disconnect from the pump and from the PEG jet, flushing the tubing with room-temperature potable water with a syringe and take their nighttime dose of oral immediate-release carbidopa-levodopa tablets as prescribed by their physician. In clinical trials, 416 patients with advanced Parkinson's disease received Duopa and 338 patients were treated with Duopa for more than one year; 233 patients were treated for more than two years; and 162 patients were treated for more than 3 years. The efficacy of Duopa was established in a random double-blind, double-dummy active control with 12 weeks noting 71 patients with advanced Parkinson's disease who are levodopa responsive and have persistent motor fluctuations while on treatment with oral immediate-release carbidopa-levodopa and other Parkinson's disease medications. Off time is reduced by four hours in the Duopa group versus 2.14 hours in the oral group. The most common adverse events in at least 7% or greater incidents in patients receiving Duopa versus those receiving immediate-release carbidopa-levodopa were complications of device insertion, nausea, depression, peripheral edema, hypertension, URI, oropharyngeal pain, incision site erythema, and atelectasis. The most common adverse events association with complications due to J-PEG insertion were upper abdominal pain, abdominal discomfort, abdominal distention, flatulence as remote peritoneum. In summary, I respectively request the committee consider Duopa for the treatment of motor fluctuations in patients with advanced Parkinson's disease. Any questions?

Carl Jeffery – We have this new class of medication. We got good overview of the Duopa and Rytery. These are all good medications. This is a good class for us to discuss. There's been some recent advancements. It seems [that] for a long time we didn't have any new therapies as far as the treatment of Parkinson's disease with the dopamine precursors here. We have the mainstay of levodopa-carbidopa has been known for a long time and the pharmacokinetics; I think we have a good overview of how all that all works there, too. The differences are how they're formulated and how they're administered. The Rytary we did a review on. It's a release capsule with a lot of different beads in it. Sinemet-CR, those are the standard, either immediate release or extended release levodopa-carbidopa combinations. The Stalevo, which is the same thing with the

entacapone in there that's a COMT inhibitor to slow down the breakdown of these agents and make them last a bit longer and then we heard about the Duopa, which is administered via the J-tube right into the jejunum over a 16-hour period. The one we didn't hear about, which is probably the most novel, the newest, is an inhaled levodopa Inbrija inhaler. It's inhaled and it can inhale up to eight capsules a day for kind of the off episodes is what they're talking about. I think what's concerning most is the Inbrija and to the point of the Duopa is the Inbrija, in the package insert, had 114 enrolled people in their study. I don't know how they couldn't find any more people with Parkinson's disease to do these studies on, so it's just a low number and it's similar with Duopa. I think they had a small number of people of how they got this through the FDA. So, we looked at the different indications. We have kind of the standard with the treatment of the Parkinson's disease. We have all the carbidopa formulations, either the IR or the ER as well as everything down to the treatment of motor functions in patients and that's where the Duopa comes in and then the intermittent alpha periods and that's where the Inbrija comes in, and then the Stalevo with the entacapone to extend the efficacy of those. When we looked at utilization, not a whole lot, so I'm kind of surprised that the numbers are so low. This is the fourth quarter of 2018, so not a whole lot of utilization. I would expect to see more than 185 claims in a quarter. You can see the other newer ones don't have any claims. Optum makes the recommendation the board consider these clinically and therapeutically equivalent.

A motion was presented to accept as clinically and therapeutically equivalent and was seconded. Voting: Ayes across the board, the motion passed.

Carl Jeffery – When it comes to our recommendations or Optum's recommendation for the preferred drug list, we limit it to the ones that are generically available, so we have the IR, the ER, the ODT versions of the levodopa-carbidopa combinations. And, then moving towards the brand name and the Stalevo, this is the carbidopa-levodopa entacapone product; this is the branded version of it. For non-preferred, we would have the generic of Stalevo, the Duopa and the Inbrija. The Duopa we talked about is just a carbidopa product by itself and it's really not used first line. It's used kind of an adjustments to that and then the Rytary all added as non-preferred.

Mark Decerbo – Before we go there, discussion to keep in mind with the trials of Rytary, I think they clearly demonstrated reduced off time. The trial that I would love to see, and the speaker kind of alluded to that, would be versus the controlled release product rather than immediate release for the triple therapy. But in a lot of that we don't have good data at least with the Rytary, we actually do have some data from two trials at least that did show a clear therapeutic advantage. That is what I am wrestling with in my head, I'm curious what the other board members think.

Sapandeep Khurana – Would a patient be able to be put on carbidopa and Inbrija?

Carl Jeffery – Technically they'd have to fail two preferred products before they could get a non-preferred. That's something that I may just remind the board, too, that's something that we've done before is the requirement of only one preferred agent be failed first and if that's the case, then they would have to be on carbidopa-levodopa, which they would anyway, and if it's insufficient they would be able to add Inbrija at that time.

Sapandeep Khurana: That would make sense if someone was on the extended release and having significant off episodes, then failing two agents would be challenging.

Kate Ward – I would agree that the patient would start with carbidopa-levodopa and then if they had to progress to the other agents, then they would go through that prior auth process because they failed the preferred product.

Mark Decerbo – What I think you're saying, is with this class, it would make sense to go with failure of one of the preferred agents before moving on. Maybe that's what we're all saying here is it sounds like it's therapeutically where they would begin and where they would go to. It's kind of hard to be seen clinically where it would make sense not to fail two agents as is the standard to move on, so I guess if that what's the committee is saying, that's what we're feeling. I would make a motion that we request to modify this class so that you only would need to fail one preferred agent before moving on to the non-preferred.

The motion was seconded.

Voting: Ayes across the board, the motion carries.

Carl Jeffery – Just for clarification, did we accept the preferred drug list as it is. Is that clear?

Gabriel Lither – It wasn't clear to me.

Holly Long – Was there the modification made where we would require one preferred to be failed?

Gabriel Lither - Yes

Holly Long -- My question would be, how is that provided to the public? Is that going to be put on the PDL? Is that going to go into the call center?

Carl Jeffery – No, I think we have only other class that's like that, but we listed right on the preferred drug list, in the center column, special notes saying that failure of only one preferred agent is required.

Mark Decerbo – So I guess with that, I make a motion with that prior motion passing that we move to accept the current PDL as presented.

The motion was seconded.

Voting: Ayes across the board, the motion carries.

5. Established Drug Classes Being Reviewed Due to the Release of New Drugs

a. Analgesics - Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Opened for public comment - No public comment.

Carl Jeffery – We've got a new product here, Sprix, a ketorolac nasal spray. It really is similar to the oral product and the injectable product that's administered in the ER. I think it's a good product. It's just used for five days just like any other ketorolac product, but all the doses need to be added to any injectable and oral products, so it's used as supplemental therapy. Two studies they did, they gave it alongside after people had

elective abdominal surgery or orthopedic surgery and they also gave people a PCA morphine pump and people who received Sprix used, you see in the first trial they used 36% less morphine and the second trial 26% less morphine, so I think there's a place in therapy for it. I don't know that it's an outpatient therapy, something that they use on the outpatient and used a whole lot. Because this came up, it gave us an opportunity to review the class as a whole so we've got a couple changes recommended but you can see utilization-wise, no Sprix utilization for that quarter and then we get down to the naproxen-ER that we wanted to talk about and celecoxib. Some decent utilization for being non-preferred, still 202. You see the ibuprofen is still by far the favorite followed by the meloxicam and the naproxen regular release. Optum recommends the board consider this class clinically and therapeutically equivalent.

A motion was presented to accept as clinically and therapeutically equivalent and was seconded. Voting: Ayes across the board, the motion passed.

Carl Jeffery – We had an opportunity to kind of change up this class a little bit. Some things have changed for the celecoxib. You saw it had some pretty good utilization even as being non-preferred. We recommend the celecoxib be moved to preferred and then naproxen tab-ER, is not called out specifically already, it's just lumped in with the regular naproxen now, but we'd like to identify it as separate and add it as non-preferred and then add the new product Sprix as non-preferred, as well.

A motion was presented to accept the preferred drug list as presented. The motion was seconded. Voting: Ayes across the board, the motion passed.

b. Biologic Response Modifiers - Multiple Sclerosis Agents - Injectable

Opened for public comment - No public comment.

Carl Jeffery – So this class will be pretty fast. There was another product that was supposed to come out its not available yet, so we'll talk about adding the new generic. There is one generic that's glatiramer, it's a generic for the Copaxone. We're going to talk about that; same clinical profile and everything. The Zinbryta was pulled off the market so we'll remove that from the preferred drug list. The utilization probably what you'd expect for the injectable products here. The Avonex and Copaxone are almost high with the utilization with the Rebif and Tysabri also with some decent utilization. With that, it's Optum's recommendation that the board consider these clinically and therapeutically equivalent.

A motion was presented to accept as clinically and therapeutically equivalent and was seconded. Voting: Ayes across the board, the motion passed.

Carl Jeffery – Not a whole lot of changes. We'll add the new generic glatiramer to non-preferred and then remove the Zinbryta since it's no longer available. No other changes.

Mark Decerbo – On the exclusive IV products Ocrevus and Tysabri those aren't there, and I saw the utilization fill and bill type drugs.

Carl Jeffery – Our preferred drug list doesn't apply to physician administered drug and so if the physician's office was to bill, buy these and bill for them Medicaid and they're not applied to the preferred drug list, it would only apply to the pharmacies billing for it and then shipping it to the doctor's office for administration.

Mark Decerbo – And the same thing with the utilization numbers we had, is that just.

Carl Jeffery – Those are point of sale, so those would all be pharmacies.

A motion was presented to accept the preferred drug list as presented. The motion was seconded. Voting: Ayes across the board, the motion passed.

c. Biologic Response Modifiers - Multiple Sclerosis Agents – Oral

Opened for public comment

Melissa Sommers – I'm Melissa Sommers with Novartis Medical Affairs here today in support of both Gilenya and Mayzent. Obviously Gilenya is on the left so I will forego that discussion unless you all have any questions. Specifically, today I did want to address Mayzent which was approved back in April with the broad indication for patients with multiple sclerosis and specifically patients with clinically isolated syndrome, relapse and remitting MS as well as secondary progressive MS. I want to point out that the pivotal trials for Mayzent studied a unique population. That is representative secondary to progressive MS population. In fact, Mayzent is the only oral agent studied and proven in a secondary progressive patient population to delay disability progression. For those of you not yet familiar, secondary progressive MS is different than relapsing remitting MS. If you look at the patient population in the Mayzent clinical trial, these patients are roughly a decade older; these patients have been suffering with MS for roughly 17-18 years and over 50% of the patients in the Mayzent clinical trial were already using ambulation assistance. The way it's looked at in clinical trials is you look at EDSS scores and 56% of these patients have an EDSS greater than or equal to 6, which is the point at which these patients need assistance with ambulation. I also want to point out that data shows that roughly 75% of patients with secondary progressive MS are already using a DMT for their MS, so if you think about that and you think about the fact that Mayzent is the only agent studied and proven in secondary progressive MS and that three-quarters of these patients are already taking something, we know that the Interferon North American study was a negative study for SPMS. We know that Tysabri, in a very similar patient population, had a negative study for secondary progressive MS and, in fact, Tecfidera terminated their secondary progressive MS study earlier. Secondary progressive MS patients are patients that will go on and increase in their disability whether that be cognition, their overall function, or their ambulation. So, what I do want to point out is that right now you have a lot of agents available on the PDL; however, again, none have been studied and proven in the secondary progressive MS patient population. With that, I do ask that the committee reconsider the recommendations placed by Optum and specifically think about these patients with secondary progressive MS. For fair balance, you can look at its warnings and precautions, contraindications in the Mayzent PDI. There is no black box warning. We will also point out Mayzent is an S1P receptive modulator; however, it is more specific, so the majority of these patients do not need a first dose observation unlike for Gilenya. With that, I am happy to answer any questions, comments, thoughts?

Sapandeep Khurana – Is there any data on Mayzent and relapses in MS?

Melissa Sommers – We did a phase 2 dose finding study and we did see a reduction in relapses in that but again, it was a phase 2 dose finding study in relapsing remitting patients.

Kaysen Bala – My name is Kaysen Bala and I'm a medical liaison with Biogen. I want to thank you for having Tecfidera preferred for your patients here and maintaining the status of. So, I don't want to talk about Tecfidera. I do want to talk about secondly progressive MS and kind of clarify a few things, specifically how the FDA is defining SPMS, which is secondary progressive MS. So, there are two components from SPMS. There's an active component which has relapses, inflammation, and gadolinium-enhancing lesions and there is a non-active portion meaning that the progressing disability without having any relapses so non-active and active. This is coming directly from the FDA that was stated March 26, 2019. In the first few years of this process, many patients continue to experience relapses, a phase of the disease described as active SPMS. Active SPMS was one of the relapsing forms of MS so they're considering active SPMS as a relapsing form of MS. Drugs approved for the treatment of relapsing forms of MS can be used to treat active SPMS. Later, many patients with SPMS stopped experiencing new relapses but the disability continues to progress phase called non-active SPMS and really non-active is really a disability for these patients, so the FDA is coming out with this distinct pronunciation, so this is gain with the FDA. They're for the support indication for the treatment of SPMS, distinct from active is critical that efficacy be established in patients with non-active SPMS, independence or relapses in active. So, with that, they have come up with this statement saying it must be emphasized that 13 different therapies have been approved for treating relapsing form of MS in this population for which the siponimod Mayzent who have indicated is the same for those drugs. So, siponimod labeling, which is Mayzent labeling, will be the first explicitly describing relapsing forms of MS including CSI, a relapsing form of MS an active secondary progressive disease. So, the Mayzent indication is for active but secondary progressive MS and not for the determining SPMS. But all sponsors and drug approved for the treatment of relapsing forms of MS will be requested to update their indication statements to conform with this contemporary, so they're requesting all factors to submit. We will have the similar label because we are relapsing form. Any questions with that?

Mark Decerbo – What's the timeline on that from the FDA?

Kaysen Baca – We don't know yet. We just got that information submitted but they just know that the label will be similar unless we have a drug that shows non-active independent of active. We're not going to get that SPMS indication.

Carl Jeffery – There's a couple new products in here. You see they're all indicated for the relapsing forms of MS and progressive forms of MS there, the Aubagio, Gilenya, and Tecfidera. Mavenclad has an interesting administered drug, it has a really funny dosing schedule as far as it's calculated total dose to give 1 to 2 tablets per day up until you're about a quarter of the dose and then 23 to 27 days later, they give another quarter of that total dose, and then you wait 43 weeks and then you do that cycle again so a quarterly dose and then you wait another 23-27 days. So, it's a little bit different. And, then you don't administer that for two years. This really is only indicated or the relapsing forms of multiple sclerosis and because

of its safety profile, it's only recommended for patients who have had an inadequate response to an alternative drug treatment of MS. You can see the clarity trial, pretty good number of patients in there, about 1300 patients did a dose comparison study with 2 different doses compared to placebo, looked at the annual relapse rate after 96 weeks. For being a relatively short course of therapy, it has some pretty good outcomes. You'll see almost 80% were relapse free after the 96 weeks versus about 61% in the placebo group. So, I think it's got some good data behind it, if people can get past the toxicity. It was originally developed as a cytotoxic agent for chemotherapy for cancer, so it has an interesting history with that one. The other one we heard about, the Mayzent, I'm not going to rehash. We heard a lot of good information about this one, but it's another oral once daily medication. It's been in trial with 1600 patients. We looked at utilization. The oral ones are Tecfidera as the number one, Aubagio second; no claims yet for the two new products. Optum makes the recommendation the board consider these clinically and therapeutically equivalent.

A motion was presented to accept as clinically and therapeutically equivalent and was seconded. Voting: Ayes across the board, the motion passed.

Carl Jeffery – Optum makes the recommendation that we keep the Aubagio, Gilenya, and Tecfidera all as preferred and add the two new products, Mavenclad and Mayzent as non-preferred.

Sapandeep Khurana – Until other agents get the same indication, what other products for progressive MS for that diagnosis do not apply?

Carl Jeffery – So you're saying to get the non-preferred first, If they get that indication and then they'd be able to… because with the other ones, they currently don't have that indication so if a patient came without trying any of those preferred agents first and wanted the Mayzent and they had secondary progressive MS, that's a unique indication right now to be able to get that first without having to try the non-preferred agents. Chances are pretty slim of them getting to that point without not having tried something.

Mark Decerbo – Carl, just to clarify there would be a process to be approved. It wouldn't be automated?

Carl Jeffery – It wouldn't be automated. It would go through the PA process first.

Mark Decerbo – Like the Ocrevus, clearly this treatment is an advancement in a subset of patients we didn't have an option for previously. Now, this latest information from the FDA is changing my decision-making process, active SPMS vs. non-active SPMS, all the other manufactures have done trials. I'm struggling what we do in the interim. What do we do with a patient with secondary progressing MS? We do have a uniquely indicated drug now, but the toxicity of cladribine, I think it leads to second line for sure. But I'm struggling with Mayzent.

Holly Long – Just to clarify on prior authorization, yes, what Carl provided is accurate. So instead of a normal case, it would be a case-by-case thing that we would look at and see that it's a unique situation. They would have to provide the two non-preferred as usual, but by

calling into the call center and providing that diagnosis they would be able to, in a way, bypass it.

Shamim Nagy – How long does the process take?

Carl Jeffery – Once the PA submitted, the PA's turnaround within 24 hours.

Sapandeep Khurana – What if the person taking the call says the status is no, what happens then?

Carl Jeffery – It would come to a secondary review and be reviewed again if they appealed that decision.

Holly Long – Realistically in a secondary review, it's caught so they would realize that this should be approved, and if for some reason it's not approved, then it would escalate to hearings and that is where it comes to Carl and I and we would identify it right away and approve it.

A motion was presented to accept the preferred drug list as presented. The motion was seconded. Voting: Ayes across the board, the motion passed.

d. Dermatological Agents - Topical Analgesics

Opened for public comment -

Carrie Wijesinghe – My name is Dr. Carrie Wijesinghe owner and medical director of Siena Pediatrics in Henderson, Nevada. I've been practicing medicine for 20 years and I'm here advocating on behalf of Eucrisa.

Carl Jeffery – We'll get to Eucrisa in just a few moments. That's a different section. There are a couple of new products in this class. We wanted to talk about real fast, the ZTLido is a lidocaine system. It's a little bit different. Same strength is the other ones but it's kind of determined to be bio-equivalent to the 5% Lidoderm patch. It has been shown to be superior to placebo in the treatment of the post herpetic neuralgia and that's all these have an indication for, all these patches only have an indication for the post herpetic neuralgia even though we get lots of requests for them for all sorts of arthritis pain and everything. Licart is the other new one and it joins the plethora of diclofenac topical systems we have. It's similar to Flector except it's just once a day instead of twice a day. Indicated for the treatment of acute pain due to minor strains, sprains, and contusions. You see our utilization up here. Lidocaine ointment is our preferred agent. I think it's being used for more than just post herpetic neuralgia or probably arthritis pain. There is no PA on it, so we don't know exactly what they're using it for. Voltaren has a lot of utilization, too, over 1000 claims for that quarter, so pretty significant utilization.

Kate Ward – Is the lidocaine, is that the patch?

Carl Jeffery – Yes. It's the generic patch.

Kate Ward – We commonly have medications that are both available as an OTC product and a prescription product on the PDL?

Carl Jeffery – We do have some that are OTC and Medicaid covers OTCs; they just need a written a prescription for the pharmacy to fill them, but like NSAIDs we discussed there are a lot of OTCs in that class, too. Optum recommends the board consider the class here as presented clinically and therapeutically equivalent.

A motion was presented to accept as clinically and therapeutically equivalent and was seconded. Voting: Ayes across the board, the motion passed.

Carl Jeffery – Optum recommends two new products, the Licart and the ZTLido be added as non-preferred and the rest of the class remain the same.

A motion was presented to accept the preferred drug list as presented. The motion was seconded. Voting: Ayes across the board, the motion passed.

e. Neurological Agents – Anticonvulsants

Opened up for public comment.

Elaine Morlock – My name's Elaine Morlock, I'm here with medical services of UCB. I just wanted to discuss some treatment needs in epilepsy associated with economic and cost burden and briefly you'll see these products for the active impact. In the U.S., 1 in 26 patients will develop epilepsy in their lifetime and 3.4 million Americans are living with epilepsy. Epilepsy is a complex and heterogeneous disease with numerous causes, seizure types, and serious comorbidities. In addition, seizures have a range of severities and the same seizure type may present differently in individual patients. Despite the availability of over 25 anti-epileptic drugs, or AED, unmet treatment needs remain. More than 30% of patients continue to experience seizures and are considered refractory to therapy. Treatment of refractory epilepsy relies on combining broad-based AEDs to obtain the best seizure control with as few side effects as possible for any one individual. Therefore, there is a need for numerous AED options. Epilepsy results in substantial socioeconomic and cost burdens. Data from 1996 to 2004 estimates the national economic impact of epilepsy medical expenditures and informal care to be 9.6 billion dollars annually in the U.S. Hospitalizations are major contributors to the cost burden of epilepsy with approximately 1.4 million hospital stays linked to epilepsy for convulsions in 2005. Of these states that had epilepsy or convulsions as a principal reason for hospitalization, nearly 1.8 billion in hospital cost is spent. Various retrospective studies had identified uncontrolled seizures, breakthrough seizures, increased seizure severity and medication non-adherence as primary patient disease characteristics that contribute to hospitalizations and ER visits related to epilepsy. A recent large claims database study across the U.S. examined healthcare factors associated with decreased hospitalizations related to epilepsy, access to AEDs, access to specialty clinicians and a medication change at the time of the epilepsy-related hospital encounter were detected as the major healthcare factors that can reduce hospitalizations in epilepsy. In the U.S., epilepsy patients face employment challenges. The unemployment rates for adults with epilepsy are two times higher than the national average. The rate is even higher in adults with uncontrolled epilepsy approaching an unemployment rate of 50% in those patients. People living with epilepsy also face daily challenges due to loss of driving privileges. Just in brief, our product, Briviact, is for the indicated for the treatment of partial-onset of seizures in patients four years of age and older.

It's a schedule-V controlled substance. Safety for the Briviact injection has not been established in pediatric patients and Briviact injection is indicated for the treatment of partial onset seizures in adults 16 years of age and older. Briviact's associated with important warnings and precautions including suicidal behavior and ideation, neurological adverse reactions, psychiatric adverse reactions and hypersensitivity reactions. Briviact is contraindicated in patients with a prior hypersensitivity reaction to brivaracetam or any of the inactive ingredients, the most common adverse reaction is somnolence and sedation, dizziness, and fatigue and nausea and vomiting. Most common adverse reactions in pediatric patients are similar to those in adult patients. Briviact is available in three formulations, tablets, oral solutions and injections for use in adults and in two formulations tablets and oral solutions in children four to less than 16 years of age. No dosage adjustments are necessary when switching between formulations allowing for uninterrupted therapy between outpatient and inpatient care settings. Vimpat oral solution and tablets are indicated for the treatment of partial onset seizures in patients four years of age and older. The safety of Vimpat injection has not been established in pediatric patients. Vimpat injections are indicated for the treatment of Parkinson's-type seizures only in adults 17 years of age and older. Vimpat is a scheduled V controlled substance. Vimpat is associated with important warnings and precautions including suicidal behavior and ideations, dizziness and ataxia, cardiac rhythm and conduction abnormalities, syncope and multi-organ hypersensitivity reactions. Adverse reactions reported in clinical studies of pediatric patients who were less than 17 years of age were similar to those seen in adult patients. Vimpat is available in multiple formulations including tablets, oral solutions, and intravenous injections. No dosage adjustments are necessary when switching between formulations allowing for uninterrupted therapy between outpatient and inpatient care settings. Vimpat oral solution and tablets are indicated for the treatment of partial onset seizures in patients four years of age and older. As a safety, Vimpat injection has not been established in pediatric patients. Vimpat injection is indicated for the treatment of partial-onset seizures only in adults 17 years of age and older. I ask you to please consider allowing continued unrestricted access to these therapies for appropriate Medicaid patients with partial onset seizures. The largest U.S. clinician organization for epilepsy in the American Epilepsy Society states that ensuring appropriate access and financial coverage of AEDs for the treatment of epilepsy contributes to ethical, high-quality care.

Lisa Wells - My name is Lisa Wells. I'm a medical science liaison for Greenwich Biosciences. I'm just going to provide a brief overview of the dialect today and then answer any questions that you may have. So, Epidiolex, or cannabidiol, is the first and only FDA-approved prescription of CBD indicated for the treatment of seizures associated with Lennox-Gastaut syndrome and Dravet syndrome in patients two years of age and older. It is schedule V in the controlled substance act. Dravet and LGS syndrome are rare intractable and severe forms of epilepsy. They onset at childhood and persist into adulthood. The CBD, Epidiolex, is highly purified and structurally distinct from other antiepileptic agents. Although its mechanism is not known, it does not appear to exert anticonvulsant effects due to cannabinoid receptors. In contrast to THC, it does not have any psychoactive or any euphoric effects thereby giving it a low abuse potential. The efficacy and safety profiles of Epidiolex have been evaluated in three randomized double-blind placebo-controlled trials where Epidiolex or placebo were added to a patient's current antiepileptic regimen. Epidiolex achieved its primary endpoint of statistically significant medium percent reduction in convulsive or dropped seizures. It showed 39 to 44% reduction over baseline across the three trials. The safety profile has also been consistent across the clinical program. The most common adverse effects that occurred in Epidiolex treated patients for somnolence, decreased appetite, diarrhea, transaminase elevations, and fatigue. In summary, this demonstrates to be effective in treatment of seizures

associated with LGS and Dravet syndrome in patients two years of age and older. Thank you for your time, and if anybody has any questions…

Carl Jeffery – We are here to talk about Diacomit it's our new product on here. It's indicated for the seizures associated with Dravet syndrome in patients two years of age or older, already taking Clobazam or the Onfi. No clinical studies are showing it is effective in the monotherapy. Two studies that were showing its effective and got it FDA approved, the clobazam and the valproate in Dravet syndrome. It's shown to be very effective with a response rate showing a decrease of 50% and seizures were significantly reduced. I think it's a good medication but like some of the other ones, and our rule that we've always used with these, that if it's used as a concomitant therapy, we add it as non-preferred. I will get to that one. Looking at the utilization, gabapentin, again as no surprise, is by far the most used. I doubt most of it is being used for seizure disorder. Again, we don't have any PA requirements on it. We don't know what they're using it for. We don't track any of that information. Going down the list, possibly being used for seizure disorder, the lamotrigine is down and likely used for other indications, as well. To save room on the slide, a lot of the drugs with low utilization were removed, so this isn't a comprehensive list. You can see the highlighted up here, the Elipsia was supposed to come out and that's what really prompted us to talk about this class, as well as the Diacomit, is not available yet but I think it will probably be out by the time of our next meeting. Optum recommends the board consider these clinically and therapeutically equivalent.

A motion was presented to accept as clinically and therapeutically equivalent and was seconded. Voting: Ayes across the board, the motion passed.

Carl Jeffery – This chart looks a little bit different than the other ones because I had to double it up because we have so many preferred products. The first two columns on the left are what we have preferred currently and the grey column on the very right is the non-preferred. Optum recommends the new product Diacomit be added as non-preferred and the rest of the class remain the same.

Sapandeep Khurana – For the specific indication, would it be preferred for that?

Carl Jeffery – Again, like some of the other ones, by the time they're treating Dravet syndrome they've probably been on a whole bunch of these anyway, so they're going to qualify anyway. If it did come to us, same scenario, it would be approved with that indication.

A motion was presented to accept the preferred drug list as presented. The motion was seconded. Voting: Ayes across the board, the motion passed.

f. Ophthalmic Agents - Antiglaucoma Agents

Opened for public comment

Jinesh Patel – Hi everyone. My name is Jinesh Patel. I'm the market access liaison with Acrie Pharmaceuticals. I can see that Rhopressa was approved last year and so was Rocklatan, our newest product. Rocklatan is a combination of netarsudil 0.02% and latanoprost 0.005%. This is a big step in ophthalmology, especially treating patients with glaucoma because prostaglandins are the most effective therapy in glaucoma and netarsudil being a different mechanism that treats the true disease tissue, which is a trabecular outflow, which passes the aqueous fluid out and provides the nutrition trabecular outflow needs in combining the two products in the form that we have called Rocklatan. It provides two different mechanisms in

one bottle that's still once daily that provides nutrition to the eye, reduces the pressure in the eye, and most importantly, does a lot of other things in the eye by working on the episode of venous pressure. Having this as a preferred class, I just want to thank you guys for considering this in Optum because it's a really big step in a fixed dose combination world because there's no fixed-combination product that was found to be superior in any study when it comes to prostaglandins. This product is really going to help our patients and I want to thank you for that consideration.

Opened for public comment - No public comment.

Carl Jeffery – Rocklatan is our one that prompted us to bring this forward. It's a combination of Xalatan essentially and the Rhopressa that we talked about last time, it's a ROCK inhibitor for the treatment of glaucoma. So, two studies show that it was effective comparing either ingredient alone shows the combo has shown its superior to either of them alone, so I think it's a pretty good medication there. We looked at the utilization, and Rocklatan doesn't have any claims for it, yet, but still latanoprost is our number one. We just heard that it is one of the most effective products. The board looks at some of those numbers. This class is a little bit unique and I think the utilization is spread a little bit wider than some of the other ones that are focused more on just a couple agents. This is a busy chart because there are a lot of products in this class. I think it's been over a year now and we made the recommendations to move all of the anti-glaucoma agents, separating them out from their different classes and putting them all into a single class and breaking out with the beta blockers versus the carbonic anhydrous inhibitors but they're all lumped into one now so I apologize if it's small, I tried to fit them all onto one slide here. Optum recommends the board consider this class clinically and therapeutically equivalent.

A motion was presented to accept as clinically and therapeutically equivalent and was seconded. Voting: Ayes across the board, the motion passed.

Carl Jeffery – Optum recommends the new drug Rocklatan be preferred. Again, this is similar to the other one the left two columns are preferred the right two with the gray is not preferred. Optum recommends the new product Rocklatan be added as preferred and the rest of the class remain the same.

A motion was presented to accept the preferred drug list as presented. The motion was seconded. Voting: Ayes across the board, the motion passed.

g. Psychotropic Agents - ADHD Agents

Opened for public comment - No public comment.

Carl Jeffery – Dr. Nagy, this is one where Optum doesn't have any recommendations. I think we're going to give it up to the board to decide if they wanted to have a discussion about this one or just move along. We don't have any recommendations for changes.

Discussion was opened.

Gabriel Lither – Were you expecting new drugs and they didn't come to market?

Carl Jeffery – Correct

Sapandeep Khurana – I wonder why the Strattera as a subclass of ADHD agents is a non-preferred agent for ADHD?

Carl Jeffery – We have the generic atomoxetine as preferred, so we just have the generic.

Sapandeep Khurana – Another question is for Concerta. There is uniqueness to the specific mechanism of delivery of that compound, it is non-preferred as well?

Carl Jeffery – The methylphenidate that's on here, it's the fourth one down here, methylphenidate ER, that accounts for all dosage forms of generic methylphenidate and so it includes the osmotic dosage forms too with the generic Concerta. The generic Concerta products are preferred. The two new ones that are supposed to come out, there's a new amphetamine and methylphenidate. That's what we need more of.

Sapandeep Khurana – It isn't on the market yet?

Carl Jeffery – It wasn't available to Kevin at the time of review so it may be up now, we just didn't have it in time.

Gabriel Lither - So this whole class will come back shortly?

Carl Jeffery – Yes, we'll see this in September likely.

h. Respiratory Agents - Long-acting/Maintenance Therapy

Opened up for public comment/discussion.

Steven Burch – Good afternoon everybody. My name is Steven Burch and I'm director of health economics and outcomes research with Sunovion Pharmaceuticals. Today I will discuss clinical and economical profile of Lonhala Magnair. Lonhala Magnair was the first nebulizer long-acting muscarinic antagonist or LAMA for short. It's indicated for the long-term twice daily maintenance treatment of COPD. Lonhala inhalation solution is available at 1 mL single use vial containing 25 mcg of glycopyrrolate for use via nebulization with the Magnair device. Lonhala is not a rescue medication. Magnair nebulizer is a closed system designed to use Lonhala pre-filled vials only. Using a vibrating membrane technology, the Magnair device is virtually silent, portable, and designed to deliver Lonhala in two to three minutes with normal tidal breathing. Lonhala may be an acceptable option for patients with low inspiratory flow rate or other complications using handheld inhaler devices. In two phase three trials, Lonhala 25 mcg was shown to be superior to placebo in improving trough FEV^1 the primary endpoint. In addition, significant improvements were observed in trough FEV and patient health-related quality of life as measured by the St. George's Respiratory Questionnaire. The most common adverse reactions in the two 12-week placebo-controlled trials were dyspnea and urinary tract infections. In a 48-week patient study evaluating glycopyrrolate 50 mcg twice daily and tiotropium 18 mcg once daily, the adverse events reported were consistent with those observed in the 12-week placebo-controlled study and were similar between treatment groups. This long-term trial also shows sustained improvements in trough FEV^1 and similar exacerbation rates to glycopyrrolate 50 mcg and tiotropium. Patients satisfaction in ease of use, and competence in using the Magnair nebulizer system with the steps have reached 48 weeks in a 12-questionnaire developed by Synovium. Regardless of prior nebulizer use, most patients, 75% reported they were satisfied or very satisfied with Magnair nebulizer system. The 83% of patients reported being confident to very confident the drug was being delivered and most cases reported that its easy to assemble - 76%, operated -79%, and cleaned -71% of patients. In Sunovion-developed

call consequence model looking at adults patients with COPD who may have difficulty in inhaling medications using inhaler handheld devices, the number needed to treat to avoid one exacerbation was 9.8 patients for Lonhala and 15.5 patients for handheld LAMA, tiotropium as compared to no treatment over a 1-year period may represent a cost-effective alternative option for patients who are unable to use handheld treatment impact model created by Sunovion evaluating the same target population covered by a hypothetical health plan, Lonhala made an impact on total health plan budget based on drug policies exacerbations avoidance. On behalf of Sunovion, I respectively request Lonhala Magnair be listed as a preferred agent on the PDL or maintain a non-preferred or relaxed prior authorization criteria for patients with COPD who have challenges using handheld inhalers to receive nebulization therapy Lonhala Magnair.

Carl Jeffery – This was another class where we thought there was going to be another new product on the market, and it didn't hit the market in time, so it gave us an opportunity to review the class and take a look at new generic products that have been out for a little bit. Exclusivity is running out on these, so the generic kind of changed in the marketplace a little bit, but we can talk about the generic for the Advair, the fluticasone propionate, and salmeterol. It's just a generic for the Advair Diskus inhaler. Utilization, again there's a lot here so, I apologize for the typing here. This is a lot of medications in here. Advair is one of our number one utilized followed by the Spiriva and the Symbicort. These are all preferred agents. I don't think there's anything that catches you off guard with this list.

Mark Decerbo – Does this include nebs as well, Pulmicort nebs?

Carl Jeffery – It would include anything dispensed by the pharmacy, so if they dispensed it then it would include those.

Kevin Whittington – The first Pulmicort is the nebs, the second is the MDI.

Carl Jeffery – So you can see the two new products that didn't make it to the market in time, the Wixela which is just a branded generic of the fluticasone salmeterol and then the other, the Duaklir, I think the aclidinium/formoterol is supposed to be out but I don't know where they stand now, but they weren't out in time for Kevin to take a look at. Optum recommends the board consider some of the new products, we won't review those yet, and Optum recommends the board consider these clinically and therapeutically equivalent.

A motion was presented to accept as clinically and therapeutically equivalent and was seconded. Voting: Ayes across the board, the motion passed.

Carl Jeffery – This gave us the opportunity to look at the marketplace currently and Optum recommends moving the generic Advair, which is the fluticasone salmeterol powder, Diskus inhaler likewise as preferred and the Advair brand Diskus to non-preferred and the rest of the class remain the same.

A motion was presented to accept the preferred drug list as presented. The motion was seconded. Voting: Ayes across the board, the motion passed.

6. Established Drug Classes

a. Cardiovascular Agents - Antihypertensive Agents - Vasodilators – Oral

Opened up for public comment. No public comment.

Carl Jeffery – I think the next section here is going to be a little faster. We have on this one is AlyQ, it's a branded generic of Adcirca. So that's all we're talking about with this one. Utilization numbers, most of the tadalafil is on the bottom there, it's a 33 utilization even though it's generic. Again, the majority of the use is the sildenafil. We did add some criteria on these with the DUR board and it was effective on June 3 that all oral pulmonary arterial hypertension agents require a diagnosis. In case there were some getting through for erectile dysfunction, I'll give you a quick overview. All the ED drugs are in the separate category and they're all listed separate but there is nothing that would stop people from filling the sildenafil or using it for ED. That came out of the PAH class, so I think that will change in the future. Optum recommends the board consider this class clinically and therapeutically equivalent.

A motion was presented to accept as clinically and therapeutically equivalent and was seconded. Voting: Ayes across the board, the motion passed.

Carl Jeffery – Again, this is to reevaluate the class with the tadalafil. We recommend making it as preferred and then the brand, the Adcirca and the AlyQ is added as non-preferred.

A motion was presented to accept the preferred drug list as presented. The motion was seconded. Voting: Ayes across the board, the motion passed.

b. Dermatological Agents - Topical Anti-inflammatory Agents - Immunomodulators: Topical

Opened up for public comment

Carl Jeffery – This is what we had the speaker earlier about.

Speaker – I'm the executive assistant for Dr. Carrie Wijesinghe, she was pulled from the meeting for a patient emergency. I'm reading this statement on her behalf- My name is Dr. Carrie Wijesinghe owner and medical director of Siena Pediatrics in Henderson, Nevada. I've been practicing medicine for over 20 years and I am here advocating on behalf of the community for Eucrisa. I'm excited about Eucrisa because it is the first non-steroid and long-term option that parents have in over 10 years. The medication is safe and is clinically indicated for patients two and up. Competing medications including Elidel and Protopic which was second line therapy and is normally indicated after trying steroids. There are limited side effects for Eucrisa patients including burning and itching at the site of application, this is less than 4% which is amazing, and that's in clinical trials and Eucrisa has benefited many of my patients who suffer from mild to moderate atopic dermatitis. I am here today asking that Eucrisa be added to the Medicaid formulary for care of my patients. Paying out of pocket for medications which may not be feasible at the time for the family. Allow the physicians to prescribe Eucrisa for the clinically indicated patient's saves time and additional doctor visits that are not needed. This makes the medication management of the patient very cost-effective for everyone. Thank you very much for your time and effort.

Dave Gross – Hi, this is Dave Gross from medical affairs division of Pfizer and since Eucrisa is listed on the preferred slide, I will relinquish this back to the committee, but I'd be glad to answer any specific question they have regarding Eucrisa.

Carl Jeffery – So we have the generic Elidel which you've just heard about. There's a new generic that's available for it. Utilization numbers show what we expect. The Eucrisa is really taking off since it's been introduced and is real popular medication, kind

of taking the market share away from the other ones. Optum recommends the board consider these clinically and therapeutically equivalent.

A motion was presented to accept as clinically and therapeutically equivalent and was seconded. Voting: Ayes across the board, the motion passed.

Carl Jeffery – As typical with the generics, when they come out, they have a period of exclusivity, and we may change this but for now, we'll keep the class the same, adding the generic pimecrolimus as non-preferred.

Motion presented for discussion.

Sapandeep Khurana – Is a PA required for this?

Carl Jeffery – A PA is required for all the class, yes.

Sapandeep Khurana – Curious as to why?

Carl Jeffery – Good question, it was a DUR board. These have been PA required for a long time.

Holly Long – It's been quite a while. I would recommend taking it back to the DUR board for review if you'd like.

Sapandeep Khurana – At least for the Eucrisa.

Holly Long – Okay. It would be addressed as a drug class as a whole, wouldn't it?

Carl Jeffery – Yes, we have the top immune modulators on there, so we can certainly bring that to a future board meeting.

A motion was presented to accept the preferred drug list as presented. The motion was seconded. Voting: Ayes across the board, the motion passed.

c. Hormones and Hormone Modifiers - Antidiabetic Agents - Insulins (Vials, Pens and Inhaled)

Opened up for public comment. No public comment.

Carl Jeffery – We'll call them authorized generics for now, but it is what it is, kind of semantics, but insulin Lispro, which is a generic Humalog, is now available. We have a couple of them now, so if you look at this chart, we can see all the different insulin Lispro that are available now. Now we have this generic within this class. I've got all the different insulins broken down by the combination and all the short-acting and rapid-acting all broken down for you. Optum recommends the board consider this class clinically and therapeutically equivalent.

A motion was presented to accept as clinically and therapeutically equivalent and was seconded. Voting: Ayes across the board, the motion passed.

Carl Jeffery – Optum recommends the new generic stay as non-preferred and we keep the rest of the class the same.

A motion was presented to accept the preferred drug list as presented. The motion was seconded. Voting: Ayes across the board, the motion passed.

d. Psychotropic Agents - Antidepressants - Selective Serotonin Reuptake Inhibitors (SSRIs)

Opened up for public comment and discussion and there was none.

Carl Jeffery – We've had the Paroxetine-ER not called out specifically and that's something we want to add to the preferred drug list. You can see the utilization numbers and I'll let the board take a look at those. I don't think there's anything surprising on here. Of the SSRIs, here's the list of these that are currently available. Optum recommends the board consider these clinically and therapeutically equivalent.

A motion was presented to accept as clinically and therapeutically equivalent and was seconded. Voting: Ayes across the board, the motion passed.

Carl Jeffery – Optum recommends the generic Paxil-CR which is the paroxetine ER be added as non-preferred and the rest of the class remain the same.

Mark Decerbo – In the class, are any of those ER?

Carl Jeffery – None of the other ones are ER.

Sapandeep Khurana – Curious why Trintellix is not on this list?

Carl Jeffery – We have Trintellix slipped in with the other as miscellaneous agents so it's in with the Effexor and so we've got it as kind of a miscellaneous class it falls into.

Sapandeep Khurana – There are lots of studies for the use of these under 18 years old. How come PA is required?

Carl Jeffery - Just for the safety; in fact, children can get one product within the class between the ages of 5 and 18, one product in this class without prior authorization. Anything, if they want a second agent, then it applies across the board to all the antidepressants.

Sapandeep Khurana – The PA applies to the second agent.

Carl Jeffery -- The psychotropic policy is such that they can have one within any of the classes: psychotropics, antipsychotics, benzodiazepines, anxieties, and anticonvulsants. There are five classes total. They can have one from each class, up to four, but the fifth class will require prior authorization, so even if they're getting one from each one, the fifth one requires a PA.

Mark Decerbo - I don't think Luvox is made any more.

A motion was presented to accept the preferred drug list as presented. The motion was seconded. Voting: Ayes across the board, the motion passed.

e. Respiratory Agents - Short-Acting/Rescue Therapy

Presented for public comment and there was none.

Carl Jeffery – Albuterol, there are now authorized generics or authorized brands for all three of the major HFA albuterol inhalers so the Proair, Proventil, and Ventolin all have generics available now. Proventil is our preferred agent. You can see the utilization, by far the most followed by the albuterol nebulizer which is also preferred. We have Proair Digihaler that's supposed to be coming out; I don't think it's quite available yet. That will probably be at a future meeting to talk about that one. Albuterol inhalation aerosol was added as the generic for the albuterol inhalers. These will all be, like the other generics, there will be time to exclusivity before we have any kind of competition between the generic manufacturers. Optum recommends the board consider this class clinically and therapeutically equivalent.

A motion was presented to accept as clinically and therapeutically equivalent and was seconded. Voting: Ayes across the board, the motion passed.

Carl Jeffery – Until more generic manufacturers start making these, Optum recommends the generic albuterol. This would include all three of the generic manufacturers, the generics for each of them, be included in the albuterol aerosol HFA and be added as a non-preferred. The rest of the class remain the same.

A motion was presented to accept the preferred drug list as presented. The motion was seconded. Voting: Ayes across the board, the motion passed.

7. Report by OptumRx on New Drugs to Market, New Generic Drugs to Market, and New Line Extensions

Carl Jeffery – The new medication for the Duchene's muscular dystrophy. Another one is for the IV once weekly, I think a weekly IV seems rather cumbersome, so we'll see how this one comes out. It better have some good clinical data behind it. Another one is for the treatment of moderate to severe RA. This one is actually kind of exciting because it did show some favorable results compared to Humira so I think that should be coming out here pretty soon, I think this is big, it's an oral Semaglutide. Its available now as a SubQ, Ozempic. I think it's probably the biggest downfall of the GLP-1 is this injection so I think having an oral agent is going to be huge. That will be coming out, but I don't have a timeline of when that will be available. The new generics that are coming out, speaking of the GLP-1, Byetta is supposed to be generic but again this will be the immediate release formulation, so I'm not sure this is big news. Evzio which we have is, it's listed as preferred on our PDLs and mandatory from the legislature but its injectable now that should hopefully bring down the price of that medication. Then Lyrica, Enbrel, and Restasis I think we've all mentioned as evidenced by the Lyrica CR that we reviewed last time, so we knew this was coming.

8. Closing Discussion

a. Public comments on any subject – no public comments.
b. Date and location of the next meeting – September 26, 2019.
c. Adjournment

Meeting adjourned 2:58 PM.

Annual Review - Established Drug Classes Being Reviewed Due to the Release of New Drugs

INTRODUCTION

- Approximately 121.5 million American adults are living with some form of cardiovascular disease (consisting of coronary heart disease, heart failure, stroke, and hypertension) according to the American Heart Association Heart Disease and Stroke Statistics 2019 update. Cardiovascular disease accounts for nearly 840,678 deaths in the United States (US) annually. (*Benjamin et al 2019*).
- Calcium channel blockade has certain effects that are specific to cardiac function. Coronary vascular smooth muscle relaxes when calcium channels are blocked which increases the flow of oxygenated blood into the myocardium and lowers coronary vascular resistance. In addition, calcium channel blocking agents (also called calcium channel blockers) decrease peripheral vascular resistance by relaxing arteriolar smooth muscle. Both coronary and systemic vasodilation serve to reduce cardiac workload (*Kannam et al 2019, Dobesh PP 2017, Michel T 2011*).
- The movement of calcium ions is essential for the function of all types of muscle, including cardiac muscle and vascular smooth muscle. For both cardiac and smooth muscle, the flow of calcium ions into the muscle cells through specific channels allows muscle contraction to occur. When this flow is reduced, the result is a weakening of muscle contraction and relaxation of muscle tissue (*Micromedex 2.0 2019, Kannam et al 2019*).
- The calcium channel blocking agents include dihydropyridines, which are similar in chemical structure, and non-dihydropyridines, which are a structurally heterogeneous group. Although they have different binding sites on the L-type calcium channel, both block the transmembrane influx of calcium ions into cardiac and vascular smooth muscle. The non-dihydropyridines also block the T-type calcium channel in the atrioventricular (AV) node (*Micromedex 2.0 2019, Kannam et al 2019, Dobesh PP 2017, Michel T 2011, Saseen 2017*).
- Dihydropyridines are more potent vasodilators than non-dihydropyridines due to greater selectivity for vascular smooth muscle. They have little effect on cardiac muscle contractility or conduction (*Micromedex 2.0 2019, Kannam et al 2019*).
  - All available dihydropyridine calcium channel blocking agents can be used in the treatment of hypertension, with the exception of nimodipine and immediate release nifedipine capsules. Although not a first-line treatment in all hypertensive patients, the dihydropyridines are generally effective but differ somewhat in other properties and effects.
  - Amlodipine, oral nicardipine, and long-acting nifedipine are effective treatment options for chronic stable angina. Short-acting agents, such as short-acting nifedipine, should be avoided due to increased cardiovascular and mortality risks in some patients as well as significant adverse effects, such as reflex tachycardia. Amlodipine is also indicated to reduce the risk of hospitalization due to angina and to reduce the risk of a coronary revascularization procedure in patients with recently documented coronary artery disease (CAD).
  - Amlodipine is the only calcium channel blocker that is Food and Drug Administration (FDA)-approved in combination with a nonsteroidal anti-inflammatory drug (NSAID). Consensi (amlodipine/celecoxib) was FDA-approved on May 31, 2018 (although not yet available) for the treatment of hypertension and osteoarthritis.
- The non-dihydropyridine calcium channel blocking agents include diltiazem and verapamil and both agents are available in a variety of modified-release delivery systems that alter their pharmacokinetic properties, including onset and duration of action (*Micromedex 2.0 2019*). Non-dihydropyridines dilate the arteries somewhat less than dihydropyridines, but they also reduce heart rate and contractility (*Micromedex 2.0 2019, Kannam et al 2019, Weber et al 2014*).
  - The non-dihydropyridine calcium channel blocking agents are indicated for use in the treatment of angina, arrhythmias, and hypertension. Diltiazem is a potent coronary vasodilator but is only a mild arterial vasodilator. Although it decreases AV node conduction, diltiazem does not have negative inotropic properties. Verapamil dilates coronary and peripheral arteries. It also slows conduction through the AV node and has negative inotropic and chronotropic effects (*Micromedex 2.0, 2019*).
  - Guidelines stipulate that a non-dihydropyridine calcium channel blocker may be prescribed in certain patients, often with co-morbid indications. Non-dihydropyridine calcium-channel blocking agents are not recommended for the routine treatment of heart failure because of their negative inotropic action and risk of worsening heart failure *(Yancy et al 2013, Yancy et al 2016, Yancy et al 2017)*. Caution is also advised in elderly patients. Guidelines generally reserve non-dihydropyridine calcium channel blockers for patients with high risk cardiovascular diseases and

arrhythmias; therefore, they are usually reserved for progressive cardiovascular and heart disease (*Al-Khatib et al 2017, American Geriatrics Society 2015, Amsterdam et al 2014, Fihn et al 2014, Go et al 2014, January et al 2014, KDIGO 2012, Williams et al 2018, Montalescot et al 2013, Page et al 2016, Rosendorff et al 2015, Weber et al 2014*).

- Calcium channel blockers are also included in various combination products (eg, amlodipine-benazepril); however, these combination agents are not included in this review.
- Since there are several branded agents that contain the same generic component, the remaining tables in the review are organized by generic name. This review encompasses all dosage forms and strengths with the exception of injectable indications and formulations used primarily in an institutional setting.
- Medispan Therapeutic Class: Calcium Channel Blockers

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Dihydropyridines	
Adalat CC (nifedipine extended-release)	✔
Afeditab CR (nifedipine extended-release)	✔
Consensi** (amlodipine/celecoxib)	-
Felodipine extended-release	✔
Isradipine	✔
Nicardipine	✔
Nimodipine	✔
Nisoldipine extended-release	✔
Norvasc (amlodipine)	✔
Nymalize (nimodipine)	-
Procardia (nifedipine)	✔
Procardia XL (nifedipine extended-release)	✔
Sular (nisoldipine extended-release)	✔
Non- dihydropyridines	
Calan (verapamil) tablet	✔
Calan SR (verapamil extended-release) tablet	✔
Cardizem (diltiazem) tablet	✔
Cardizem CD* (diltiazem extended-release) capsule	✔
Cardizem LA† (diltiazem extended-release) tablet	✔
Dilacor XR‡ (diltiazem extended-release) capsule	✔
Tiazac§ (diltiazem extended-release) capsule	✔
Verelan (verapamil sustained-release) capsule	✔
Verelan PM (verapamil extended-release) capsule	✔

*Cartia XT is a branded generic of Cardizem CD.
**Consensi was FDA-approved in May 2018; however, it is not yet available.
†Matzim LA is the branded generic of Cardizem LA.
‡Dilacor XR is no longer manufactured, but included in this review because its branded generic, DILT-XR, is still on the market.
§Taztia XT and Diltzac are branded generics of Tiazac.

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications – Dihydropyridines

Indication	Amlodipine	Consensi (amlodipine/ Celecoxib)	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
Angina Pectoris								
Treatment of chronic stable angina	✔ *		-	-	✔ †	-	-	-

Indication	Amlodipine	Consensi (amlodipine/ Celecoxib)	Felodipine	Isradipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
Treatment of chronic stable angina without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta blockers and/or organic nitrates or who cannot tolerate those agents	-		-	-	-	✔ (capsule, ER tablet [Procardia XL])	-	-
Treatment of vasospastic angina	✔ ‡		-	-	-	✔ (capsule, ER tablet [Procardia XL])§	-	-
CAD								
Reduce the risk of hospitalization due to angina and to reduce the risk of a coronary revascularization procedure in patients with recently documented CAD by angiography and without heart failure or an ejection fraction < 40%	✔		-	-	-	-	-	-
Hypertension								
Treatment of hypertension	✔ ‖	✔ **	✔ ‖	✔ ¶	✔ ‖	✔ (ER tablet)‖	-	✔ ‖
Treatment of hypertension to lower blood pressure which reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions	✔ ‖		✔ ‖	-	-	✔ (ER tablet [Procardia XL])‖	-	-
Miscellaneous								
Improvement of neurological outcome by reducing the incidence and severity of ischemic deficits in subarachnoid hemorrhage from ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition (ie, Hunt and Hess Grades I-V)	-		-	-	-	-	✔	-
Management of the signs and symptoms of osteoarthritis		✔ **						

*Alone or in combination with other antianginal agents.
**Consensi was FDA-approved in May 2018, however, it is not yet available.
†Alone or in combination with beta blockers.
‡Confirmed or suspected vasospastic angina. Alone or may be used in combination with other antianginal agents.
§Vasospastic angina confirmed by any of the following criteria: 1) classical pattern of angina at rest accompanied by ST segment elevation, 2) angina or coronary artery spasm provoked by ergonovine, or 3) angiographically demonstrated coronary artery spasm.
‖Alone or in combination with other antihypertensive agents.
¶Alone or in combination with thiazide-type diuretics.

(Prescribing information: Adalat CC 2016, Afeditab CR 2014, Consensi 2018, felodipine ER 2018, isradipine 2017, nicardipine capsule 2017, nimodipine 2015, nisoldipine extended-release tablet 2017, Norvasc 2019, Nymalize 2018, Procardia 2016, Procardia XL 2016, Sular 2017)

Table 3. Food and Drug Administration Approved Indications – Non-Dihydropyridines

Indication	Diltiazem	Verapamil
Angina Pectoris		
Angina due to coronary artery spasm or vasospastic angina	✔ (tablet [Cardizem], extended-release capsule [Cardizem CD])	✔ (Calan)
Chronic stable angina	✔	✔ (Calan)
Unstable angina	-	✔ (Calan)
Arrhythmias		

Indication	Diltiazem	Verapamil
Control of ventricular rate at rest and during stress in patients with chronic atrial flutter and/or atrial fibrillation in association with digitalis	-	✔ (Calan)
Prophylaxis of repetitive paroxysmal supraventricular tachycardia	-	✔ (Calan)
Hypertension		
Hypertension	✔ *(with the exception of Cardizem)	-
Hypertension to lower blood pressure which reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions.	✔ *(Cardizem LA)	✔

*May be used alone or in combination with other antihypertensive agents.

(Prescribing Information: Calan 2017, Calan SR 2017, Cardizem 2016, Cardizem CD 2017, Cardizem LA 2016, DILT-XR 2017, Tiazac 2016, Verelan 2016, Verelan PM 2016)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Dihydropyridines

- Clinical trials have demonstrated the efficacy of these agents for their respective indications.
- In a crossover study for the treatment of angina, amlodipine and felodipine have been shown to be more effective than placebo, though no significant difference between the 2 active treatment groups was observed (*Koenig 1997*).
- Numerous clinical trials have shown that the dihydropyridines can effectively lower systolic and diastolic blood pressure when administered alone or in combination with other agents. In trials comparing combination therapy to monotherapy, the more aggressive treatment regimens lowered blood pressure to a greater extent than the less intensive treatment regimens. Some comparative trials have demonstrated slight differences in blood pressure effects among the various dihydropyridines; however, the clinical significance of these differences remains to be established (*Sheehy et al 2000, Mounier-Vehier et al 2002, Kes et al 2003, Ryuzaki et al 2007, Saito et al 2007, Pepine et al 2003, Whitcomb et al 2000, White et al 2003b, Lenz et al 2001, Drummond et al 2007, Mazza et al 2002, Hollenberg et al 2003, White et al 2003a, Jordan et al 2007, Messerli et al 2002, Chrysant et al 2012, Messerli et al 2000, Jamerson et al 2004, Neutel et al 2005, Chrysant et al 2007, Chrysant et al 2004, Minami et al 2007, Jamerson et al 2007, Malacco et al 2002, Kereiakes et al 2007, Tatti et al 1998, Miranda et al 2008, Fogari et al 2007, Ribeiro et al 2007, Chrysant et al 2008, Chrysant et al 2009, Oparil et al 2009, Braun et al 2009, Littlejohn et al 2009a, Littlejohn et al 2009b, Sharma et al 2007, Neutel et al 2012, Maciejewski et al 2006, Ichihara et al 2006, Karpov et al 2012, Philipp et al 2007, Philipp et al 2011, Schunkert et al 2009, Ke et al 2010, Destro et al 2008, Flack et al 2009, Schrader et al 2009, Sinkiewicz et al 2009, Fogari et al 2009, Poldermans et al 2007, Calhoun et al 2009a, Calhoun et al 2009b, Crikelair et al 2009, Pareek et al 2010, Gustin et al 1996, Karotsis et al 2006, Lindholm et al 2005, Van Bortel et al 2008, Wiysonge et al 2007, Baguet et al 2007*).
  - In-class comparisons for the treatment of hypertension have found better compliance and a higher response rate with amlodipine compared to felodipine, though van der Krogt and colleagues found similar decreases in overall systolic and diastolic blood pressures between groups (*Sheehy et al 2000, Van der Krogt et al 1996*).
  - The most clinical trial experience has been with amlodipine and nifedipine, which have been shown to have beneficial effects on cardiovascular and stroke outcomes in hypertension trials (*Rahman et al 2012, Black et al 2008, ALLHAT 2002, Julius et al 2004, Zanchetti et al 2006, Nissen et al 2004, Ogihara et al 2008, Jamerson et al 2008, Weber et al 2010, Weber et al 2013, Brown et al 2000*).
- The dihydropyridines have been shown to have favorable effects on cardiovascular morbidity and mortality, and several studies have demonstrated comparable efficacy with beta blockers, diuretics, angiotensin-converting enzyme (ACE) inhibitors, and angiotensin receptor blockers (ARBs) in select diseases (*Pitt et al 2000, Dahlöf et al 2005, Chapman et al 2007, Nissen et al 2004, ALLHAT 2002, Black et al 2008, Rahman et al 2012, Ogihara et al 2008, Julius et al 2004, Zanchetti et al 2006, Jamerson et al 2008, Bakris et al 2010, Weber et al 2010, Weber et al 2013, Hansson et al 1999, National Intervention Cooperative Study 1999, Brown et al 2000, Estacio et al 1998*).
  - In the ALLHAT study, ACE inhibitors had a 51% higher rate (relative risk [RR], 1.51; 95% confidence interval [CI], 1.22 to 1.86) of stroke in patients of African or Caribbean descent (Black) when used as initial therapy compared to

calcium channel blockers. ACE inhibitors were also less effective in reducing blood pressure in Black patients compared to a calcium channel blocker (*Rahman et al 2012, Black et al 2008, ALLHAT 2002*).

- An unpublished phase III randomized controlled trial compared amlodipine/celecoxib (Consensi) with its individual components and matching placebo in 152 patients with hypertension *(Smith et al, 2018)*. After 2 weeks of treatment, the primary endpoint of change in mean daytime ambulatory systolic blood pressure was noninferior with amlodipine/celecoxib vs amlodipine (-10.6 vs -8.8 mmHg; p < 0.001), and the secondary endpoint of mean 24-hour diastolic blood pressure was superior with amlodipine/celecoxib vs amlodipine (-7.1 vs -4.8 mmHg; p = 0.38).
- A Cochrane review determined that calcium channel blockers do not have a role in the management of patients with acute ischemic stroke (*Zhang et al 2019*).

Non-dihydropyridines

- The non-dihydropyridine calcium channel blockers are indicated to treat hypertension and angina, in addition to slowing ventricular rate in patients with atrial fibrillation/atrial flutter. Clinical trials demonstrate the efficacy of these agents for their respective indications.
- For the treatment of angina, diltiazem and verapamil have been shown to be effective in improving exercise tolerance and reducing heart rate, angina frequency and nitroglycerin use *(De Rosa et al 1998, Chugh et al 2001, van Kesteren et al 1998, Frishman et al 1999).*
  - A direct comparison between diltiazem and verapamil found no significant differences between the agents in exercise tolerance; however, resting heart rate, angina frequency and nitroglycerin use were all significantly lower in the diltiazem group *(De Rosa et al 1998).*
- Both diltiazem and verapamil have shown efficacy in the treatment of hypertension, but comparisons with other classes of medications have not consistently demonstrated “superiority” of either agent (*Wright et al 2004, Rosei et al 1997*).
  - Wright and colleagues compared diltiazem and amlodipine in African American patients with hypertension and demonstrated significantly greater reductions in diastolic blood pressure during the first 4 hours after awakening in addition to greater reductions in heart rate with diltiazem; however, mean 24-hour systolic blood pressure reductions were significantly greater with amlodipine *(Wright et al 2004).*
- Studies evaluating the efficacy of the non-dihydropyridine calcium channel blockers for various cardiovascular outcomes generally demonstrated no significant difference between verapamil or diltiazem compared to other agents including beta blockers and diuretics *(Hansson et al 2000, Pepine et al 2003, Mancia et al 2007, Bangalore et al 2008, Black et al 2003).*

CLINICAL GUIDELINES

- There are several national and international evidence-based antihypertensive guidelines that provide recommendations regarding the use of calcium channel blocking agents. Most recommend that the selection of an antihypertensive agent be based on compelling indications for use:
  - Most guidelines recommend a thiazide-type diuretic, an ACE inhibitor, an ARB, or a calcium channel blocker as first-line therapy (*Go et al 2014, James et al 2014, Williams et al 2018, Weber et al 2014, Carey et al 2018*). The 2018 European Society of Cardiology/European Society of Hypertension (ESC/ESH) guideline generally recommends that combination therapy include an ACE inhibitor or ARB with a calcium channel blocker and/or a thiazide-type diuretic *(Williams et al 2018)*.
  - In Black hypertensive patients, thiazide-type diuretics or calcium channel blockers are recommended specifically as first-line therapy *(James et al 2014, Williams et al 2018, Weber et al 2014*).
  - In patients with chronic kidney disease, calcium channel blockers are generally recommended after ACE inhibitors or ARBs (*KDIGO 2012, Go et al 2014, Williams et al 2018, Weber et al 2014*).
  - Consensus guidelines recommend calcium channel blockers as an option in pregnant patients with severe hypertension to prevent stroke; nifedipine is one of the only dihydropyridines tested in these patients *(Bushnell et al 2014, Williams et al 2018).*
  - A long-acting dihydropyridine calcium channel blocker may be added to a basic hypertensive regimen, particularly after a beta blocker and ACE inhibitor, in hypertensive patients with CAD and stable angina *(Rosendorff et al 2015).*
  - A non-dihydropyridine calcium channel blocker may be prescribed for hypertensive patients with CAD who have an intolerance or contraindication to a beta blocker; however, a combination of a beta blocker and a non-dihydropyridine calcium channel blocker may increase the risk of bradyarrhythmias and heart failure *(Rosendorff et al 2015)*.

- Non-dihydropyridine calcium-channel blocking agents are not recommended for the routine treatment of heart failure because of their negative inotropic action and risk of worsening heart failure *(Yancy et al 2016, Yancy et al 2017).*
- The 2018 ESC/ESH guidelines recommend calcium channel blockers, ACE inhibitors, and ARBs over beta-blockers or diuretics in patients with left ventricular (LV) hypertrophy *(Williams et al 2018)*. However, in general, calcium channel blocking agents are not recommended for the routine treatment of heart failure *(Ponikowski et al 2016, Yancy et al 2013, Yancy et al 2016, Yancy et al 2017)*, although, some guidelines agree that some dihydropyridine calcium channel blockers may be used in certain co-morbid conditions if the patient has preserved LV function *(Ponikowski et al 2016).*
- In November 2017, the American College of Cardiology (ACC)/American Heart Association (AHA) released the 2017 Guideline for the Prevention, Detection, Evaluation and Management of High Blood Pressure in Adults. For initial first-line therapy for stage 1 hypertension, they list thiazide diuretics, calcium channel blockers, and ACE inhibitors or ARBs. In African American adults with hypertension but without heart failure or CKD, including those with diabetes, initial antihypertensive treatment should include a thiazide-type diuretic or calcium channel blocker. Two or more antihypertensive medications are recommended to achieve a BP target of < 130/80 mm Hg in most adults, especially in African American adults, with hypertension *(Whelton et al 2017)*.
- In August 2017, the American Academy of Pediatrics (AAP) published practice guidelines for screening and management of high blood pressure in children and adolescents. In hypertensive children and adolescents who have failed lifestyle modifications (particularly those who have LV hypertrophy on echocardiography, symptomatic hypertension, or stage 2 hypertension without a clearly modifiable factor [eg, obesity]), the guidelines recommend initiating pharmacologic treatment with an ACE inhibitor, ARB, long-acting calcium channel blocker, or thiazide diuretic *(Flynn et al 2017).*

- For the treatment of chronic angina, beta blockers are recommended as initial therapy; however, long-acting calcium channel blocking agents may be used if beta blockers are contraindicated or if additional therapy is required *(Fihn et al 2012, Fihn et al 2014, O'Gara et al 2013, Montalescot et al 2013).* Beta blockers and calcium channel blockers have similar clinical outcomes, but beta blockers may have fewer adverse events in patients with stable angina. Long-acting calcium channel blockers may be used in combination with beta blockers when beta blocker monotherapy is unsuccessful *(Montalescot et al 2013, Amsterdam et al 2014)*. Other guidelines recommend long-acting calcium channel blockers and nitrates as a treatment option for coronary artery spasm. For vasospastic (Prinzmetal) angina, guidelines recommend calcium channel blockers alone or in combination with nitrates *(Amsterdam et al 2014).*
- For the treatment of aneurysmal SAH, oral nimodipine is recommended to reduce poor outcome related to SAH *(Connolly et al 2012, Diringer et al 2011).*
- For patients with ventricular tachycardias, non-dihydropyridine calcium channel blockers have a limited role and administration of these agents can lead to further cardiovascular decompensation (*Al-Khatib et al 2017)*. Verapamil is effective in treating idiopathic interfascicular reentrant left ventricular tachycardia.

SAFETY SUMMARY

Dihydropyridine

- All of the dihydropyridine calcium channel blocking agents are contraindicated in patients with hypersensitivity to any component of the medication. Nicardipine is contraindicated in patients with advanced aortic stenosis. The Adalat CC formulation of nifedipine is contraindicated in patients with cardiogenic shock and in patients who are concomitantly using strong CYP450 inducers such as rifampin. Nimodipine capsule is contraindicated for concomitant administration with strong CYP3A4 inhibitors such as some macrolide antibiotics, some anti-HIV protease inhibitors, some azole antimycotics and some antidepressants because of risk of significant hypotension.
- Intravenous administration of the contents of nimodipine capsules has resulted in serious adverse consequences including death, cardiac arrest, cardiovascular collapse, hypotension and bradycardia. As such, nimodipine capsules have a boxed warning against the use of nimodipine capsules for intravenous administration.
- Hypotension may occur occasionally during the initial titration or with dosage increases, and hence, blood pressure should be monitored during initial administration and titration. Dihydropyridines, specifically felodipine and nisoldipine, should be used cautiously in patients with congestive heart failure.
- Dihydropyridine calcium channel blockers can produce negative inotropic effects and exacerbate heart failure and as a result, patients with heart failure should be monitored carefully.
- Caution should be exercised when using dihydropyridine calcium channel blockers in patients with impaired hepatic function or reduced hepatic blood flow because these agents are extensively metabolized by the liver.

- In general, monitoring should be performed for blood pressure (with initiation and titration), heart rate and anginal pain. Patients should also be monitored for signs and symptoms of edema.
- Consensi (amlodipine/celecoxib) carries a boxed warning for the risk of serious cardiovascular and gastrointestinal (GI) events. Consensi is contraindicated in the setting of coronary artery bypass surgery. The celecoxib component is associated with serious GI adverse events, such as bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal.

Non-dihydropyridine

- Diltiazem is contraindicated in patients with i) acute myocardial infarction and pulmonary congestion documented by X-ray on admission, ii) hypersensitivity to the drug, iii) hypotension (< 90 mm Hg systolic), iv) second or third degree AV block except in the presence of a functioning ventricular pacemaker, and v) sick sinus syndrome except in the presence of a functioning ventricular pacemaker. Verapamil is contraindicated in patients with i) atrial fibrillation or flutter and an accessory bypass tract (Wolff-Parkinson-White, Lown-Ganong-Levine syndromes), ii) hypersensitivity to the drug, iii) hypotension (< 90 mm Hg systolic), iv) second or third degree AV block except in the presence of a functioning ventricular pacemaker, v) severe left ventricular dysfunction, and vi) sick sinus syndrome except in the presence of a functioning ventricular pacemaker.
- The precautions for diltiazem include the following: may have an additive effect on heart rate with concomitant use of beta blockers or digitalis; dermatologic reactions leading to erythema multiforme and/or exfoliative dermatitis have been reported; increased risk of toxicity with hepatic and/or renal impairment; hypotension; impaired ventricular function and worsening congestive heart failure have also been reported. The precautions for verapamil include the following: concomitant use of a beta blocker in patients with any degree of ventricular dysfunction and concomitant use of quinidine in patients with hypotrophic cardiomyopathy should be avoided; congestive heart failure may occur; elevated liver enzymes, particularly serum transaminase levels, have been reported; first-degree AV block, marked, or progression to second- or third-degree block may occur; hepatic function impairment may occur; sinus bradycardia, pulmonary edema, severe hypotension, second-degree AV block, sinus arrest, and death have been reported in patients with hypertrophic cardiomyopathy; hypotension and/or dizziness may occur; pulmonary edema may occur.
- In general, patients taking non-dihydropyridine calcium channel blocking agents should have their blood pressure monitored weekly during the initial period of titration. Heart rate and anginal pain should also be monitored. Patients should have their liver function monitored periodically. Electrocardiogram (ECG) should be monitored for PR interval prolongation in patients with impaired renal or hepatic function using verapamil. If the medication is being used for arrhythmia, then ECG and reduction in signs and symptoms should be monitored.
- The common adverse effects of diltiazem include bradyarrhythmia, cough, dizziness, fatigue, headache and peripheral edema. The common adverse effects of verapamil include constipation, dizziness, edema, headache, hypotension, influenza-like symptoms, pharyngitis, and sinusitis.

(Facts and Comparisons 2019, Micromedex 2.0 2019)

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration - Dihydropyridine

Drug	Available Formulations	Usual Recommended Frequency	Comments
Amlodipine	Oral tablets	Angina pectoris (chronic stable and vasospastic): Tablet: maintenance, 5 to 10 mg once daily; maximum, 10 mg once daily CAD: Tablet: maintenance, 5 to 10 mg once daily; maximum, 10 mg once daily Hypertension:	Doses in excess of 5 mg daily have not been studied in pediatric patients. In general, wait 7 to 14 days between titration steps. Titrate more rapidly, however, if clinically warranted, provided the patient is assessed frequently.

Drug	Available Formulations	Usual Recommended Frequency	Comments
		Tablet: initial, 5 mg once daily; maintenance, 5 to 10 mg once daily; maximum, 10 mg once daily Hypertension in children 6 to 17 years of age: Tablet: initial, 2.5 mg once daily; maintenance, 2.5 to 5 mg once daily; maximum, 5 mg once daily	
Consensi (amlodipine/celecoxib)	Oral tablets	Hypertension and osteoarthritis: Initial, 5 mg/200 mg once daily (or 2.5 mg/200 mg in small, elderly, or frail patients or those with hepatic impairment); titrate to 5 mg/200 mg or 10 mg/200 mg once daily as needed.	The lowest effective dose of celecoxib for the shortest duration should be used Consensi may be substituted for its individual components
Felodipine	Oral extended-release tablets	Hypertension: Extended-release tablet: initial, 5 mg once daily; maintenance, 2.5 to 10 mg once daily	Dose adjustments should occur generally at intervals of not less than 2 weeks. Should be swallowed whole and not crushed or chewed; take without food or with a light meal
Isradipine	Oral capsules	Hypertension: Capsule: initial, 2.5 mg twice daily; maximum, 20 mg/day	Dose adjustments should occur in increments of 5 mg/day at 2 to 4 week intervals.
Nicardipine	Oral capsules	Angina pectoris (chronic stable): Capsule: initial, 20 mg 3 times daily; maintenance, 20 to 40 mg 3 times daily Hypertension: Capsule: initial, 20 mg 3 times daily; maintenance, 20 to 40 mg 3 times daily	Allow at least 3 days before increasing the dose to ensure achievement of steady state plasma drug concentrations (capsule formulation).
Nifedipine	Immediate-release capsules Extended-release tablets	Angina pectoris (chronic stable): Capsule: initial, 10 mg 3 times daily; maintenance, 10 to 20 mg 3 times daily; maximum, 180 mg/day Extended-release tablet: initial, 30 or 60 mg once daily; maximum, 90 mg/day Angina pectoris (vasospastic): Capsule: initial, 10 mg 3 times daily; maintenance, 20 to 30 mg 3 to 4 times daily; maximum, 180 mg/day	Titration should proceed over a 7- to 14-day period. Extended-release tablets should be swallowed whole, not bitten or divided and should be taken on an empty stomach; co-administration with grapefruit juice should be avoided.

Drug	Available Formulations	Usual Recommended Frequency	Comments
		Extended-release tablet: initial, 30 or 60 mg once daily; maximum, 90 mg/day Hypertension: Extended-release tablet: initial, 30 or 60 mg once daily; maintenance, 30 to 90 mg once daily; maximum, 120 mg/day	
Nimodipine	Oral capsules Oral solution	Subarachnoid hemorrhage: Capsule: 60 mg every 4 hours for 21 consecutive days Oral solution: 20 mL (60 mg) every 4 hours for 21 consecutive days	Dosing should be started within 96 hours of subarachnoid hemorrhage. Capsules should be swallowed whole with a little liquid and oral solution should only be administered enterally, preferably not less than 1 hour before or 2 hours after meals; grapefruit juice should be avoided; capsules should not be administered intravenously or by other parenteral routes.
Nisoldipine	Extended-release tablets	Hypertension: Extended-release tablet: initial, 20 mg once daily; maintenance, 20 to 40 mg/day; maximum, 60 mg/day Extended-release tablet (Sular and its generics): initial, 17 mg once daily; maintenance, 17 to 34 mg once daily; maximum, 34 mg once daily	Dose adjustments should occur at intervals of not less than 1 week. Extended-release tablets should be swallowed whole, not bitten, divided or crushed; should be taken on an empty stomach (1 hour before or 2 hours after a meal); grapefruit products should be avoided; administration with a high fat meal can lead to excessive peak drug concentration and should be avoided.

See the current prescribing information for full details

Table 5. Dosing and Administration – Non-dihydropyridine

Drug	Available Formulations	Usual Recommended Frequency	Comments
Diltiazem	Extended-release capsules Extended-release tablets	Angina pectoris (chronic stable): Extended-release capsule: initial, 120 or 180 mg once daily;	Tablet formulation should be taken before meals and at bedtime. Tiazac (extended-release) capsule formulation

Drug	Available Formulations	Usual Recommended Frequency	Comments
	Tablets	maintenance, 180 to 540 mg once daily; maximum, 540 mg once daily Extended-release tablet: initial, 180 mg once daily; maximum, 360 mg once daily Tablet: initial, 30 mg 4 times daily; maintenance, 180 to 360 mg/day (divided in 3 to 4 doses) Angina pectoris (due to coronary artery spasm): Extended-release capsule (Cardizem CD): initial, 120 or 180 mg once daily; maintenance, adjust dosage to each patient's needs up to 480 mg once daily Tablet: initial, 30 mg 4 times daily; maintenance, 180 to 360 mg/day (divided in 3 to 4 doses) Hypertension: Extended-release capsule: initial, 120 to 240 mg once daily; maintenance, 120 to 540 mg once daily; maximum, 540 mg once daily Extended-release tablet: initial, 180 to 240 mg once daily, although some patients may respond to lower doses; maximum, 540 mg once daily	may also be administered by opening the capsule and sprinkling the capsule contents on a spoonful of applesauce; the applesauce should be swallowed immediately without chewing and followed with a glass of cool water to ensure complete swallowing of the capsule contents. Cardizem LA (extended-release) tablets should be swallowed whole and not chewed or crushed.
Verapamil	Extended-release capsules Extended-release tablets Sustained-release capsules Tablets	Angina pectoris (chronic stable, unstable, and vasospastic): Tablet: maintenance, 80 to 120 mg 3 times daily Arrhythmias: Tablet: maintenance, 240 to 320 mg/day, divided in 3 to 4 doses; maximum, 480 mg/day Hypertension: Sustained-release capsule: initial, 120 to 240 mg once daily; maintenance, 180 mg to 480 mg/day; maximum, 480 mg/day Extended-release capsule: initial, 100 mg to 200 mg once daily at bedtime; maintenance, 200 mg to	Calan 80 mg tablets are scored and can be divided into halves to provide a 40 mg dose. Calan SR should be administered with food and if needed the caplets can be divided in half without compromising the sustained-release properties of the drug. Verelan and Verelan PM capsules should not be crushed or chewed and they may be administered by opening the capsule and sprinkling the capsule contents on a spoonful of applesauce; the applesauce should be swallowed immediately without chewing and followed with a glass of cool water to ensure complete

Drug	Available Formulations	Usual Recommended Frequency	Comments
		400 mg once daily; maximum, 400 mg/day Extended-release tablet: initial, 120 to 180 mg in the morning; maintenance, 180 to 480 mg/day in 1 to 2 divided doses, maximum, 480 mg/day Tablet: initial, 80 mg 3 times daily; maintenance, 360 to 480 mg/day divided (3 to 4 times daily); maximum, 480 mg/day	swallowing of the capsule contents.

See the current prescribing information for full details

CONCLUSION

- All of the dihydropyridines, with the exception of nimodipine, are approved for the treatment of hypertension. Amlodipine, nicardipine, and nifedipine are also indicated for the treatment of angina. Additionally, amlodipine reduces the risk of hospitalization due to angina and reduces the risk of coronary revascularization procedures in patients with recently documented CAD. Consensi, a combination of amlodipine and celecoxib, was recently FDA-approved for the treatment of patients with hypertension and osteoarthritis. Nimodipine improves the neurological outcome of patients with an SAH by reducing the incidence and severity of ischemic deficits in patients with ruptured intracranial berry aneurysms regardless of their post-ictus neurological condition (ie, Hunt and Hess Grades I-V).
- Numerous clinical trials have shown that the dihydropyridines can effectively lower systolic and diastolic blood pressure when administered alone or in combination with other agents. In trials comparing combination therapy to monotherapy, the more aggressive treatment regimens lowered blood pressure to a greater extent than the less intensive treatment regimens. Some comparative trials have demonstrated slight differences in blood pressure effects among the various dihydropyridines; however, the clinical significance of these differences remains to be established.
- The dihydropyridines have been shown to favorably affect cardiovascular morbidity and mortality, and several studies have demonstrated comparable efficacy with beta blockers, diuretics, ACE inhibitors, and ARBs in select diseases. However, the ALLHAT study demonstrated that patients of African or Caribbean descent (Black) had a lower rate of stroke when therapy was initiated with a calcium channel blocker compared to an ACE inhibitor.
- There is insufficient evidence to support that one dihydropyridine calcium channel blocker is safer or more efficacious than another, although most clinical trial experience has been with amlodipine and nifedipine.
- The non-dihydropyridine calcium channel blocking agents are approved for the treatment of angina, arrhythmias, and hypertension. Diltiazem and verapamil are available in a variety of modified-release delivery systems that alter their pharmacokinetic properties, including onset and duration of action.
- Clinical trials demonstrate that diltiazem and verapamil can effectively treat angina and improve blood pressure. Both agents have been shown to reduce mortality and cardiovascular event rates compared to placebo. Evidence suggests that there is no overall difference between diltiazem and verapamil compared to other antihypertensive agents (beta blockers, diuretics) in reducing cardiovascular events and mortality in patients with hypertension. There is insufficient evidence to support that one non-dihydropyridine calcium channel blocking agent is safer or more efficacious than another.
- For the treatment of chronic angina, beta blockers are recommended as initial therapy; however, long-acting calcium-channel blocking agents may be used if beta blockers are contraindicated or if additional therapy is required. Beta blockers and calcium channel blockers have similar clinical outcomes, but beta blockers may have fewer adverse events in patients with stable angina. Long-acting calcium channel blockers may be used in combination with beta blockers when beta blocker monotherapy is unsuccessful. Long-acting calcium-channel blocking agents are also recommended in patients with variant angina and for patients with coronary artery spasm(s), known as vasospastic angina, with or without nitrates.
- Treatment options for atrial fibrillation include ventricular rate control or drug therapy to maintain sinus rhythm. The AFFIRM, RACE and HOT CAFE trials demonstrated similar outcomes with rate control compared to rhythm control

strategies. Beta blockers or non-dihydropyridine calcium channel blockers are recommended for patients with persistent, paroxysmal, or permanent atrial fibrillation; however, in patients with decompensated heart failure or pre-excitation and atrial fibrillation, non-dihydropyridine calcium channel blockers should not be administered. Propafenone or flecainide ("pill-in-the-pocket") in combination with a beta blocker or non-dihydropyridine calcium channel blocker are options to terminate atrial fibrillation outside of a hospital for select patients. Non-dihydropyridine calcium channel blockers may also be prescribed as monotherapy or in combination with other treatment in patients with atrial fibrillation and co-morbid hypertrophic cardiomyopathy, certain acute coronary syndrome patients, or chronic obstructive pulmonary disease. In cases of ventricular and supraventricular arrhythmias, intravenous non-dihydropyridine calcium channel blockers are recommended. Oral non-dihydropyridine calcium channel blockers may be used for the chronic management of patients with symptomatic supraventricular tachycardia without ventricular excitation.

- Caution is advised with use in elderly patients with systolic heart failure; non-dihydropyridine calcium channel blockers have the potential to promote fluid retention and/or exacerbate heart failure.

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Therapeutic Class Overview
Statins (HMG-CoA Reductase Inhibitors)

INTRODUCTION

- The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (also known as statins) include single entity agents (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, and simvastatin), as well as fixed-dose combination products (amlodipine/atorvastatin, ezetimibe/atorvastatin, and ezetimibe/simvastatin). The statins work by inhibiting HMG-CoA reductase, which is the rate-limiting enzyme involved in hepatic cholesterol synthesis. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, which is a cholesterol precursor. Inhibition of HMG-CoA reductase decreases hepatic cholesterol synthesis, causing up-regulation of low-density lipoprotein cholesterol (LDL-C) receptors. Statins also decrease the release of lipoproteins from the liver.
- The statins are the most effective class of oral drugs to lower LDL-C. Depending on the agent selected, moderate-intensity statins can decrease LDL-C by 30 to 49% and high-intensity statins can decrease LDL-C levels ≥ 50%. The effects on LDL-C are dose-dependent and log-linear. Statins also decrease triglycerides (TG) and increase high-density lipoprotein cholesterol (HDL-C) by varying levels (Stone et al, 2014).
- Ezetimibe inhibits the intestinal absorption of cholesterol, which decreases the delivery of cholesterol to the liver. This causes a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood.
- Amlodipine is a calcium channel blocker that is approved for the treatment of hypertension (HTN), chronic stable angina and vasospastic angina, as well as to reduce the risks of hospitalization or revascularization in patients with angiographically confirmed coronary artery disease (CAD).
- Statins that are included in this review are listed in Table 1. All products are now available in a generic formulation except for ALTOPREV (lovastatin extended-release tablet), FLOLIPID (simvastatin oral suspension), ZYPITAMAG (pravastatin tablet), and EZALLOR (rosuvastatin capsule) (Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2019).
- The combinations niacin/lovastatin (ADVICOR®) and niacin/simvastatin (SIMCOR®) were removed from the market because the Food and Drug Administration (FDA) determined that a reduction in TG and increase in HDL-C do not contribute to decreased cardiovascular events according to the newest evidence (AbbVie, 2016).
- The agents included in this review are listed in Table 1 by brand name. Since there are some branded agents that contain the same generic component, the remaining tables in the review are organized by generic name.

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ALTOPREV (lovastatin extended-release)	Covis Pharma	06/26/2002	-
CRESTOR, EZALLOR (rosuvastatin)	AstraZeneca Pharmaceuticals (CRESTOR) Sun Pharmaceutical Industries, Inc. (EZALLOR)	08/12/2003 12/18/2018	✔ -
FLOLIPID (simvastatin oral suspension)	Salerno Pharmaceuticals LP	04/21/2016	-
LESCOL (fluvastatin)*	Novartis	12/31/1993	✔
LESCOL XL (fluvastatin extended-release)	Novartis	10/06/2000	✔
LIPITOR (atorvastatin)	Pfizer	12/17/1996	✔
LIVALO, ZYPITAMAG (pitavastatin)€	Kowa Company (LIVALO) Medicure (ZYPITAMAG)	08/03/2009	✔ -

Drug	Manufacturer	FDA Approval Date	Generic Availability
MEVACOR (lovastatin)*	Merck & Co., Inc	08/31/1987	✔
PRAVACHOL (pravastatin)	Bristol Myers Squibb Company	10/31/1991	✔
ZOCOR (simvastatin)	Merck & Co., Inc.	12/31/1991	✔
CADUET (amlodipine/ atorvastatin)	Pfizer	01/30/2004	✔
LIPTRUZET† (ezetimibe/atorvastatin)	Watson Labs Teva	04/26/2017	✔
VYTORIN (ezetimibe/simvastatin)	Merck & Co., Inc.	07/23/2004	✔

*The brands, LESCOL and MEVACOR, have been discontinued, but the generic formulations are available.
€The brand NIKITA was discontinued.
†The brand, LIPTRUZET, by Merck was discontinued in 2015. A generic formulation by Watson Labs Teva was recently approved by the FDA, however, current market availability is unknown.

(Drugs@FDA, 2019; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2019)

INDICATIONS

Table 2. FDA-approved indications

Indications	Single-Entity Agents							Combination Products		
	atorvastatin	fluvastatin	lovastatin	pitavastatin	pravastatin	rosuvastatin	simvastatin	amlodipine/ atorvastatin	ezetimibe/ atorvastatin	ezetimibe/ simvastatin
Hypertriglyceridemia										
Reduce elevated TG in patients with hypertriglyceridemia							✔			
Treatment of adult patients with hypertriglyceridemia in combination with diet	✔				✔	✔ δ		✔ (atorvastatin)		
Primary Hypercholesterolemia and Mixed Dyslipidemia										
Reduce elevated total cholesterol (TC), LDL-C, apolipoprotein B (apo B), TG, and non-HDL-C (Vytorin and rosuvastatin only) and increase HDL-C in patients with primary hyperlipidemia and mixed dyslipidemia	✔	✔	✔ (ER)	✔	✔	✔	✔	✔ (atorvastatin)	✔	✔
Reduce TC, LDL-C, and apo B levels in children with heterozygous familial hypercholesterolemia (HeFH) if after an adequate trial of diet therapy the following findings are present: LDL-C remains ≥189 (lovastatin only) or 190 mg/dL OR LDL-C remains ≥160 mg/dL and there is a positive family history of premature cardiovascular disease (CVD) or two or more other cardiovascular risk factors are present in the pediatric patient	✔ ¶	✔ #	✔ ** (IR)		✔ ††	✔ ††	✔ **	✔ (atorvastatin)		
Reduce elevated TG and very low-density lipoprotein-cholesterol (VLDL-C) in patients with primary dysbetalipoproteinemia							✔			
Reduce TC and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH) as an adjunct to other lipid-lowering treatments or if such treatments are unavailable	✔						✔	✔ (atorvastatin)	✔	✔
Reduce TC, LDL-C, and apo B in adults with HoFH						✔ δ				
Reduce LDL-C, TC, non HDL-C and apo B in children and adolescents with HoFH, as monotherapy or with other lipid-lowering therapies						✔ ~~A~~				

Reduction of elevated TC and LDL-C levels in patients with primary hypercholesterolemia			✔ § (IR)							
Treatment of patients with primary dysbetalipoproteinemia who do not respond adequately to diet	✔				✔	✔ δ		✔ (atorvastatin)		
Prevention of CVD										
Adjunctive therapy to diet to slow the progression of atherosclerosis in adult patients as part of a treatment strategy to lower TC and LDL-C to target levels						✔				
Reduce the risk of myocardial infarction (MI) and stroke in patients with type 2 diabetes, and without clinically evident coronary heart disease (CHD), but with multiple risk factors for CHD such as retinopathy, albuminuria, smoking, or HTN	✔							✔ (atorvastatin)		
Reduce the risk of MI, stroke, revascularization procedures, and angina in adult patients without clinically evident CHD, but with multiple risk factors for CHD such as age, smoking, HTN, low HDL-C, or a family history of early CHD	✔							✔ (atorvastatin)		
Reduce the risk of MI, undergoing myocardial revascularization procedures, and cardiovascular mortality with no increase in death from noncardiovascular causes in patients with hypercholesterolemia without clinically evident CHD					✔					
Reduce the risk of MI, unstable angina, and coronary revascularization procedures in patients without symptomatic CVD			✔ ɣ							
Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for congestive heart failure, and angina in patients with clinically evident CHD	✔							✔ (atorvastatin)		
Reduce the risk of stroke, MI, and arterial revascularization procedures in patients without clinically evident CHD but with an increased risk of CVD based on age ≥50 years old in men and ≥60 years old in women, high sensitivity C-reactive protein ≥2 mg/L, and the presence of at least one additional CVD risk factor such as HTN, low HDL-C, smoking, or a family history of premature CHD						✔				
Reduce the risk of total mortality by reducing coronary death, MI, undergoing myocardial revascularization procedures, stroke and stroke/transient ischemic attack, and to slow the progression of coronary atherosclerosis in patients with clinically evident CHD					✔					

Reduce the risk of total mortality by reducing CHD deaths, non-fatal MI and stroke, and need for coronary and non-coronary revascularization procedures in patients at high risk of coronary events because of existing CHD, diabetes, peripheral vascular disease, history of stroke or other cerebrovascular disease							✔			
Reduce the risk of undergoing coronary revascularization procedures and slow the progression of coronary atherosclerosis in patients with clinically evident CHD		✔								
Slow the progression of coronary atherosclerosis in patients with CHD as part of a treatment strategy to lower TC and LDL-C to target levels			✔							
Other										
Reduce the risk of hospitalization for angina and to reduce the risk of a coronary revascularization procedure in patients with recently documented CAD by angiography and without heart failure or an ejection fraction <40%								✔ (amlodipine)		
Symptomatic treatment of chronic stable angina								✔ (amlodipine)		
Treatment of confirmed or suspected vasospastic angina								✔ (amlodipine)		
Treatment of HTN, to lower blood pressure								✔ (amlodipine)		

Abbrv: CAD=coronary artery disease, CHD=coronary heart disease, ER=extended-release, IR=immediate-release, HTN=hypertension, MI=myocardial infarction.
§When the response to diet restricted in saturated fat and cholesterol and to other nonpharmacological measures alone has been inadequate.
¶In boys and postmenarchal girls 10 to 17 years of age.
#In adolescent boys and adolescents girls who are at least one year post-menarche, 10 to 16 years of age.
**In adolescent boys and girls who are at least one year post-menarche, 10 to 17 years of age.
††In children and adolescent patients eight to 17 years of age
~~Ѧ~~In children and adolescents ages seven to 17 years of age
ɣFor ER lovastatin, for patients at high risk; for IR lovastatin, for patients with average to moderately elevated TC and LDL-C and below average HDL-C
δApproved indications for rosuvastatin capsules (EZALLOR)

(Prescribing information: ALTOPREV®, 2018; CADUET®, 2018; CRESTOR®, 2018; EZALLOR, 2018; FLOLIPID, 2017; Fluvastatin, 2017; LESCOL XL®, 2017; LIPITOR®, 2019; LIVALO®, 2016 Lovastatin 2017; PRAVACHOL®, 2017; VYTORIN®, 2019; ZOCOR®, 2019, ZYPITAMAG, 2018)
Clinical Pharmacology, 2019

Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Numerous clinical trials have demonstrated that the statins (single-entity and combination products) can effectively lower LDL-C, non-HDL-C, total cholesterol (TC), and TG, as well as positively impact other lipid/lipoprotein parameters. Additionally, many studies have compared active treatment to placebo or compared combination therapy to monotherapy. In these studies, the more aggressive treatment regimens often improved lipid parameters to a greater extent than the less-intensive treatment regimens (Ai et al, 2008; Alvarez-Sala et al, 2008; Arca et al, 2007; Avis et al, 2007; Avis et al, 2010; Ballantyne et al, 2003; Ballantyne et al, 2004; Ballantyne et al, 2005; Ballantyne et al, 2006; Ballantyne et al, 2007; Ballantyne et al, 2008; Bardini et al, 2010; Bays et al, 2004; Bays et al, 2010; Bays et al, 2013; Bays et al, 2008a; Bays et al, 2008b; Becker et al, 2008; Betteridge et al, 2007a; Betteridge et al, 2007b; Braamskamp et al, 2015; Brown et al, 1990; Bullano et al, 2006; Bullano et al, 2007; Calza et al, 2008; Catapano et al, 2006; Charland et al, 2010; Chenot et al, 2007; Clearfield et al, 2006; Coll et al, 2006; Conard et al, 2008; Constance et al, 2007; Davidson et al, 2002; Deedwania et al, 2007a; Derosa et al, 2009; Erdine et al, 2009; Eriksson et al, 1998; Eriksson et al, 2011; Faergeman et al, 2008; Farnier et al, 2007; Farnier et al, 2008; Farnier et al, 2009; Feldman et al, 2004; Feldman et al, 2006; Ferdinand et al, 2006; Ferdinand et al, 2012; Flack et al, 2008; Florentin et al, 2011; Foody et al, 2010; Fox et al, 2007a; Fox et al, 2007b; Gagné et al, 2002; Gaudiani et al, 2005; Goldberg et al, 2004; Goldberg et al, 2006; Goldberg et al, 2009; Grimm et al, 2010; Gumprecht et al, 2011; Hall et al, 2009; Harley et al, 2007; Hing Ling et al, 2012; Hobbs et al, 2009; Hogue et al, 2008; Hunninghake et al, 2001; Illingworth et al,1994; Insull et al, 2007; Jones et al, 2003; Jones et al, 2009a; Jones et al, 2009b; Kerzner et al, 2003; Kipnes et al, 2010; Knapp et al, 2001; Koshiyama et al, 2008; Kumar et al, 2009; Lee et al, 2007; Leiter et al, 2007; Leiter et al, 2008; Lewis et al, 2007; Lloret et al, 2006; Marais et al, 2008; May et al, 2008; Mazza et al, 2008; Melani et al, 2003; Meredith et al, 2007; Messerli et al, 2006; Milionis et al, 2006; Mohiuddin et al, 2009; Motomura et al, 2009; Neutel et al, 2009; Nicholls et al, 2010; Ose et al, 2007; Ose et al, 2009; Ose et al, 2010; Park et al, 2005; Park et al, 2010; Pearson et al, 2007; Piorkowski et al, 2007; Polis et al, 2009; Preston et al, 2007; Reckless et al, 2008; Robinson et al, 2009; Rodenburg et al, 2007; Roeters van Lennep et al, 2008; Rogers et al, 2007; Rosenson et al, 2009; Rotella et al, 2010; Roth et al, 2010; Saito et al, 2002; Sansanayudh et al, 2010; Sasaki et al, 2008; Shafiq et al, 2007; Stalenhoef et al, 2005; Stein et al, 2003; Stein et al, 2004; Stein et al, 2007; Stein et al, 2008; Viigimaa et al, 2010; Vuorio et al, 2014; Winkler et al, 2007; Winkler et al, 2009; Wlodarczyk et al, 2008; Wolffenbuttel et al, 2005; Yoshitomi et al, 2006; Zieve et al, 2010).
- All of the statins, with the exception of pitavastatin, have been shown to have beneficial effects on CHD outcomes, and the majority of them (atorvastatin, pravastatin, rosuvastatin, and simvastatin) have also been shown to decrease the risk of stroke (Afilalo et al, 2007; Afilalo et al, 2008; Ahmed et al, 2006; Amarenco et al, 2009a; Amarenco et al, 2009b; Asselbergs et al, 2004; Athyros et al, 2002; Athyros et al, 2007; Baigent et al, 2005; Barter et al, 2007; Briel et al, 2006; Bushnell et al, 2006; Byington et al; 1995; Cannon et al, 2004; Cannon et al, 2006; Cannon et al, 2015; Chan et al, 2010; Cholesterol Treatment Trialists' (CTT) Collaborators, 2008; Chonchol et al, 2007; Colhoun et al, 2004; Collins et al, 2003; Crouse et al, 2007; de Lemos et al, 2004; Deedwania et al, 2006; Deedwania et al, 2007b; Downs et al, 1998; Everett et al, 2010; Ford et al, 2007; Furberg et al, 1994; Hitman et al, 2007; Hulten et al, 2006; Khush et al, 2007; Knopp et al, 2006; Koenig et al, 2001; Koga et al, 2018; LaRosa et al, 2005; LaRosa et al, 2007; Liem et al, 2002; Meaney et al, 2009; Mood et al, 2007; Mora et al, 2010; Murphy et al, 2007; Nakamura et al, 2006; Neil et al, 2006; Nicholls et al, 2006; Nissen et al, 2004; Nissen et al, 2005; Nissen et al, 2006; No authors listed, 1994; No authors listed, 2002; No authors listed, 2007; Olsson et al, 2007; O'Regan et al, 2008; Pedersen et al, 2005; Pitt et al, 1999; Pitt et al, 2012; Ray et al, 2005; Ray et al, 2006; Ridker et al, 2008; Ridker et al, 2009; Ridker et al, 2010; Rossebø et al, 2008; Sacks et al,1996; Sakamoto et al, 2007; Sato et al, 2008; Schmermund et al, 2006; Schoenhagen et al, 2006; Schouten et al, 2009; Schwartz et al, 2005; Scirica et al, 2006; Serruys et al, 2002; Sever et al, 2003; Sever et al, 2005; Shah et al, 2008; Shepherd et al, 1995; Shepherd et al, 2007; Shepherd et al, 2006; Shepherd J et al, 2002; Strandberg et al, 2009; Tavazzi L et al, 2008; Taylor et al, 2013; The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group, 2002; The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) Study Group, 1998; The Pravastatin Multinational Study Group for Cardiac Risk Patients (PMS-CRP), 1993; Thompson et al, 2004; Tikkanen et al, 2009; Waters et al, 2006; Wenger et al, 2007; Yu et al, 2007).
- Two early primary prevention trials (West of Scotland Coronary Prevention Study [WOSCOPS] and Air Force/Texas Coronary Atherosclerosis Prevention Study [AFCAPS/TexCAPS) demonstrated that the use of statins significantly reduced the risk for major coronary events (Downs et al, 1998; Shepard et al, 1995).

- Specifically, the WOSCOPS trial (N=6959) demonstrated that compared to placebo, pravastatin (40 mg/day) was associated with a significant 31% reduction in the risk of the combined endpoint of CHD death and nonfatal MI (P<0.001). A reduction in the secondary endpoint of cardiovascular death was also significant in favor of pravastatin (32%; P=0.033) (Shepard et al, 1995). Results of a 20-year observational follow-up of this trial continued to show beneficial effects of pravastatin on reduction of CHD. Among those with and without LDL-C ≥190 mg/dL (N=5529), pravastatin reduced the risk of CHD by 27% (*P*=0.002) and MACE by 25% (*P*=0.004). Among individuals with LDL-C ≥190 mg/dL (N=2560), pravastatin reduced the risk of CHD-related death, cardiovascular death, and all-cause mortality by 28% (*P*=0.020), 25% (*P*=0.009), and 18% (*P*=0.004), respectively (Vallejo-Vaz et al, 2017).
- The AFCAPS/TexCAPs trial (N=6,605) demonstrated similar benefits but with lovastatin (20 to 40 mg/day). In this trial, lovastatin was associated with a significant 37% reduction in the risk of the combined endpoint of fatal or nonfatal MI, unstable angina or sudden cardiac death (P<0.001). The AFCAPS/TexCAPs trial contained too few events to perform survival analysis on cardiovascular and CHD mortality (Downs et al, 1998).
- The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT, N=10,305) was terminated early (median duration, 3.3 years) due to the significant benefits observed with atorvastatin. In this trial, patients had average cholesterol concentrations but were at an increased risk for CHD due to the presence of HTN and three additional CHD risk factors. Compared to placebo, atorvastatin significantly reduced the risk of the combined endpoint of CHD death and nonfatal MI by 35% (P=0.0005) (Sever et al, 2003).
- Despite not demonstrating any benefit on all-cause mortality within the ASCOT trial (P=0.1649), atorvastatin has been associated with significant reductions in all-cause mortality in other primary prevention trials (Colhoun et al, 2004; Sever et al, 2003; Sever et al, 2005).
- A benefit in all-cause mortality, as well as other cardiovascular outcomes, with rosuvastatin in primary prevention was demonstrated in the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial (N=17,802). This trial sought to evaluate the efficacy of rosuvastatin in reducing cardiac events in patients with elevated high sensitivity C-reactive protein levels, which they note as being a predictor for cardiac events. This trial was terminated early (median duration 1.9 years) due to the significant benefits observed with rosuvastatin. Compared to placebo, rosuvastatin significantly reduced the risk of a first major cardiovascular event (nonfatal MI, nonfatal stroke, hospitalization for unstable angina, revascularization procedure or cardiovascular death) by 44% (P<0.0001). When analyzed individually, rosuvastatin was associated with a significant benefit for all primary outcomes, as well as all-cause mortality (P=0.02) (Ridker et al, 2008).
- Meta-analyses support the findings observed in the individual primary prevention trials (Adams et al, 2018; Baigent et al, 2005; CTT Collaborators et al, 2008; Mora et al, 2010; O'Regan et al, 2008; Taylor et al, 2011, Nunes et al, 2017).
- The Incremental Decrease in Endpoints Through Aggressive Lipid Lowering (IDEAL) trial (N=8,888) compared intensive lipid lowering therapy with atorvastatin 80 mg/day to moderate therapy with simvastatin 20 mg/day (with the potential to increase to 40 mg/day based on improvements in lipid profile). In this trial, atorvastatin did not significantly reduce the risk of the primary composite endpoint of CHD death, nonfatal MI, or cardiac arrest with resuscitation (hazard ratio [HR], 0.89; 95% confidence interval [CI], 0.78 to 1.01; P=0.07). Atorvastatin was associated with a significant reduction in the risk of major cardiovascular events compared to simvastatin (12.0 vs 13.7%; HR, 0.87; P=0.02). Atorvastatin was associated with a significant reduction in the risk of any CHD event compared to simvastatin (20.2 vs 23.8%; HR, 0.84; P<0.001) and for the risk of any cardiovascular events compared to simvastatin (26.5 vs 30.8%; HR, 0.84; P<0.001). For the individual events, atorvastatin had a lower rate of nonfatal acute MI than simvastatin (7.2% vs. 6.0%; HR, 0.83; 95% CI, 0.71 to 0.98; P=0.02), but the treatments were no different in terms of all-cause (P=0.81) or noncardiovascular (P=0.47) mortality. In addition, intensive therapy with atorvastatin 80 mg/day was associated with a significantly higher incidence of discontinuations due to adverse events (P<0.001) (Pedersen et al, 2005). A total of 94 patients (2.2%) receiving atorvastatin and 135 patients (3.2%) receiving simvastatin developed peripheral arterial disease (HR, 0.7; 95% CI, 0.53 to 0.91; P=0.007) (Stoekenbroek et al, 2015).
- Several trials have demonstrated that statins are effective in delaying the progression of atherosclerotic disease in patients with CHD. Included in these is the head-to-head REVERSAL trial that demonstrated that intensive lipid lowering with atorvastatin 80 mg/day was associated with a significantly lower median percentage change in atheroma volume compared to moderate lipid lowering with pravastatin 40 mg/day after 18 months (P=0.02) (Byington et al, 1995; Chan et al, 2010; Crouse et al, 2007; Furberg et al, 1994; Karlson et al, 2018; Nicholls et al, 2006; Nissen et al, 2004; Nissen et al, 2005; Nissen et al, 2006; Schmermund et al, 2006; Schoenhagen et al, 2006). A meta-analysis comparing the efficacy and safety of atorvastatin and pitavastatin on the regression of atherosclerosis did not find a statistically significant difference between these agents when evaluating changes in plaque volume, lumen

volume, and external elastic membrane. However, atorvastatin was potentially more effective than pitavastatin at reducing LDL-C and improving HDL-C (Liu et al, 2018).

- The majority of secondary prevention trials have evaluated the use of statins initiated three to six months after an acute cardiac event; however, evidence supports the use of these agents initiated right after an acute event (Briel et al, 2006; Cannon et al, 2004; de Lemos et al, 2004; Liem et al, 2002).
- The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) trial (N=3,086), a placebo-controlled trial with atorvastatin, is noteworthy as it demonstrated that when initiated in the hospital following an acute coronary syndrome (ACS), atorvastatin was safe and associated with a 16% reduction in the composite of death, nonfatal acute MI, resuscitated cardiac arrest, or recurrent symptomatic myocardial ischemia after 16 weeks (P=0.048) (Schwartz et al, 2005). However, a 2018 randomized, controlled trial (RCT) that included 4191 patients with ACS and planned PCI found that 2 loading doses of atorvastatin 80 mg before and 24-hours after surgery did not reduce the rate of MACE at 30 days when compared to placebo (absolute difference, 0.85%; 95% CI, -0.70% to 2.41%; hazard ratio, 0.88; 95% CI, 0.69-1.11; P=0.27) (Berwanger et al, 2018).
- The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) investigated the efficacy of the addition of ezetimibe to simvastatin for the prevention of stroke and other adverse cardiovascular events in 18,144 patients. After 7 years, the combination of ezetimibe and simvastatin significantly reduced the risk of stroke of any etiology (HR, 0.83; 95% CI, 0.70-0.98; P=0.029) and ischemic stroke (HR, 0.76; 95% CI, 0.63-0.91; P=0.003) when compared to simvastatin monotherapy. Significant benefits were also observed in the subgroup of patients with prior stroke (Bohula et al, 2017).
- Of the head-to-head trials, the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT–TIMI 22) trial (N=4,162) again compared intensive lipid therapy with atorvastatin 80 mg/day to standard therapy with pravastatin 40 mg/day (with a potential to increase to 80 mg/day based on improvements in lipid profile). Patients who were hospitalized with an ACS within the preceding 10 days were enrolled. After two years, atorvastatin significantly reduced the combined endpoint of all-cause mortality, MI, unstable angina requiring hospitalization, coronary revascularization performed >30 days after randomization, and stroke by 16% compared to pravastatin (P=0.005). Among the individual endpoints, atorvastatin was significant for reducing the risk of revascularization (P=0.04) and unstable angina (P=0.02). In this trial, discontinuations due to adverse events were similar between the two treatments (P=0.11) (Cannon et al, 2004).
- A meta-analysis which assessed the efficacy of high dose atorvastatin in patients who underwent percutaneous coronary intervention (PCI) (N=2,850) found that atorvastatin significantly reduced the risk of MI in patients with PCI compared to placebo (RR, 0.62; 95% CI, 0.49 to 0.78) (Lu et al, 2017).
- A meta-analysis evaluated the efficacy and safety of dosing statins on alternative days (N=505) compared to daily dosing (N=518). Although there was no differences on TG, the reduction in TC (P<0.00001) and LDL-C (P=0.003) was significantly greater in the daily dosing group (Awad et al, 2017).
- A Cochrane review assessed the effectiveness of statins in children aged 4 to 18 years with HeFH and found that statin treatment is effective. Statin therapy was found to be safe with no significant safety issues in the short-term (Vuorio et al, 2017).
- A meta-analysis involving data from 28 RCTs recently assessed the efficacy and safety of statin therapy in older individuals (*Cholesterol Treatment Trialists' Collaboration 2019*). Results revealed that statin therapy was associated with a significant reduction in major vascular events regardless of age; however, there was less direct evidence of a beneficial impact among patients > 75 years who did not already have evidence of occlusive vascular disease.

SAFETY SUMMARY

- Statins are contraindicated in documented hypersensitivity to the agent, unexplained elevations in serum transaminases, active liver disease, and patients who are pregnant or nursing.
- The statins are generally well-tolerated, and the most common side effects are gastrointestinal disturbances, headache, insomnia, myalgia, and rash. Muscle aches and weakness are reported by 1 to 2% of patients taking statins. The symptoms are usually mild and generally do not lead to discontinuation, however, myopathy can sometimes take the form of rhabdomyolysis, with or without acute renal failure secondary to myoglobinuria. Rare fatalities have occurred. The risk of myopathy is increased by high levels of HMG-CoA reductase inhibitory activity in plasma. All statins can increase hepatic transaminase levels and creatinine kinase.
- In December 2018, the AHA published its first scientific statement specifically aimed at reviewing statin harms. Approximately 10% of patients stop taking a statin because of subjective complaints, most commonly muscle

symptoms without raised creatinine kinase. Randomized clinical trials, however, have found that the difference in the incidence of muscle symptoms without significantly raised creatinine kinase in statin-treated compared with placebo-treated participants is < 1%, and it is even smaller (0.1%) for patients who discontinued treatment due to muscle symptoms. This suggests that muscle symptoms are usually not caused by pharmacological effects of the statin. Restarting statin therapy in these patients, especially those at high risk of cardiovascular events, should be prioritized, as the benefits of these agents outweigh their risks (Newman et al 2018).

- Increases in hemoglobin A1c (HbA1c) and fasting serum glucose have been reported with statins. New-onset diabetes is increased in patients treated with statins; however, it is dose-related, occurs primarily in patients on metformin and a sulfonylurea, appears to be less common with pravastatin and possibly pitavastatin, and occurs overall to a lesser extent than the associated decrease in atherosclerotic cardiovascular disease (ASCVD) (Jellinger et al, 2017).
- Pravastatin is the only statin that does not undergo cytochrome (CYP) 450 metabolism, and is therefore associated with a lower risk for drug interactions. Atorvastatin (to a lesser extent), lovastatin, and simvastatin are primarily metabolized by the CYP3A4 isoenzyme, while fluvastatin, pitavastatin, and rosuvastatin are metabolized by the CYP2C9 isoenzyme, which may result in differences in their drug interaction profiles (Wiggins et al, 2016).
- The 2016 scientific statement written by the American Heart Association (AHA) stated that the risk for interactions between statins and other cardiovascular drugs may be unavoidable for heart patients, but it can be reduced with proper clinical management. A review of all of the medications that statin-treated patients are taking should be done at each patient visit, so that potential drug interactions can be identified early. Some key recommendations include:
    - Concomitant use of lovastatin, pravastatin, or simvastatin with gemfibrozil should be avoided. When gemfibrozil is used with other statins, a lower statin dose should be utilized.
    - A non-CYP3A4-metabolized statin should be used in combination with verapamil and diltiazem (calcium channel blockers). The dose of lovastatin or simvastatin should be limited to 20 mg daily or less when given with the calcium channel blocker, amlodipine.
    - The concomitant use of cyclosporine, everolimus, sirolimus, or tacrolimus should be avoided with lovastatin, simvastatin, and pitavastatin, as the combination could be potentially harmful.
    - Numerous other drug interactions are listed, many of which require dose adjustment of statin therapy or drug level monitoring (e.g. digoxin) (Wiggins et al, 2016).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Single-Entity Agents				
Atorvastatin	Tablet: 10 mg 20 mg 40 mg 80 mg	Hyperlipidemia: Tablet: initial, 10 to 40 mg once daily; maintenance, 10 to 80 mg/day Adjunct to diet for the treatment of patients with elevated serum TG levels, reduce TC and LDL-C in patients with HoFH as an adjunct to other lipid lowering treatments or if such treatments are unavailable, treatment of patients with primary dysbetalipoproteinemia: Tablet: 10 to 80 mg/day HeFH in pediatric patients 10 to 17 years old: Tablet: initial dose 10 mg/day, maximum dose 20 mg/day	After initiation and/or upon titration, lipid levels should be analyzed within two to four weeks and dosage adjusted accordingly. Dosage adjustments may be necessary in patients taking cyclosporine, clarithromycin, itraconazole, or	May be administered with or without food. Tablets may be taken at any time during the day.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			certain protease inhibitors.	
Fluvastatin	Capsule: 20 mg 40 mg Extended-release tablet: 80 mg	Hypercholesterolemia (including HeFH and nonfamilial) and mixed dyslipidemia in adults: Capsule: 40 mg once daily or 40 mg twice daily Patients requiring LDL-C reductions ≥25% should initiate fluvastatin therapy at 40 mg once daily or 80 mg in divided doses of the 40 mg capsule given twice daily. Patients requiring LDL-C reductions < 25% should initiate a starting dose of 20 mg. Extended-release tablet: 80 mg once daily HeFH in pediatric patients: Capsule: 20 mg daily, maximum dose 40 mg twice daily Extended-release tablet: 80 mg once daily	After initiation and/or upon titration, lipid levels should be analyzed after four weeks and dosage adjusted accordingly. Max dose is 20 mg twice daily when used with cyclosporine or fluconazole.	Capsules should be taken in the evening if dosed once daily. If 80 mg/day is used, it should be administered in two divided doses (immediate-release capsule). May be administered with or without food. Tablets may be taken at any time during the day (extended-release tablet). Tablets should be swallowed whole. (extended-release tablet).
Lovastatin	Extended-release tablet: 20 mg 40 mg 60 mg Tablet: 10 mg 20 mg 40 mg	Hyperlipidemia: Extended-release tablet: initial, 20 to 60 mg once daily; maintenance, 20 to 60 mg/day Tablet: initial, 20 mg once daily; maintenance, 10 to 80 mg/day in single or two divided doses; maximum, 80 mg/day Prevention of CVD: Extended-release tablet: initial, 20 to 60 mg once daily; maintenance, 20 to 60 mg/day Tablet: initial, 20 mg once daily; maintenance, 10 to 80 mg/day in single or two divided doses; maximum, 80 mg/day	Prior to initiation and periodically during therapy, lipid levels should be analyzed and dosage adjusted accordingly.	Extended-release tablet should be taken at bedtime. Extended-release tablets should be swallowed whole. Immediate-release tablet should be taken with an evening meal.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Pitavastatin	Tablet: 1 mg 2 mg 4 mg	Hyperlipidemia: Tablet: initial, 2 mg once daily; maintenance, 1 to 4 mg/day; maximum, 4 mg/day	After initiation and/or upon titration, lipid levels should be analyzed after four weeks and dosage adjusted accordingly. Do not exceed 4 mg once daily dosing due to increased risk of severe myopathy Max dose is 1 mg/day when used with erythromycin. Max dose is 2 mg/day when used with rifampin. Use caution in patients receiving ≥ 1 gram daily of niacin-containing products.	May be administered with or without food. Tablets may be taken at any time during the day.
Pravastatin	Tablet: 10 mg* 20 mg 40 mg 80 mg	Hyperlipidemia: Tablet: initial, 40 mg once daily; maintenance, 40 to 80 mg once daily Prevention of CVD: Tablet: initial, 40 mg once daily; maintenance, 40 to 80 mg once daily Pediatric patients: Ages eight to 13 years old: 20 mg once daily Ages 14 to 18 years old: 40 mg once daily	After initiation and/or upon titration, lipid levels should be analyzed after four weeks and dosage adjusted accordingly. Max dose in patients taking cyclosporine is 20 mg/day. Max dose in patients taking clarithromycin is 40 mg/day.	May be administered with or without food. Tablets may be taken at any time during the day.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Rosuvastatin	Tablet: 5 mg 10 mg 20 mg 40 mg Capsule: 5 mg 10 mg 20 mg 40 mg	Tablets: Hyperlipidemia: Initial, 10 to 20 mg once daily; maintenance, 5 to 40 mg/day Reduce TC, LDL-C and apo B in patients with HoFH: Initial, 20 mg once daily; Ages 7 to 17 years: 20 mg once daily Reduce TC, LDL-C and apo B in pediatric patients with HeFH: Aged 8 to less than 10 years: maintenance, 5 to 10 mg/day Aged 10 to 17 years: maintenance, 5 to 20 mg/day Capsules: Initial, 10 to 20 mg once daily; usual starting dose in HoFH is 20 mg once daily Maximum dose: 40 mg once daily	After initiation and/or upon titration, lipid levels should be analyzed within two to four weeks and dosage adjusted accordingly. Dosing in Asian patients: initial, 5 mg once daily Max dose is 5 mg once daily when used with cyclosporine and 10 mg once daily when used with gemfibrozil, atazanavir/ ritonavir, lopinavir/ritonavir, or simeprevir.	May be administered with or without food. May be taken at any time during the day.
Simvastatin	Tablet: 5 mg 10 mg 20 mg 40 mg 80 mg Oral suspension: 20 mg/5 mL 40 mg/5 mL	Hyperlipidemia: Tablet: initial, 10 or 20 mg once daily; maintenance, 5 to 40 mg/day Reduce TC and LDL-C in patients with HoFH as an adjunct to other lipid lowering treatments or if such treatments are unavailable: Tablet: 40 mg once daily Prevention of CVD: Tablet: initial, 10 or 20 mg once daily; maintenance, 5 to 40 mg/day Reduce TC, LDL-C and apo B in pediatric patients with HeFH: Aged 10 to 17 years: Tablet: initial, 10 mg/day; maintenance, 10 to 40 mg/day; maximum dose is 40 mg/day	After initiation and/or upon titration, lipid levels should be analyzed after four weeks and dosage adjusted accordingly. Dose should be decreased by 50% if initiating lomitapide. Simvastatin dosage should not exceed 20 mg/day (or 40 mg/day for patients who have previously taken simvastatin 80 mg/day chronically (e.g.	Tablets should be taken in the evening. The oral suspension should be taken on an empty stomach. Shake oral suspension bottle for at least 20 seconds. Use accurate measuring device. Due to the increased risk of myopathy, including rhabdomyolysis, particularly during the first year of treatment, use of the 80 mg dose should be restricted to patients who

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			for 12 months or more) without evidence of muscle toxicity) while taking lomitapide. Use caution in Chinese patients receiving doses >20 mg with niacin-containing products. Max dose is 10 mg/day when used with verapamil, diltiazem, or dronedarone. Max dose is 20 mg/day when used with amiodarone, amlodipine, or ranolazine. Simvastatin is contraindicated for use with strong CYP3A4 inhibitors. For patients at high risk for a CHD event due to existing CHD, diabetes, peripheral vessel disease, history of stroke or other cerebrovascular disease, the recommended starting dose is 40 mg/day.	have been taking the 80 mg dose chronically without evidence of muscle toxicity.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			Use caution in patients receiving ≥ 1 gram daily of niacin-containing products.	
Combination Products				
amlodipine/ atorvastatin	Tablet: 2.5/10 mg 2.5/20 mg 2.5/40 mg 5/10 mg 5/20 mg 5/40 mg 5/80 mg 10/10 mg 10/20 mg 10/40 mg 10/80 mg	Dosage of amlodipine/atorvastatin must be individualized on the basis of both effectiveness and tolerance for each individual component in the treatment of hypertension/angina and hyperlipidemia. Select doses of amlodipine and atorvastatin independently. The usual starting dose for amlodipine is 5 mg daily and for atorvastatin 10 to 20 mg daily. The maximum dose is amlodipine 10 mg daily and atorvastatin 80 mg daily. Patients requiring large LDL-C reductions (>45%) should initiate atorvastatin therapy at 40 mg once daily. <u>HeFH in pediatric patients 10 to 17 years old:</u> *Atorvastatin* Tablet: initial dose 10 mg/day, maximum dose 20 mg/day *Amlodipine [age 6 to 17 years old]* Tablet: initial dose 2.5 to 5 mg maximum dose 5 mg	After initiation and/or upon titration, lipid levels should be analyzed within two to four weeks and dosage adjusted accordingly. Dosage should be adjusted to achieve blood pressure goals. In general, wait seven to 14 days between titration steps. Titration may proceed more rapidly if clinically warranted, provided the patient is assessed frequently.	May be administered with or without food. Tablets may be taken at any time during the day.
ezetimibe/ atorvastatin	Tablet: 10/10 mg 10/20 mg 10/40 mg 10/80 mg	<u>Usual starting dose:</u> 10/10 mg or 10/20 mg once daily. Usual dose range is 10/10 mg to 10/40 mg once daily. May initiate at 10/40 mg once daily for patients requiring a larger LDL-C reduction (> 55%). <u>HoFH:</u> 10/40 mg once daily.	After initiation or titration of doses, lipid levels may be analyzed after two or more weeks. For patients taking clarithromycin, itraconazole, saquinavir +	Tablets may be taken at any time of the day. May be administered with or without food.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			ritonavir, darunavir + ritonavir, or fosamprenair alone or with ritonavir: Do not exceed 10/20 mg once daily. For patients taking nelfinavir: Do not exceed 10/40 mg once daily.	
ezetimibe/ simvastatin	Tablet: 10/10 mg 10/20 mg 10/40 mg 10/80 mg	Hyperlipidemia: Adjunct to diet to reduce elevated TC, LDL-C, apo B, TG, and non-HDL-C levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia, reduce TC and LDL-C in patients with HoFH as an adjunct to other lipid lowering treatments or if such treatments are unavailable: Tablet: initial, 10/10 or 10/20 mg once daily; maintenance, 10/10 to 10/40 mg/day	After initiation and/or upon titration, lipid levels should be analyzed within two or more weeks and dosage adjusted accordingly. Decrease dose of VYTORIN by 50% if initiating lomitapide. VYTORIN dosage should not exceed 10/20 mg once day (or 10/40 mg once daily for patients who have previously taken simvastatin 80 mg once day chronically, e.g., for 12 months or more, without evidence of muscle toxicity) while taking lomitapide. Max dose is 10/10 mg/day when used with	May be administered with or without food. Tablets should be taken in the evening. Due to the increased risk of myopathy, particularly during the first year of treatment, use of the 10/80 mg dose should be restricted to patients who have been taking the 10/80 mg dose chronically.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			verapamil, diltiazem, or dronedarone. Max dose is 10/20 mg/day when used with amiodarone, amlodipine, or ranolazine. VYTORIN is contraindicated for use with strong CYP3A4 inhibitors. Use caution in patients receiving ≥ 1 gram daily of niacin-containing products.	

*Pravachol 10 mg is no longer available, however, generic pravastatin 10 mg remains available.

Clinical Pharmacology, 2019

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
Atorvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in children 10 to 17 years of age for the treatment of HeFH. Doses of >20 mg have not been studied in this population. Safety and efficacy in children <10 years of age have not been established.	No dosage adjustment required.	Contraindicated in active liver disease or in patients with unexplained persistent elevations or serum transaminases.	Unclassified† Contraindicated in pregnant women. Contraindicated during breastfeeding.
Fluvastatin	No evidence of overall differences in safety or	Approved for use in children 9 to 16 years of age for	No dosage adjustment required in mild to	Contraindicated in active liver disease or unexplained	Unclassified† Contraindicated in women who

	efficacy observed between elderly and younger adult patients.	the treatment of HeFH. Safety and efficacy in children for other approved indications have not been established.	moderate renal dysfunction. Use with caution in severe renal dysfunction; doses above 40 mg per day have not been studied.	persistent elevations in serum transaminases.	are pregnant or may become pregnant. Potential excretion into breast milk; contraindicated during breastfeeding
Lovastatin	No dosage adjustment required in the elderly. The initial starting dose of lovastatin extended-release should not exceed 20 mg/day (ALTOPREV).	Approved for use in children 10 to 17 years of age for the treatment of HeFH (MEVACOR); maximum dose of 40 mg/day. Safety and efficacy in children <10 years of age have not been established (MEVACOR). Safety and efficacy in children have not been established (ALTOPREV).	Renal dosage adjustment is required; for creatinine clearances <30 mL/minute, use with caution and carefully consider doses >20 mg/day.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Pregnancy Category X (MEVACOR) No data on excretion in breast milk; not recommended (MEVACOR) Unclassified† (ALTOPREV) Contraindicated in pregnant women (ALTOPREV). Contraindicated during breastfeeding (ALTOPREV).
Pitavastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Safety and efficacy in children have not been established.	Renal dosage adjustment is required; for creatinine clearances 15 to 59 mL/ minute or end-stage renal disease receiving hemodialysis, an initial dose of 1 mg once daily and a maximum dose of 2 mg/day is re-commended.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Unclassified† Contraindicated in pregnant women. Contraindicated during breastfeeding.

Pravastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in children eight to 18 years of age for the treatment of HeFH. Safety and efficacy in children <8 years of age have not been established.	Renal dosage adjustment is required in severe renal impairment; an initial dose of 10 mg/day is recommended.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Unclassified† Contraindicated in pregnant women. Pravastatin is present in breast milk; contraindicated during breastfeeding.
rosuvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in children 8 to 17 years of age for the treatment of HeFH and 7 to 17 years of age for the treatment of HoFH. Safety and efficacy in children <7 years of age have not been established. Pediatric dosing is approved for CRESTOR; however, due to marketing exclusivity rights, EZALLOR is not labeled with similar pediatric dosage information.	No dosage adjustment required in mild to moderate renal dysfunction. Renal dosage adjustment required; for creatinine clearances <30 mL/minute, an initial dose of 5 mg/day and a maximum dose of 10 mg/day are recommended.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Unclassified† Contraindicated in pregnant women. Limited data indicate that the drug is in breast milk; contraindicated during breastfeeding.
Simvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in children 10 to 17 years of age for the treatment of HeFH. Doses greater than 40 mg have not been studied in this population. Safety and efficacy in children <10 years of age have not been established.	No dosage adjustment required in mild to moderate renal dysfunction. Renal dosage adjustment required for severe renal impairment: an initial dose of 5 mg/day with close	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Pregnancy Category X Unknown whether excreted in breast milk; contraindicated during breastfeeding.

			monitoring is recommended.		
Combination Products					
amlodipine/ atorvastatin	Safety and efficacy in elderly patients have not been established. Elderly patients have decreased clearance of amlodipine; lower initial doses of amlodipine may be required.	Safety and efficacy in children have not been established. Safety and efficacy of atorvastatin in children <10 years and amlodipine in children <6 years of age have not been established	No dosage adjustment required.	Contraindicated in active liver disease.	Unclassified† Contraindicated for use during pregnancy and in women who may become pregnant. Contraindicated for use during breastfeeding.
ezetimibe/ atorvastatin	The maximum dosage limit is 10/80 mg once daily for most patients.	Safety and efficacy have not been established.	No dosage adjustment is needed.	Contraindicated in patients with active hepatic disease or unexplained transaminase elevations.	Unclassified† Contraindicated for use during pregnancy and in women who may become pregnant. Contraindicated for use during breastfeeding.
ezetimibe/ simvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients; prescribe with caution.	Safety and efficacy in children < 10 years old have not been established.	Use with caution doses exceeding 10/20 mg in patients with moderate to severe renal dysfunction.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Pregnancy Category X Unknown whether excreted in breast milk; contraindicated during breastfeeding.

* Pregnancy Category X = Contraindicated in pregnant women due to evidence of fetal abnormalities from adverse effects data from investigational or marketing experience. Risks of use of the drug in pregnant women clearly outweigh potential benefits.

†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

Clinical Pharmacology, 2019

CONCLUSION

- Statins are approved for the treatment of a variety of lipid disorders, including primary hypercholesterolemia, mixed dyslipidemia, and hypertriglyceridemia.
- The fixed-dose combination products (CADUET [amlodipine/atorvastatin], ezetimibe/atorvastatin, and VYTORIN [ezetimibe/simvastatin]) are indicated for use when dual therapy is appropriate.

- Statins decrease LDL-C according to the intensity of statin used and TG by 7% to 30%, as well as increase HDL-C by 5% to 15% when administered as monotherapy. The effects on LDL-C are dose-dependent and log-linear. Statins also decrease TG and increase HDL-C by varying levels.
- All products in this review are now available in a generic formulation except for ALTOPREV® (lovastatin extended-release), FLOLIPID (simvastatin oral suspension), and Zypitamag (pitavastatin), and EZALLOR (rosuvastatin capsule) (Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2019).
- In general, therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia. When LDL-C lowering is required, initial treatment with a statin is recommended.
- In 2018, ACC/AHA and a variety of other organizations released a new guideline on the management of blood cholesterol (Grundy et al, 2018). Statins remain the cornerstone of therapy; however, this guideline also contains very specific recommendations for clinicians in a newly defined "very high risk of ASCVD" category, which refers to patients who continue to have LDL-C levels ≥ 70 mg/dL after maximizing statin therapy. In these patients, the guideline recommends considering the addition of a non-statin medications, such as ezetimibe or a PCSK9 inhibitor.
- The 2013 American College of Cardiology/American Heart Association (ACC/AHA) Guidelines on Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults focus on primary and secondary atherosclerotic cardiovascular disease (ASCVD) risk reduction in adults (Stone et al, 2014).
    - These guidelines established four statin benefit groups: (1) individuals with clinical ASCVD (2) individuals with primary elevations of LDL–C >190 mg/dL (3) individuals with diabetes aged 40 to 75 years with LDL–C 70 to 189 mg/dL and without clinical ASCVD, and (4) individuals aged 40 to 75 years without clinical ASCVD or diabetes with LDL–C 70 to 189 mg/dL and estimated 10-year ASCVD risk >7.5%
    - Intensity of statin therapy (high, moderate, and low) is the new goal of treatment in the benefit groups for use in primary and secondary prevention of ASCVD.
    - A new cardiovascular risk tool, based on pooled cohort equations, has been created to estimate absolute 10-year ASCVD risk (defined as first occurrence nonfatal and fatal MI, and nonfatal and fatal stroke). The Pooled Cohort Equations should be used to estimate 10-year ASCVD risk for individuals without clinical ASCVD or diabetes and LDL–C 70 to189 mg/dL to guide the initiation of statin therapy. For the primary prevention of ASCVD in individuals with diabetes (diabetes mellitus type-1 and type-2), estimated 10-year ASCVD risk can also be used to guide the intensity of statin therapy. For those with clinical ASCVD or with LDL–C ≥190 mg/dL who are already in a statin benefit group, it is not necessary to estimate 10-year ASCVD risk (Stone et al, 2014).
    - Statins are the primary medications to utilize for ASCVD risk reduction according to the 2013 guidelines, which focus on treatments proven to reduce ASCVD and not comprehensive lipid management.
- The 2015 AHA Scientific Statement on Familial Hypercholesterolemia (FH) recommends aggressive pharmacological treatment for patients with HeFH beginning at age eight to 10 years. Pharmacological treatment may also be considered in younger patients (less than eight years of age) with extreme elevation of LDL-C or those with other major risk factors suggesting very premature CVD. In HeFH pediatric patients, LDL-C goals are not well defined; however, treatment is recommended based on LDL-C levels and not based on genetic abnormalities or other clinical features. In adult patients with HeFH, the initial goal is to reduce LDL-C by 50% and treatment with a high-intensity statin (rosuvastatin or atorvastatin) is recommended. If LDL-C levels remain above goal after three months, then ezetimibe may be added. If LDL-C continues to be above goal after three months of two-drug therapy, then the addition of a PCSK9 inhibitor, bile acid sequestrant, or niacin can be considered. In patients with HoFH, lipid-lowering therapy should be initiated as soon as possible, with statins providing a 10 to 25% reduction in LDL-C (Gidding et al, 2015).
- The 2016 United States Preventive Services Task Force (USPSTF) recommendations for statin use for the primary prevention of cardiovascular disease in adults note the following:
    - Adults without a history of CVD should use a low- to moderate-dose statin for the prevention of CVD events and mortality when the following criteria are met: (1) they are aged 40 to 75 (2) they have one or more CVD risk factor such as dyslipidemia, diabetes, hypertension, or smoking (3) they have a calculated 10-year risk of a cardiovascular risk of 10% or more.
    - Although statin use may be beneficial for the primary prevention of CVD in some adults with a 10-year cardiovascular risk of <10%, the benefits are likely smaller. A low- to moderate-dose statin may be offered to certain adults without a history of CVD when all of the following criteria are met: (1) they are aged 40 to 75

years (2) they have one or more CVD risk factor (3) they have a calculated 10-year risk of a cardiovascular event of 7.5 to 10%.
    - There is insufficient evidence to assess the balance of benefits to risks of initiating a statin for the primary prevention of CVD and mortality in patients ≥76 years without a history of MI or stroke (US Preventative Task Force, 2016).
- In 2017, the American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) recommended the addition of another agent when statin therapy alone does not achieve therapeutic goals; their guidance offers cholesterol absorption inhibitors, bile acid sequestrants, and proprotein convertase subtilisin/kexin type 9 (PCSK-9) inhibitors as options (Jellinger et al, 2017). The recommendations for statin therapy for managing dyslipidemia and prevention of cardiovascular disease are stated as the following:
    - Statin therapy is recommended as the primary pharmacologic agent to achieve target LDL-C goals on the bases of morbidity and mortality outcome trials.
    - For clinical decision making, mild elevations in blood glucose levels and/or an increased risk of new-onset type 2 diabetes mellitus associated with intensive statin therapy do not outweigh the benefits of statin therapy for ASCVD risk reduction.
    - In individuals within high-risk and very high-risk categories, further lowering of LDL-C beyond established targets with statins results in additional ASCVD event reduction and may be considered.
    - Very high-risk individuals with established coronary, carotid, and peripheral vascular disease, or diabetes who also have at least 1 additional risk factor should be treated with statins to target a reduced LDL-C treatment goal of <70 mg/dL.
    - Extreme-risk individuals should be treated with statins to target an even lower LDL-C treatment goal <55 mg/dL.
- Numerous clinical trials have demonstrated that the statins (single entity and combination products) can effectively lower LDL-C, non-HDL-C, TC, and TG, as well as positively impact other lipid/lipoprotein parameters. Many studies have compared active treatment to placebo or compared combination therapy to monotherapy. In these studies, the more aggressive treatment regimens often improved lipid parameters to a greater extent than the less-intensive treatment regimens.
- All of the statins, with the exception of pitavastatin, have been shown to have beneficial effects on CHD outcomes, while the majority of them (atorvastatin, pravastatin, rosuvastatin, and simvastatin) have also been shown to decrease the risk of stroke.
- Atorvastatin, fluvastatin, pravastatin, rosuvastatin, and simvastatin have been shown to reduce cardiovascular events in patients with clinically evident CHD (secondary prevention). In addition, fluvastatin, lovastatin, pravastatin, and rosuvastatin have been shown to slow progression of coronary atherosclerosis in patients with CHD.
- No incremental benefit of the combination statin products on cardiovascular morbidity and mortality has been established over and above that demonstrated for the single entity statin products.
- The statins are generally well-tolerated, and the most common side effects are gastrointestinal disturbances, headache, insomnia, myalgia, and rash. Muscle aches and weakness are reported by one to two percent of patients taking statins. The symptoms are usually mild and generally do not lead to discontinuation. All statins can increase hepatic transaminase levels and creatinine kinase.
- The 2018 AHA scientific statement regarding statin safety emphasized restarting statin therapy in patients who have discontinued due to muscle-related complaints, as the benefits of these agents outweigh their risks (Newman et al 2018).
- Pravastatin is the only statin that does not undergo cytochrome (CYP) 450 metabolism, and is therefore associated with a lower risk for drug interactions. Atorvastatin (to a lesser extent), lovastatin, and simvastatin are primarily metabolized by the CYP3A4 isoenzyme, while fluvastatin, pitavastatin, and rosuvastatin are metabolized by the CYP2C9 isoenzyme, which may result in differences in their drug interaction profiles.
- There is insufficient evidence to support that one statin is safer or more efficacious than another statin.

Table 5. Advantages and Disadvantages of Statins

Drug	Advantages	Disadvantages
Atorvastatin	• Available generically both alone and in combination with ezetimibe	• Associated with drug-drug interactions through the CYP3A4 isoenzyme system

Drug	Advantages	Disadvantages
	• Has been documented to have more potency in cholesterol-lowering than certain other statins • Cardiovascular outcomes studies support the use of the 80 mg strength in certain populations (e.g., as secondary prophylaxis following ST elevation MI)	
Fluvastatin	• Available generically • Available in an extended-release formulation • Not associated with drug-drug interactions through the CYP3A4 isoenzyme system	• Associated with drug-drug interactions through the CYP2C9 isoenzyme system
Lovastatin	• Available generically (immediate release formulation) • Available in an extended-release formulation	• Associated with drug-drug interactions through the CYP3A4 isoenzyme system
Pitavastatin	• Available generically	• Effect on cardiovascular morbidity and mortality has not been determined
Pravastatin	• Available generically • Not associated with drug-drug interactions through the CYP isoenzyme system	
Rosuvastatin	• Available generically (tablet formulation) • Has been documented to have more potency in cholesterol-lowering than certain other statins	
Simvastatin	• Available as an oral suspension • Tablet form is available generically • Available both alone and in combination with ezetimibe	• Associated with drug-drug interactions through the CYP3A4 isoenzyme system

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Therapeutic Class Overview
Attention-Deficit/Hyperactivity Disorder (ADHD) Agents

INTRODUCTION

- Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder among children, with an estimated prevalence of up to 10% of school-age children in the United States (U.S.). It is more common in boys than girls and frequently persists into adulthood (*Feldman et al 2014*). Epidemiologic studies of adult ADHD have estimated the current prevalence to be 4.4% in the U.S. (*Bukstein 2018*).
  - In children, this chronic disorder is characterized by symptoms of hyperactivity, impulsivity, and/or inattention. These symptoms affect cognitive, academic, behavioral, emotional, and social functioning (*Krull 2019a*). Common comorbid psychiatric disorders include oppositional defiant disorder, conduct disorder, depression, anxiety disorder, and learning disabilities (*Krull 2019b*). Approximately 20% of children with ADHD develop chronic tic disorders and approximately 50% of children with chronic tics or Tourette syndrome have comorbid ADHD (*Krull 2018*).
  - ADHD in adults is characterized by symptoms of inattention, impulsivity, and restlessness. Impairment in executive function and emotional dysregulation frequently occur. Common comorbid psychiatric disorders include mood and anxiety disorders, substance use disorder, and intermittent explosive disorder (*Bukstein 2018*).
- For children < 17 years of age, the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) diagnosis of ADHD requires ≥ 6 symptoms of hyperactivity and impulsivity or ≥ 6 symptoms of inattention. For adolescents ≥ 17 years of age and adults, ≥ 5 symptoms of hyperactivity and impulsivity or ≥ 5 symptoms of inattention are required.
  - The symptoms of hyperactivity/impulsivity or inattention must occur often; be present in more than 1 setting; persist for at least 6 months; be present before the age of 12 years; impair function in academic, social, or occupational activities; and be excessive for the developmental level of the child.
  - Other physical, situational, or mental health conditions that could account for the symptoms must be excluded.
- Treatment of ADHD may involve behavioral/psychologic interventions, medication, and/or educational interventions, alone or in combination (*Krull 2019c*).
  - For preschool children (age 4 through 5 years), behavioral therapy is considered the first-line treatment; when medication is necessary, methylphenidate is generally recommended.
  - For children and adolescents with moderate to severe ADHD, medication and behavioral therapy are recommended. In general, stimulants are the first-line agents; however, non-stimulant medications may be more appropriate for certain children.
    - About 30% of patients do not respond to or may not tolerate the initial stimulant treatment. At least one-half of children who do not respond to one type of stimulant will respond to the other. If there is still no improvement, consideration should be given to switching to or adding a non-stimulant ADHD medication (*Pharmacist's Letter 2015, Krull 2019d*).
- Multiple agents are currently approved by the Food and Drug Administration (FDA) for the treatment of ADHD. They include central nervous system (CNS) stimulants (amphetamine- and methylphenidate-based formulations), as well as non-stimulants: a selective norepinephrine reuptake inhibitor (SNRI), atomoxetine, and 2 alpha$_2$-adrenergic agonists, clonidine extended-release (ER) and guanfacine ER.
  - Due to the potential for abuse, the stimulant agents are classified as Schedule II controlled substances.
  - Several stimulants are also approved for the treatment of narcolepsy and exogenous obesity; the use of stimulants for the treatment of obesity will not be covered in this review. Lisdexamfetamine dimesylate is the only FDA-approved drug for the treatment of binge eating disorder (BED).
- In August of 2018, an extended-release methylphenidate capsule (Jornay PM) was approved by the FDA. In addition, an orally disintegrating amphetamine sulfate tablet (Evekeo ODT) was also approved in late January 2019. Launch dates have not yet been announced for either product.
- Medispan Classes: ADHD Agents – Amphetamines, Dexmethylphenidate, Methylphenidate, Selective Alpha Adrenergic Agonists, Selective Norepinephrine Reuptake Inhibitor

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Stimulants	
Evekeo (amphetamine sulfate)	✔
Evekeo ODT (amphetamine sulfate)†	-
Adderall (mixed amphetamine salts)	✔
Focalin (dexmethylphenidate hydrochloride [HCl])	✔
ProCentra (dextroamphetamine sulfate)	✔
Zenzedi (dextroamphetamine sulfate)	✔
Desoxyn (methamphetamine HCl)	✔
methylphenidate HCl chewable tablets	✔
Methylin Oral Solution (methylphenidate HCl)	✔
Ritalin (methylphenidate HCl)	✔
Dexedrine Spansule (dextroamphetamine sulfate sustained-release)	✔
Adzenys ER (amphetamine ER)	-
Adzenys XR-ODT (amphetamine ER)	-
Dyanavel XR (amphetamine ER)	-
Adderall XR (mixed amphetamine salts ER)	✔
Mydayis (mixed amphetamine salts ER)	-
Focalin XR (dexmethylphenidate HCl ER)	✔
Vyvanse (lisdexamfetamine dimesylate)	-
Aptensio XR (methylphenidate HCl ER)	-
Concerta (methylphenidate HCl ER)	✔
Cotempla XR-ODT (methylphenidate ER)	-
Jornay PM (methylphenidate HCl ER)†	-
methylphenidate HCl ER (CD)	✔
methylphenidate HCl ER	✔
QuilliChew ER (methylphenidate HCl ER)	-
Quillivant XR (methylphenidate HCl ER)	-
Ritalin LA (methylphenidate HCl ER)	✔
Daytrana (methylphenidate transdermal system)	-
Non-stimulants	
Strattera (atomoxetine HCl)	✔
Kapvay (clonidine HCl ER)	✔
Intuniv (guanfacine HCl ER)	✔

†An extended-release methylphenidate capsule (Jornay PM) and an orally disintegrating amphetamine sulfate tablet (Evekeo ODT) have both been recently approved by the FDA; however, launch dates have not yet been announced for either product.

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019, Facts & Comparisons 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Evekeo (amphetamine sulfate)	Evekeo ODT (amphetamine sulfate)	Adzenys ER, Adzenys XR-ODT, Dyanavel XR (amphetamine ER)	Adderall (mixed amphetamine salts)	Adderall XR, Mydayis (mixed amphetamine salts ER)	Strattera (atomoxetine HCl)	Kapvay (clonidine HCl ER)	Focalin (dexmethylphenidate IR); Focalin XR (dexmethylphenidate ER)	ProCentra, Zenzedi (dextroamphetamine sulfate IR); Dexedrine Spansule (dextroamphetamine sulfate SR)	Intuniv (guanfacine HCl ER)	Vyvanse (lisdexamfetamine dimesylate)	Desoxyn (methamphetamine HCl)	Methylin Oral Solution, Ritalin methylphenidate HCl IR); methylphenidate HCl chewable tablets; Metadate ER (methylphenidate ER)	Aptensio XR, Concerta , Cotempla XR-ODT, Daytrana, methylphenidate ER (CD), Jornay PM, QuilliChew ER, Quillivant XR, Ritalin LA (methylphenidate ER)
ADHD*		✓	✓	✓	✓	✓		✓			✓			✓
ADHD, as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, and social) for a stabilizing effect in pediatric patients with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal electroencephalogram (EEG) may or may not be present, and a diagnosis of CNS dysfunction may or may not be warranted.*	✓								✓			✓	✓	
Treatment of ADHD as monotherapy and as adjunctive therapy to stimulant medications							✓			✓				
Narcolepsy**	✓			✓					✓				✓	
Exogenous obesity, as a short term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction for patients refractory to alternative therapy	✓											✓		

(eg, repeated diets, group programs, and other drugs).†														
Moderate to severe BED in adults											✓			

(*Prescribing Information*: *Adderall 2017*, *Adderall XR 2018*, *Adzenys ER 2017*, *Adzenys XR-ODT 2018*, *Aptensio XR 2017*, *Concerta 2017*, *Cotempla 2017*, *Daytrana 2017, Desoxyn 2017, Dexedrine Spansule 2019*, *Dyanavel XR 2019*, *Evekeo 2016*, *Evekeo ODT 2019*, *Focalin 2019*, *Focalin XR 2019*, *Intuniv 2018, Jornay PM 2018, Kapvay 2018, Mydayis 2017, Methylin Oral Solution 2017, methylphenidate chewable tablets 2018, methylphenidate ER 2017, methylphenidate ER (CD) 2018, ProCentra 2017*, *QuilliChew ER 2018*, *Quillivant XR 2018*, *Ritalin 2019*, *Ritalin LA 2019*, *Strattera 2017*, *Vyvanse 2018, Zenzedi 2017*)

* Adderall, Evekeo, ProCentra, and Zenzedi are approved for use in children 3 years of age and older. Daytrana, Desoxyn, Dexedrine Spansule, Dyanavel XR, Intuniv, and Kapvay are approved for use in children 6 years of age and older. Adderall XR, Adzenys ER, Adzenys XR-ODT, Aptensio XR, Focalin, Focalin XR, Jornay PM, methylphenidate ER (CD), Methylphenidate ER, Methylin Oral Solution, methylphenidate chewable tablets, QuilliChew ER, Quillivant XR, Ritalin, Ritalin LA, Strattera, and Vyvanse are approved for use in patients 6 years of age and older. Cotempla XR-ODT and Evekeo ODT are approved for use in pediatric patients 6 to 17 years of age. Concerta is approved for use in children 6 years of age and older, adolescents, and adults up to 65 years of age. Mydayis is approved for use in patients 13 years of age and older.
**These drugs are approved for use in patients 6 years of age and older.
†These drugs are not recommended for use in children under 12 years of age for treatment of exogenous obesity. The limited usefulness of these products should be weighed against possible risks inherent in use of the drugs.

- Limitation of use:
  - Lisdexamfetamine: Lisdexamfetamine is not indicated or recommended for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular (CV) adverse events (AEs). The safety and effectiveness of this drug for the treatment of obesity have not been established.
  - Mydayis: Pediatric patients 12 years and younger experienced higher plasma exposure than patients 13 years and older at the same dose and experienced higher rates of AEs, mainly insomnia and decreased appetite.

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Randomized trials, systematic reviews, and meta-analyses have found stimulants, atomoxetine, and alpha$_2$-adrenergic agonists to be more efficacious than placebo in reducing the core symptoms of ADHD in children and adolescents.
  - Adzenys ER, an amphetamine ER oral suspension, was approved under the 505(b)(2) regulatory pathway and was found to be bioequivalent to Adderall XR. No clinical efficacy studies were conducted.
  - Evekeo ODT, an orally disintegrating amphetamine tablet, was approved under the 505(b)(2) regulatory pathway. The safety and effectiveness of Evekeo ODT for the treatment of ADHD was established based on an adequate and well-controlled study of Evekeo (amphetamine sulfate).
  - Cotempla XR-ODT, a new methylphenidate ER orally disintegrating tablet formulation, was approved based on a randomized, double-blind (DB), multi-center (MC), placebo-controlled (PC) laboratory classroom study (*Childress et al 2017*) (N = 87) which found that the average Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP)-Combined score was significantly better for Cotempla XR-ODT than for placebo (least squares [LS] mean 14.3 [95% CI, 12.2 to 16.4] vs 25.3 [9% CI, 23.0 to 27.6], respectively, $p < 0.0001$).
  - Jornay PM, an ER methylphenidate capsule formulation, was approved based on the results of 2 clinical studies conducted in patients 6 to 12 years of age with ADHD:
    - The first study was a 6-week open-label (OL) dose-optimization study, followed by a 1-week DB, PC withdrawal phase where patients were randomized to continue treatment with Jornay PM or switch to placebo (*Jornay PM Prescribing Information 2018*). The study, which was conducted in an analog classroom setting and included 117 children aged 6 to 12 years, found that Jornay PM was associated with a significant reduction in the SKAMP symptom score over a 12-hour period (difference in least squares [LS] mean -5.9; 95% CI, -9.1 to -2.7).

- A randomized, DB, MC, PC, parallel group, forced-dose titration trial conducted over 3 weeks in 161 children 6 to 12 years of age with ADHD (*Pliszka et al 2017*). The study found that 40 to 80 mg/day of Jornay PM achieved significant improvements vs placebo in ADHD symptoms (LS mean ADHD rating scale-IV 24.1 vs 31.2; p = 0.002) at 3 weeks. Significant improvements were also seen vs placebo in key secondary outcomes including at-home early morning and late afternoon/evening functional impairment at 3 weeks. The most commonly reported treatment-emergent AEs were insomnia and decreased appetite.

- Mydayis, a new mixed amphetamine salts product, was approved for the treatment of ADHD based on the results of 5 MC, DB, PC, randomized controlled trials (RCTs): 3 in adults and 2 in pediatric patients 13 to 17 years of age. The studies found that Mydayis demonstrated a statistically significant treatment effect compared with placebo on various ADHD outcomes measures (eg, ADHD-Rating Scale [ADHD-RS] score, Permanent Product Measure of Performance [PERMP] score) (*Mydayis Prescribing Information 2017, Weisler et al 2017*) (see results below in Table 3 below).

Table 3. Summary of Primary Efficacy Results for Mydayis

Study Number (Age range)	Primary Endpoint	Treatment Group	Mean Baseline Score (SD)	LS Mean Change from Baseline	Placebo-subtracted Difference (95% CI)
Adult Studies					
Study 1 (18 to 55 years)	ADHD-RS	Mydayis 12.5 mg/day§ Mydayis 37.5 mg/day§ Placebo	39.8 (6.38) 39.9 (7.07) 40.5 (6.52)	-18.5 -23.8 -10.4	-8.1 (-11.7 to -4.4) -13.4 (-17.1 to -9.7)
Study 2 (18 to 55 years)	Average PERMP	Mydayis 50 mg/day§ Placebo	239.2 (75.6)† 249.6 (76.7)†	293.23* 274.85*	18.38 (11.28 to 25.47)
Study 3 (18 to 55 years)	Average PERMP	Mydayis 25 mg/day§ Placebo	217.5 (59.6)† 226.9 (61.7)†	267.96* 248.67*	19.29 (10.95 to 27.63)
Pediatric Studies					
Study 4 (13 to 17 years)‡	ADHD-RS-IV	Mydayis 12.5 to 25 mg/day§ Placebo	36.7 (6.15) 38.3 (6.67)	-20.3 -11.6	-8.7 (-12.6 to -4.8)
Study 5 (13 to 17 years)	Average PERMP	Mydayis 25 mg/day§ Placebo	214.5 (87.8)† 228.7 (101)†	272.67* 231.41*	41.26 (32.24 to 50.29)

SD= standard deviation; LS = least squares; CI = confidence interval
†Pre-dose PERMP total score
*LS mean for PERMP is post-dose average score over all sessions of the treatment day, rather than change from baseline
‡Results are for a subgroup of study 4 and not the total population
§Doses statistically significant for placebo

- A systematic (Cochrane) review of 185 RCTs (*Storebø et al 2015*) (N = 12,245) in children and adolescents with ADHD found that methylphenidate may improve teacher-rated ADHD symptoms, teacher-reported general behavior, and parent-reported quality of life (QOL) vs placebo. However, the evidence was of low quality.
- An RCT called the Preschool ADHD Treatment Study (PATS) (*Greenhill et al 2006*) evaluated the efficacy of methylphenidate immediate-release (IR) in 303 preschool children with ADHD and found that it demonstrated significant reductions on ADHD symptom scales; however, the effect sizes (0.4 to 0.8) were smaller than those generally reported for school-age children.
- A systematic (Cochrane) review of 23 PC, RCTs (*Punja et al 2016*) (N = 2675) found that amphetamines were effective at improving the core symptoms of ADHD, but they were also associated with a higher risk of AEs compared to placebo. There was no evidence that one kind of amphetamine was better than another and there was no difference between short-acting and long-acting formulations.
- A meta-analysis of 25 DB, PC, RCTs (*Schwartz et al 2014*) (N = 3928) in children and adolescents with ADHD found atomoxetine to be superior to placebo for overall ADHD symptoms, with a medium effect size (-0.64).

- A meta-analysis of 12 RCTs (*Hirota et al 2014*) (N = 2276) in pediatric patients with ADHD found that alpha$_2$-adrenergic agonists were significantly superior to placebo for overall ADHD symptoms both as monotherapy and, to a lesser extent, as augmentation therapy to stimulants.
  - Meta-analytic results failed to demonstrate a significant difference in efficacy between alpha$_2$-adrenergic agonists. In sub-analyses of individual formulations, the ER formulations separated robustly from placebo whereas the IR formulations did not separate from placebo.
- A systematic review of 16 RCTs and 1 meta-analysis (*Chan et al 2016*) (N = 2668) found evidence supporting the use of methylphenidate ER and amphetamine ER formulations, atomoxetine, and guanfacine ER for the treatment of ADHD in adolescents. For the primary outcome measure of mean change in ADHD-RS total symptom score, both stimulant and non-stimulant medications led to clinically significant reductions of 14.93 to 24.60 points.

- For the treatment of ADHD in children and adolescents, stimulants typically have a slightly larger treatment effect size (standardized mean difference [SMD]) than non-stimulants (approximately 1.0 vs approximately 0.7 for both atomoxetine and alpha$_2$-adrenergic agonists). However, there is insufficient evidence to definitively conclude that one stimulant is more efficacious than another (*Krull 2019d*, *AAP 2011).*
  - An Agency for Healthcare Research and Quality (AHRQ) review of 78 studies (*Jadad et al 1999*) evaluating the efficacy of various interventions for the treatment of ADHD in children and adults found few, if any, differences between methylphenidate and dextroamphetamine.
  - A meta-analysis of 23 DB, PC trials (*Faraone 2010a*) comparing the efficacy of methylphenidate and amphetamine formulations found that amphetamine products may be moderately more efficacious than methylphenidate products.
  - A DB, PC, RCT (*Newcorn et al 2008*) (N = 516) comparing the efficacy of atomoxetine vs methylphenidate ER (osmotic-release formulation) in patients 6 to 16 years of age with ADHD found that both drugs were superior to placebo in terms of response rate, and that methylphenidate ER was superior to atomoxetine.
  - A meta-analysis of 29 DB, PC trials (*Faraone et al 2006*) evaluated the efficacy of various medications (methylphenidate and amphetamine compounds, atomoxetine, pemoline [no longer available in the U.S.], bupropion, and modafinil) for the treatment of ADHD. The effect sizes for non-stimulant medications were significantly less than those for IR stimulants or long-acting stimulants. The 2 classes of stimulant medications did not differ significantly from one another.
  - A meta-analysis of 28 DB, PC, RCTs (*Stuhec et al 2015*) (N = 4699) compared the efficacy of various medications for the treatment of ADHD in children and adolescents. Efficacy in reducing ADHD symptoms compared to placebo was small for bupropion (SMD = -0.32; 95% confidence interval [CI], -0.69 to 0.05), modest for atomoxetine (SMD = -0.68; 95% CI, -0.76 to -0.59) and methylphenidate (SMD = -0.75; 95% CI, -0.98 to -0.52), and highest for lisdexamfetamine (SMD = -1.28; 95% CI, -1.84 to -0.71).
  - A network meta-analysis and mixed treatment comparison of 36 RCTs (*Joseph et al 2017*) evaluating the comparative efficacy and safety of ADHD pharmacotherapies in children and adolescents found that lisdexamfetamine had greater efficacy than guanfacine ER, atomoxetine, and methylphenidate ER. Guanfacine ER had a high posterior probability of being more efficacious than atomoxetine, but their credible intervals overlapped.
  - A network meta-analysis of 48 DB, RCTs (*Padilha et al 2018*) compared the safety and efficacy of various ADHD medications in children and adolescents. Of the 12 trials that were evaluated for efficacy, analysis was performed using the Clinical Global Impression Improvement (CGI-I) scale for 3 drugs, which showed that methylphenidate was more effective than atomoxetine (MD, 3.15; 95% CI, 0.75 to 13.71) and guanfacine (MD, 1.92; 95% CI, 0.64 to 5.94). Thirty-three trials were evaluated for safety. Ranking of AEs showed that lisdexamfetamine was more likely to cause sleep disorders, loss of appetite, and behavior problems compared to other treatments.
- Alpha$_2$-adrenergic agonists have been associated with improvements in ADHD symptoms and comorbid tics.
  - A meta-analysis of 9 DB, PC, RCTs (*Bloch et al 2009*) (N = 477) was conducted to determine the relative efficacy of different medications in treating ADHD and tic symptoms in children with both Tourette syndrome and ADHD.
  - Methylphenidate seemed to offer the greatest improvement of ADHD symptoms and did not seem to worsen tic symptoms.
  - Alpha$_2$-adrenergic agonists offered the best combined improvement in both tic and ADHD symptoms.
  - Atomoxetine significantly improved both tic and ADHD severity compared to placebo.
  - One small study found that tic severity was significantly increased with higher doses of dextroamphetamine treatment.
  - A Cochrane review of 8 RCTs (*Osland et al 2018*) including 510 children with both ADHD and a chronic tic disorder found low-quality evidence for improvement of ADHD symptoms with methylphenidate, atomoxetine, and clonidine, and very low-quality evidence for desipramine, dextroamphetamine, guanfacine, and deprenyl. Tic symptoms improved with guanfacine, desipramine, methylphenidate, clonidine, and a combination of methylphenidate and

clonidine. The authors noted that in 1 study with a short duration (3 weeks), high doses of dextroamphetamine worsened tics.

- There are limited efficacy data regarding the treatment of ADHD in the adult population. Comparison of effect sizes in clinical trials suggests that stimulant medications are more efficacious in adult ADHD than non-stimulants.
  - In a meta-analysis of 12 clinical trials (*Cunill et al 2009*) (N = 3375) comparing atomoxetine with placebo in adult ADHD, atomoxetine led to a modestly greater reduction in ADHD symptom severity, but was associated with higher all-cause discontinuation.
  - A meta-analysis (*Faraone 2010b*) of 19 randomized trials of 13 medications for adult ADHD found a greater average effect size for reduction in ADHD symptoms in patients receiving short- and long-acting stimulant medications (vs placebo; 0.86 and 0.73, respectively) compared with patients receiving non-stimulant medication (vs placebo; 0.39). No difference in effect size was found between short- and long-acting stimulants.
  - A meta-analysis of 20 randomized trials (*Stuhec et al 2018*) compared the efficacy, acceptability, and tolerability of lisdexamfetamine, mixed amphetamine salts, methylphenidate, and modafinil in the treatment of ADHD in adults. The highest effect size in reducing ADHD symptoms was found with lisdexamfetamine (SMD -0.89; 95% CI, -1.09 to -0.70), while moderate reductions in symptoms were seen with mixed amphetamine salts (SMD -0.64; 95% CI, -0.83 to -0.45) and methylphenidate (SMD -0.50; 95% CI, -0.58 to -0.41). No efficacy was reported with modafinil.
  - A Cochrane review of 19 studies (*Castells et al 2018*, N = 2521) comparing dextroamphetamine, lisdexamfetamine, and mixed amphetamine salts for the treatment of ADHD in adults found that overall, amphetamines reduced the patient- and clinician-rated severity of ADHD symptoms compared to placebo; however, they did not improve retention in treatment. Amphetamines were associated with an increased proportion of patients who withdrew because of AEs. When comparing different types of amphetamines, lisdexamfetamine and mixed amphetamine salts reduced the severity of ADHD symptoms as rated by clinicians, but dextroamphetamine did not. No differences in any outcome were found when comparing immediate- and sustained-release formulations.
  - Another meta-analysis (*Cortese et al 2018*) of 133 RCTs comparing the use of amphetamines, atomoxetine, bupropion, clonidine, guanfacine, methylphenidate, and modafinil for the treatment of ADHD found that all drugs were superior to placebo for ADHD core symptoms as rated by clinicians in children and adolescents, and all drugs except for modafinil were more efficacious than placebo in adults.
    - When comparing the various drugs based on teachers' ratings in children and adolescents, only methylphenidate and modafinil were found to be more efficacious than placebo.
    - In head-to-head comparisons, differences in efficacy based on clinicians' ratings were found, favoring amphetamines over modafinil (SMD -0.39; 95% CI -0.67 to -0.12), atomoxetine (SMD -0.46; 95% CI, -0.65 to -0.27), and methylphenidate (SMD-0.24; 95% CI, -0.44 to -0.05) in children and adolescents. Efficacy results based on clinicians' ratings were similar for adults, and favored amphetamines over modafinil (SMD -0.94; 95% CI -1.43 to -0.46), atomoxetine (SMD -0.34; 95% CI, -0.58 to -0.10), and methylphenidate (SMD-0.29; 95% CI, -0.54 to -0.05).
- Lisdexamfetamine dimesylate has demonstrated efficacy in the treatment of BED. Direct comparison trials between lisdexamfetamine and other drugs used off-label to treat BED are lacking.
  - In 2 Phase 3, 12-week, randomized, DB, PC trials (*McElroy et al 2016*) (N = 773) in patients with moderate to severe BED, lisdexamfetamine-treated patients had a statistically significantly greater reduction from baseline in mean number of binge days per week at week 12 vs placebo (treatment difference in study 1: -1.35 [-1.70 to -1.01]; study 2: -1.66 [-2.04 to -1.28]; both $p < 0.001$).
    - A 12-month, OL extension study (*Gasior et al 2017*) (N = 599) in adults with BED found that the long-term safety and tolerability of lisdexamfetamine were generally consistent with the safety profile observed in 3 previous short-term trials in BED as well as its established profile for ADHD. Common treatment-emergent AEs included dry mouth, headache, insomnia, and upper respiratory tract infection. Weight loss and increases in blood pressure and pulse rate were also observed.
  - In a phase 3, DB, randomized, PC, withdrawal study (*Hudson et al 2017*) (N = 418) in adults with moderate to severe BED, responders to lisdexamfetamine during a 12-week OL phase were randomized to placebo or continued lisdexamfetamine during a 26-week, DB phase. The percentage of patients meeting relapse criteria was 3.7% with lisdexamfetamine vs 32.1% with placebo; time to relapse statistically favored lisdexamfetamine ($p < 0.001$). The hazard ratio (HR) was 0.09 (95% CI, 0.04 to 0.23).
  - A systematic review and meta-analysis of 9 waitlist-controlled psychological trials and 25 PC trials evaluating pharmacologic (n = 19) or combination (n = 6) treatment for BED (*Brownley et al 2016*) found that therapist-led CBT, lisdexamfetamine, and second-generation antidepressants (SGAs) increased binge-eating abstinence (relative risk

[RR], 4.95 [95% CI, 3.06 to 8.00], 2.61 [CI, 2.04 to 3.33], and 1.67 [CI, 1.24 to 2.26], respectively), while lisdexamfetamine and SGAs decreased binge-eating frequency (mean difference in days/week, -1.35 [CI, -1.77 to -0.93] and -0.67 [CI, -1.26 to -0.09], respectively). Topiramate and other forms of CBT also increased abstinence and reduced binge-eating frequency.

- A 2018 systematic review and meta-analysis of 45 RCTs (*Ghaderi et al 2018*) compared various psychological, pharmacological, and combined treatments for BED, and found moderate support for the efficacy of cognitive behavioral therapy (CBT) and CBT-guided self-help (moderate quality of evidence), and low quality evidence to support interpersonal psychotherapy, selective serotonin reuptake inhibitors, and lisdexamfetamine for the cessation of or reduction in the frequency of binge eating. Only lisdexamfetamine showed a modest effect on weight loss (SMD for body mass index -5.23; 95% CI, -6.52 to -3.94).

CLINICAL GUIDELINES

ADHD

- Several clinical guidelines have provided recommendations on the treatment of ADHD in children and adolescents.
  - According to the American Academy of Pediatrics (AAP) guidelines (2011), the evidence is particularly strong for stimulant medications, and sufficient but less strong for atomoxetine, guanfacine ER, and clonidine ER (in that order). Guanfacine ER and clonidine ER have evidence to support their use as adjunctive therapy with stimulant medications. Methylphenidate is recommended for preschool-aged children who have had an inadequate response to behavioral interventions.
  - The American Academy of Child and Adolescent Psychiatry (AACAP) guidelines (*Pliszka et al 2007*) state that both methylphenidate and amphetamines are equally efficacious in the treatment of ADHD. The long-acting formulations are equally efficacious as the IR formulations and may be used as initial therapy. Short-acting stimulants are often used as initial treatment in small children (< 16 kg in weight), for whom there are no long-acting preparations in a sufficiently low dose. Some patients may respond similarly to different stimulant classes, whereas other patients may respond preferentially to only 1 of the classes of stimulants. Although stimulants have demonstrated greater efficacy compared to atomoxetine in published studies, atomoxetine may be used first-line in patients with an active substance abuse problem, comorbid anxiety or tics, and in those who experience severe AEs with stimulants.
  - The Medical Letter (2015) recommends that treatment of ADHD in school-age children or adults should begin with an oral stimulant, either a methylphenidate- or amphetamine-based formulation. Mixing short- and long-acting stimulants can be helpful to achieve an immediate effect for early-morning school classes or for reducing rebound irritability or overactivity, especially in the evening. An ER alpha$_2$-adrenergic agonist may be helpful as adjunctive therapy with a stimulant in patients who cannot tolerate usual doses of the stimulant, particularly those with tics. Atomoxetine is an alternative for patients who cannot tolerate stimulants or for whom treatment with a controlled substance is undesirable.
  - The AACAP practice parameter for the treatment of children and adolescents with tic disorders (2013) states that alpha$_2$-adrenergic agonists have demonstrated an effect size of 0.5 for the amelioration of tics and may be preferred by some prescribers over antipsychotics due to their relatively favorable AE profile.

Narcolepsy

- The American Academy of Sleep Medicine (AASM) practice parameters (*Morgenthaler et al 2007*) recommend various drugs for the treatment of daytime sleepiness due to narcolepsy including modafinil (high degree of clinical certainty); amphetamine, methamphetamine, dextroamphetamine, and methylphenidate (moderate degree of clinical certainty); sodium oxybate (high degree of clinical certainty); and selegiline (uncertain clinical certainty).

BED

- According the American Psychiatric Association (APA) practice guidelines on eating disorders (*Yager et al 2006*, *Yager et al 2012* [guideline watch update]), treatment of BED may include the following:
  - Nutritional rehabilitation and counseling
  - Psychosocial treatment
    - CBT, behavior therapy, dialectical behavior therapy (DBT), and interpersonal therapy (IPT) have all been associated with binge frequency reduction rates of 67% or more and significant abstinence rates during active treatment.
    - Self-help programs using self-guided, professionally designed manuals have been effective in reducing the symptoms of BED in the short-run for some patients and may have long-term benefit.
  - Medications

- Antidepressant treatment is associated with short-term reductions in binge-eating but generally does not result in substantial weight loss. Selective serotonin reuptake inhibitors (SSRIs) have the fewest difficulties with AEs and the most evidence for efficacy when used at the high end of the recommended dose range.
- Topiramate can reduce bingeing and decrease weight, but its use may be limited by AEs.

o Combination psychotherapy and pharmacotherapy
- For most patients, adding antidepressant therapy to a behavioral weight control and/or CBT regimen does not have a significant effect on binge suppression.
- Although limited evidence is available, combined treatment is frequently used in clinical practice.

- The American Association of Clinical Endocrinologists and the American College of Endocrinology (AACE/ACE) guidelines for medical care of patients with obesity (*Garvey et al 2016*) recommend the following for patients with overweight or obesity who have BED:
  - o Patients should be treated with a structured behavioral/lifestyle program, combined with CBT or other psychological interventions
  - o Treatment with orlistat or approved medications containing topiramate or bupropion may be considered in conjunction with structured lifestyle therapy, CBT, and/or psychological interventions
- The Task Force on Eating Disorders of the World Federation of Societies of Biological Psychiatry (*Aigner et al 2011*) concluded that for the treatment of BED, grade A evidence supports the use of imipramine (moderate risk-benefit ratio), sertraline (good risk-benefit ratio), citalopram/escitalopram (good risk-benefit ratio), orlistat (low to moderate risk-benefit ratio), and topiramate (moderate risk-benefit ratio). Atomoxetine has grade B evidence supporting its use.

SAFETY SUMMARY

- Due to the potential for abuse, the stimulants are classified as Schedule II controlled substances. Atomoxetine, clonidine ER, and guanfacine ER are not classified as controlled substances.
- Various stimulants are contraindicated for use in patients with advanced arteriosclerosis, symptomatic CV disease, moderate to severe hypertension, hyperthyroidism, hypersensitivity to sympathomimetic amines, glaucoma, agitated states, history of drug abuse, tics, and in those using monoamine oxidase inhibitors (MAOIs). The stimulants carry a boxed warning for potential drug abuse and dependence. They also have warnings for increased risks of serious CV reactions, psychiatric AEs, suppression of growth, peripheral vasculopathy, and priapism. Amphetamines have a warning for risk of serotonin syndrome when used in combination with other drugs affecting the serotonergic neurotransmitter systems.
  - ○ Common AEs of stimulants include anorexia, decreased weight, tachycardia, anxiety, irritability, and insomnia.
  - ○ Refer to the prescribing information for details on warnings, precautions, and AEs for individual products. For example:
    - QuilliChew ER can be harmful to patients with phenylketonuria (PKU) since it contains phenylalanine.
    - Because the Concerta tablet is nondeformable and does not appreciably change in shape in the gastrointestinal tract, it should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing.
    - The use of Daytrana may result in chemical leukoderma and contact sensitization; in addition, exposure of the application site to external heat sources should be avoided due to increased absorption of the drug.
- Atomoxetine is contraindicated for use in patients with narrow angle glaucoma, pheochromocytoma, severe CV disorders, hypersensitivity to any component of the product, and in those taking MAOIs. It carries a boxed warning for rare increased risk of suicidal ideation in children and adolescents. It also has warnings for serious CV events, effects on blood pressure and heart rate, effects on growth, psychiatric AEs, rare cases of severe liver injury, and priapism.
  - ○ Common AEs associated with atomoxetine include somnolence, nausea, and vomiting.
- The alpha$_2$-adrenergic agonists are contraindicated in patients known to be hypersensitive to any constituent of the product. They carry warnings for increased risk of hypotension, bradycardia, and syncope; sedation and somnolence; rebound hypertension; and cardiac conduction abnormalities.
  - ○ Common AEs associated with clonidine ER include somnolence, fatigue, and irritability while common AEs with guanfacine ER include somnolence, fatigue, and hypotension.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Stimulants					
Evekeo (amphetamine)	4 to 6 h	Tablets	Oral	*ADHD, narcolepsy*: Daily up to divided doses daily *Exogenous obesity*: Divided doses daily	*ADHD and narcolepsy* The first dose should be given upon awakening; additional doses at intervals of 4 to 6 hours.
Evekeo ODT (amphetamine)	4 to 6 h	Orally disintegrating tablets	Oral	Once or twice daily in the morning	As soon as the blister pack is opened, the tablet should be placed on the patient's tongue and allowed to disintegrate without chewing or crushing. The tablet will disintegrate in saliva so that it can be swallowed.
Adzenys ER (amphetamine ER)	10 to 12 h	Suspension	Oral	Daily in the morning	
Adzenys XR-ODT (amphetamine ER)	10 to 12 h	Orally disintegrating tablets	Oral	Daily in the morning	As soon as the blister pack is opened, the tablet should be placed on the patient's tongue and allowed to disintegrate without chewing or crushing. The tablet will disintegrate in saliva so that it can be swallowed.
Dyanavel XR (amphetamine ER)	Up to 13 h	Suspension	Oral	Daily in the morning	The bottle should be shaken before administration.
Adderall (mixed amphetamine salts)	4 to 6 h	Tablets	Oral	*ADHD, narcolepsy*: Daily up to divided doses daily	The first dose should be given on awakening, then additional doses at intervals of 4 to 6 hours.
Adderall XR (mixed amphetamine salts ER)	10 to 12 h	Capsules	Oral	Daily in the morning	Capsules may be taken whole, or the capsule may be opened and the entire contents

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
					sprinkled on applesauce and consumed immediately. The dose of a single capsule should not be divided.
Mydayis (mixed amphetamine salts ER)	16 h	Capsules	Oral	Daily in the morning	Dosage adjustment is needed for severe renal impairment. Use in end stage renal disease (ESRD) is not recommended. Capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce and consumed immediately in its entirety without chewing. The dose of a single capsule should not be divided.
Focalin (dexmethylphenidate)	5 to 6 h	Tablets	Oral	Twice daily	
Focalin XR (dexmethylphenidate ER)	10 to 12 h	Capsules	Oral	Daily in the morning	ER capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce.
ProCentra, Zenzedi (dextroamphetamine)	4 to 6 h	Solution (ProCentra) Tablets (Zenzedi)	Oral	*ADHD, narcolepsy*: Daily up to divided doses daily	The first dose should be given upon awakening; additional doses at intervals of 4 to 6 hours
Dexedrine Spansule (dextroamphetamine SR)	6 to 8 h	Capsules	Oral	*ADHD* Daily or twice daily Narcolepsy Daily	

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Vyvanse (lisdexamfetamine)	10 to 12 h	Capsules, chewable tablets	Oral	*ADHD, BED*: Daily in the morning	Dosage adjustment is needed for renal impairment/ESRD. The capsules may be swallowed whole or can be opened, emptied, and mixed with yogurt, water, or orange juice and consumed immediately. A single capsule should not be divided. The chewable tablets must be chewed thoroughly before swallowing. A single dose should not be divided.
Desoxyn (methamphetamine)	3 to 5 h	Tablets	Oral	*ADHD*: Daily to twice daily *Obesity*: 30 min before each meal	
Methylin, Ritalin (methylphenidate)	3 to 5 h	Chewable tablets, tablets (Ritalin), solution (Methylin)	Oral	Twice daily to 3 times daily	The chewable tablets should be taken with at least 8 ounces (a full glass) of water or other fluid. The liquid should be given 30 to 45 minutes before meals. The ER tablets may be used in place of the IR tablets when the 8-hour dosage of the ER product corresponds to the titrated 8-hour dosage of the IR products.
Methylphenidate ER	3 to 8 h	Tablets			

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
					The ER tablets must be swallowed whole and never crushed or chewed.
Aptensio XR (methylphenidate ER)	12 h	Capsules	Oral	Daily in the morning	The capsules may be taken whole or they can be opened and sprinkled onto applesauce; the applesauce should be consumed immediately and it should not be chewed. The dose of a single capsule should not be divided.
Concerta (methylphenidate ER)	10 to 12 h	Tablets	Oral	Daily in the morning	The tablets should not be chewed or crushed. Note: An FDA analysis of methylphenidate ER products manufactured by UCB/Kremers (formerly Kudco) and Mallinckrodt indicated that in some individuals, they may deliver the drug in the body at a

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Methylphenidate ER					slower rate during the 7- to 12-hour range. As a result, the FDA changed the therapeutic equivalence of these products from AB to BX. Because these manufacturers have subsequently failed to demonstrate that their products are bioequivalent to the brand-name reference drug, the FDA proposes to withdraw their approval (*FDA 2016*).
Cotempla XR-ODT (methylphenidate ER)	12 h	Orally disintegrating tablets	Oral	Daily in the morning	As soon as the blister pack is opened, the tablet should be placed on the patient's tongue and allowed to disintegrate without chewing or crushing. The tablet will disintegrate in saliva so that it can be swallowed.
Jornay PM (methylphenidate ER)	Peak concentration occurs 14 hours after dose with gradual decline thereafter.	Capsules	Oral	Daily in the evening	The capsules may be swallowed whole or it may be opened and the contents sprinkled onto applesauce and given immediately. The capsule contents must not be crushed or chewed, the dose of a single capsule should not be divided, and the contents of the entire capsule should be taken at the same time.

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Methylphenidate ER (CD)	8 to 12 h	Capsules	Oral	Daily in the morning	The capsule may be swallowed whole or it may be opened and the contents sprinkled onto a small amount (tablespoon) of applesauce and given immediately. The capsule contents must not be crushed or chewed.
QuilliChew ER (methylphenidate ER)	12 h	Chewable tablets	Oral	Daily in the morning	A 10 mg or 15 mg dose can be achieved by breaking in half the functionally scored 20 mg and 30 mg tablets, respectively.
Quillivant XR (methylphenidate ER)	12 h	Suspension	Oral	Daily in the morning	The bottle of Quillivant XR should be shaken vigorously for 10 seconds prior to administration. The suspension is stable for up to 4 months once reconstituted.
Ritalin LA (methylphenidate ER)	8 to 12 h	Capsules	Oral	Daily in the morning	The capsule may be swallowed whole or may be administered by sprinkling the capsule contents on a small amount of applesauce; the contents should not be crushed, chewed, or divided. The mixture should be consumed immediately.
Daytrana (methylphenidate transdermal system)	10 to 12 h	Transdermal system	Transdermal	The patch should be applied 2 hours before an effect is needed and removed within 9	

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
				hours. It may be removed earlier than 9 hours if a shorter duration of effect is desired or late day side effects appear.	
Non-stimulants					
Strattera (atomoxetine)	24 h	Capsules	Oral	Daily in the morning or divided dose in the morning and late/afternoon early evening	Dosage adjustment is recommended for patients with moderate or severe hepatic insufficiency. The capsules are not intended to be opened and should be taken whole.
Kapvay (clonidine ER)	12 h	Tablets	Oral	Daily at bedtime or twice daily divided doses.	With twice daily dosing, either an equal or higher split dosage should be given at bedtime. The tablets should not be crushed, chewed, or broken prior to swallowing. The initial dosage should be based on the degree of renal impairment.
Intuniv (guanfacine ER)	8 to 24 h	Tablets	Oral	Daily in the morning or evening	The tablets should not be crushed, chewed, or broken prior to swallowing; they should not be administered with high fat meals, due to increased exposure It may be necessary to reduce the dosage in patients with significant renal and hepatic impairment.

See the current prescribing information for full details
*References: Prescribing information for individual products, *Medical Letter 2015, Pharmacist's Letter 2016, Krull 2019d*

CONCLUSION

- Both CNS stimulants and non-stimulants may be used for the treatment of ADHD. In general, stimulants are first-line treatment due to their superior efficacy. Clinical evidence suggests that methylphenidate and amphetamines are equally efficacious, but some patients may respond to one stimulant and not the other. Various short-, intermediate- and long-acting formulations (eg, tablets/capsules, chewable/orally disintegrating tablets, solution/suspension, transdermal patch) are available to provide a range of dosing options. Although non-stimulants such as atomoxetine and alpha$_2$-adrenergic agonists have smaller effect sizes, they may be used in patients who have failed or are intolerant to stimulants or when there is concern about possible abuse or diversion. The alpha$_2$-adrenergic agonists are approved both as monotherapy and as adjunctive therapy to stimulants, and they have been shown to improve both tic and ADHD symptoms in patients with comorbid tic disorder.
  - Current consensus clinical guidelines for the treatment of children and adolescents with ADHD recommend that stimulants are highly effective for reducing core symptoms of ADHD in children (*AACAP 2007*; *AAP 2011*).
- Ultimately, the choice of the initial agent for treatment of ADHD depends upon various factors such as: duration of desired coverage; ability of the child to swallow pills; coexisting tic disorder (use of alpha$_2$-adrenergic agonists may be warranted); potential AEs, history of substance abuse in the patient or household member (eg, avoid stimulants or use stimulants with less potential for abuse [eg, lisdexamfetamine, osmotic-release preparation, methylphenidate patch]); and preference of the patient and parent/guardian (*Krull 2019d*).
- Various stimulants are indicated for treatment of narcolepsy and are generally considered to be second-line agents after modafinil/armodafinil due to their sympathomimetic AEs (*Scammell 2019*).
- Lisdexamfetamine is the only FDA-approved drug indicated for the treatment of moderate to severe BED, with demonstrated efficacy in reduction of mean binge days per week vs placebo. Direct comparison trials between lisdexamfetamine and other drugs used off-label to treat BED are lacking.

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INTRODUCTION

- Narcolepsy is a lifelong neurological sleep disorder of hypersomnia characterized by excessive daytime sleepiness (EDS) and intermittent manifestations of rapid eye movement (REM) sleep during wakefulness. Excessive sleepiness is defined by the International Classification of Sleep Disorders, third edition (ICSD-3) as "daily episodes of an irrepressible need to sleep or daytime lapses into sleep" (*Sateia 2014*).
- Patients with narcolepsy often have many nighttime arousals and sleep disturbances that contribute to excessive drowsiness during the day. EDS can vary in severity, and some patients involuntarily fall asleep during normal daily activities. This can put the patient or others at risk if these daytime lapses into sleep occur during activities such as operating a motor vehicle. While all patients with narcolepsy experience EDS, additional symptoms may include cataplexy, which is the sudden and complete loss of muscle tone, dream-like images or hallucinations at sleep onset or awakening, and sleep paralysis (*National Institute of Neurological Disorders and Stroke [NINDS] 2017, Scammell 2019).*
- The ICSD-3 establishes 2 subtypes of narcolepsy: narcolepsy type 1 and narcolepsy type 2. Patients are diagnosed with narcolepsy type 1 if they have 1 or both of the following: (1) a cerebrospinal fluid (CSF) hypocretin-1 deficiency; (2) clear cataplexy and a mean sleep latency of < 8 minutes on the multiple sleep latency test (MSLT) with evidence of 2 sleep-onset rapid-eye movement periods (SOREMPs), one of which may be seen on a preceding overnight polysomnogram. A diagnosis of narcolepsy type 2 also requires a mean sleep latency of < 8 minutes on the MSLT and at least 2 SOREMPs, but cataplexy must be absent and CSF hypocretin-1 levels must not meet the type 1 criterion *(Sateia 2014).*
- Narcolepsy affects males and females equally. While symptoms typically begin to present in the teens or early twenties, they can occur at any time throughout a patients' life (*NINDS 2017, Scammell 2019*). It is estimated that approximately 135,000 to 200,000 people in the United States (US) are diagnosed with narcolepsy; however, this number may actually be higher as many patients often go undiagnosed (*NINDS 2017).* Narcolepsy is a chronic condition, but does not typically get worse over time. There is no cure for narcolepsy but there are pharmacological and nonpharmacological options that can be implemented to help patients manage their symptoms. The goal of therapy is to mitigate symptoms in order to improve the patient's quality of life (*Morgenthaler et al 2007a, NINDS 2017*).
- This review will focus on 2 wakefulness promoting agents, modafinil (Provigil) and armodafinil (Nuvigil), 1 central nervous system (CNS) depressant agent, sodium oxybate (Xyrem), and 1 dopamine norepinephrine reuptake inhibitor (DNRI), solriamfetol (Sunosi). These 4 medications are approved by the US Food and Drug Administration (FDA) for the symptomatic treatment of narcolepsy. There are several amphetamine-like stimulant medications indicated for the treatment of narcolepsy; however, they will not be covered in this review.
- Modafinil and armodafinil (the longer half-life R-enantiomer of modafinil) are both FDA-approved to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnea (OSA), and shift work disorder (SWD). OSA is a sleep disorder that is characterized by obstructive apneas and hypopneas, causing patients to have frequent sleep interruptions due to increased respiratory effort. Often, patients do not feel rested in the morning and continue to have excessive sleepiness throughout the day (*American Academy of Sleep Medicine [AASM] 2009, Strohl 2019*). SWD is a circadian rhythm sleep disorder that occurs in individuals who work non-traditional hours and is characterized by excessive sleepiness and/or insomnia (*Morgenthaler et al 2007b*). Modafinil and armodafinil have been shown to produce psychoactive and euphoric effects similar to CNS stimulants, as well as alterations in mood, perception, thinking and feelings. As a result, these agents are classified as Schedule IV controlled substances.
- Sodium oxybate is gamma-hydroxybutyric acid (GHB), a known drug of abuse. It is FDA-approved for the treatment of EDS and cataplexy in patients ≥ 7 years of age with narcolepsy and is classified as a Schedule III controlled substance for these indications. However, non-medical uses of sodium oxybate are classified under Schedule I. Sodium oxybate carries a boxed warning regarding CNS depression, abuse, and misuse, and may only be dispensed to patients enrolled in the Xyrem Risk Evaluation and Mitigation Strategy (REMS) program using a specially certified pharmacy. Prescribers and patients must also be enrolled in this REMS program (*Xyrem REMS Web site).*
- Solriamfetol is FDA-approved to improve wakefulness in adult patients with EDS associated with narcolepsy or OSA. Solriamfetol is pending U.S. Controlled Substances Act scheduling (*Sunosi dossier 2019*).

- While placebo-controlled (PC) clinical studies document the efficacy of these agents, the exact mechanisms of action are not completely understood. Head-to-head studies are limited, and current clinical guidelines recommend modafinil and sodium oxybate as first-line treatments for EDS and cataplexy, respectively.
- Medispan class: Stimulants – misc.; Anti-cataplectic agents.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Nuvigil (armodafinil)	✔
Provigil (modafinil)	✔
Sunosi (solriamfetol)	-
Xyrem (sodium oxybate)	-

(*Drugs@FDA 2019, Orange Book: approved drug products with therapeutic equivalence evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Nuvigil (armodafinil)	Provigil (modafinil)	Sunosi (solriamfetol)	Xyrem (sodium oxybate)
To improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, OSA, or SWD	✔	✔		
To improve wakefulness in adult patients with EDS associated with narcolepsy or OSA			✔	
For the treatment of cataplexy and EDS in narcolepsy in patients ≥ 7 years of age				✔

(*Prescribing information: Nuvigil 2018, Provigil 2018, Sunosi 2019, Xyrem 2018*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Narcolepsy

- The efficacy of modafinil for EDS associated with narcolepsy was established in 2 multicenter (MC), double-blind (DB), PC, randomized controlled trials (RCTs). In both studies, patients treated with modafinil showed statistically significant improvement in objective measures of excessive sleepiness as measured by the MSLT and Maintenance of Wakefulness Test (MWT); and the subjective Epworth Sleepiness Scale (ESS) compared to placebo ($p < 0.001$ for all endpoints in both studies). Overall clinical condition as rated by the Clinical Global Impression of Change (CGI-C) at the final visit was also significantly improved over baseline for patients treated with modafinil compared to placebo in both studies ($p < 0.005$ and $p < 0.03$) (*US Modafinil in Narcolepsy Multicenter Study Group 1998, US Modafinil in Narcolepsy Multicenter Study Group 2000).*
- The efficacy of armodafinil for EDS associated with narcolepsy was established in a MC, DB, PC, RCT. Patients treated with armodafinil showed a statistically significant enhanced ability to remain awake as measured by the MWT compared to placebo ($p < 0.01$), as well as improvement in overall clinical condition as rated by the CGI-C compared to placebo ($p < 0.0001$). Armodafinil was also associated with statistically significant improvements in memory, attention, and fatigue ($p < 0.05$) (*Harsh et al 2006).*
- The effectiveness of sodium oxybate in the treatment of EDS in patients with narcolepsy was established in 2 MC, DB, PC, RCTs.

- In the first study, patients treated with sodium oxybate 6 and 9 grams per night achieved statistically significant improvements on the ESS, MWT, and CGI-C compared to the placebo group ($p < 0.001$ for all) (*Xyrem International Study Group 2005a*).
- The second study required patients to be taking a stable dose of modafinil before study randomization. Patients were randomized to placebo, sodium oxybate, modafinil, or sodium oxybate plus modafinil. Patients who were switched from modafinil to sodium oxybate did not experience any decrease in sleep latency, suggesting that both medications are equally effective for EDS. Patients taking sodium oxybate alone and sodium oxybate plus modafinil had statistically significant improvements in sleep latency from baseline as measured by MWT compared to the placebo group ($p < 0.001$). The sodium oxybate plus modafinil group showed a significantly greater increase in sleep latency from baseline compared to the sodium oxybate alone group ($p < 0.001$), suggesting that the combination of drugs had an additive effect (*Black & Houghton 2006*).

- The efficacy of sodium oxybate in the treatment of cataplexy in patients with narcolepsy was established in 2 DB, PC, RCTs.
  - In the first study, patients treated with 6 and 9 grams per night saw a significant decrease in cataplexy attacks compared to placebo ($p < 0.05$ for both doses) (*U.S. Xyrem Multicenter Study Group 2002*).
  - The second study was a randomized withdrawal trial including narcoleptic patients already established on sodium oxybate therapy prior to study entry. Patients were randomized to continue treatment with sodium oxybate or to placebo, which included discontinuation of sodium oxybate therapy. Patients who discontinued sodium oxybate experienced a significant increase in cataplexy attacks compared to patients who remained on sodium oxybate ($p < 0.001$) (*U.S. Xyrem Multicenter Study Group 2004*).
- The efficacy of solriamfetol for the treatment of narcolepsy or narcolepsy with cataplexy was evaluated in a DB, PC, MC, RCT (*Thorpy et al 2019*). Patients were stratified on the basis of presence or absence of cataplexy. Cataplexy was present in 50.8% of patients overall, with similar percentages of patients with cataplexy in each of the treatment groups. At week 12, treatment with solriamfetol significantly improved mean sleep latency measured by the MWT vs placebo ($p < 0.0001$) and ESS scores ($p \leq 0.02$). Significantly higher percentages of patients treated with solriamfetol also reported improvements in Patient Global Impression of Change (PGI-C) vs placebo ($p < 0.0001$). There was no clear effect of solriamfetol on the number of cataplexy attacks per week among patients with cataplexy, although this study was not powered or designed to rigorously evaluate the effects of solriamfetol on cataplexy (data not shown).

OSA

- The efficacy of modafinil for EDS associated with OSA was established in 2 DB, PC, RCTs. In both studies, patients treated with modafinil saw a statistically significant improvement in wakefulness compared to placebo ($p < 0.001$ for both) (*Black et al 2005, Pack et al 2001*).
- The efficacy of armodafinil for EDS associated with OSA was established in 2 PC, DB, RCTs. In both studies, patients treated with armodafinil showed a statistically significant improvement in the ability to remain awake as measured by the MWT ($p < 0.001$ and $p = 0.0003$) and overall clinical condition per the CGI-C compared to placebo ($p < 0.001$ and $p = 0.0069$) (*Roth et al 2006, Hirshkowitz et al 2007*).
- The efficacy of solriamfetol for the treatment of EDS in patients with OSA with current or prior sleep apnea treatment was demonstrated in a DB, PC, MC, RCT (*Schweitzer et al 2018*). At week 12, solriamfetol-treated patients had significantly greater improvements in mean sleep latency assessed by the MWT ($p < 0.001$) and ESS score ($p \leq 0.02$). At week 12, higher percentages of patients on solriamfetol reported overall improvement on the PGI-C vs placebo ($p < 0.0001$).
- A randomized withdrawal study evaluated the maintenance of efficacy and safety of solriamfetol vs placebo for the treatment of EDS in adults with OSA (*Strollo et al 2019*). After 2 weeks of clinical titration and 2 weeks of stable dose administration, patients who reported “much improved” or “very much improved” on the PGI-C and had numerical improvements on the MWT and ESS were randomly assigned to placebo or solriamfetol for 2 additional weeks. From baseline to week 4, mean sleep latency on the MWT and ESS scores improved. From weeks 4 to 6 (randomized withdrawal phase), solriamfetol-treated patients maintained improvements in MWT and ESS. During the randomized withdrawal phase, more patients who were switched to placebo reported worsening on the PGI-C and CGI-C vs those who continued solriamfetol.

- An OL extension study evaluated the long-term safety and maintenance of efficacy of solriamfetol for up to 52 weeks in the treatment of patients with narcolepsy or OSA who completed previous trials of solriamfetol (*Sunosi dossier 2019*). In

a 2-week OL titration phase, patients received solriamfetol, titrated to a maximum tolerated dose, followed by a maintenance phase. During a 2-week PC randomized withdrawal phase ~6 months later, patients were randomized either to placebo or to continue their maintenance solriamfetol dose for 2 weeks. From the beginning to the end of the randomized withdrawal phase, the ESS score was significantly improved with solriamfetol vs placebo ($p < 0.0001$). The percentage of patients who were reported as worse on the PGI-C at the end of the randomized withdrawal phase was greater for patients randomized to placebo compared to patients on solriamfetol ($p < 0.0001$). Long-term maintenance of efficacy of solriamfetol was demonstrated by sustained reductions in ESS scores. During the randomized withdrawal period, patients did not demonstrate rebound sleepiness or withdrawal after abrupt discontinuation of solriamfetol.

SWD

- The efficacy of modafinil in treating EDS associated with SWD was evaluated in a DB, PC, RCT. Patients treated with modafinil showed a statistically significant improvement in nighttime sleep latency as measured by the MSLT ($p = 0.002$) (*Czeisler et al 2005*).
- The efficacy of armodafinil in treating EDS associated with SWD was evaluated in a DB, PC, RCT. Patients treated with armodafinil showed a statistically significant improvement in sleep latency as measured by nighttime MSLT compared to placebo ($p < 0.001$) (*Czeisler et al 2009*).
- A head-to-head study conducted by Tembe et al compared armodafinil to modafinil in patients with SWD. The study compared the response rate, defined as the proportion of patients showing ≥ 2 grades of improvement based on the Stanford Sleepiness Score (SSS). After 12 weeks of therapy, there was no statistically significant different in response rates between patients treated with armodafinil vs modafinil ($p = 0.76$). Compliance to therapy and adverse events (AEs) were also similar between groups ($p = 0.63$ and $p = 0.78$, respectively) (*Tembe et al 2011*).

- Armodafinil, modafinil, sodium oxybate, and solriamfetol have all been shown to be more effective compared to placebo for their respective FDA-approved indications, as demonstrated by significant improvements in objective and subjective measures of EDS. In addition, sodium oxybate has been shown to significantly reduce the rate of cataplexy attacks in narcolepsy patients compared to placebo. While there is insufficient evidence to suggest that one agent is more efficacious than another, some studies have demonstrated that concurrent therapy with sodium oxybate and modafinil had a greater effect on EDS and wakefulness than either agent on its own, suggesting an additive effect (*Alshaikh et al 2012, Billiard et al 1994, Black & Houghton 2006, Black et al 2010a, Black et al 2010b, Black et al 2016, Broughton et al 1997, Kuan et al 2016, Xyrem International Study Group 2005b, Schwartz et al 2010, Weaver et al 2006).*

CLINICAL GUIDELINES

Narcolepsy:

- The 2007 AASM practice parameters for the treatment of narcolepsy and other hypersomnias of central origin (*Morgenthaler et al 2007a*) recommend pharmacologic therapy based on the diagnosis and targeted symptoms. Most of the agents used to treat EDS have little effect on cataplexy or other REM sleep associated symptoms, while most antidepressants and anticataplectics have little effect on alertness; however, some medications act on both symptoms. Co-administration of 2 or more drug classes may be required in some patients to adequately address their symptoms. Scheduled naps may be beneficial, but seldom suffice as primary therapy for narcolepsy. The guidelines state that modafinil is effective for treatment of EDS due to narcolepsy and sodium oxybate is effective for treatment of cataplexy, EDS, and disrupted sleep due to narcolepsy. Sodium oxybate may be effective for treatment of hypnagogic hallucinations and sleep paralysis. Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for treatment of EDS due to narcolepsy. Antidepressants (tricyclics, selective serotonin reuptake inhibitors [SSRIs], venlafaxine) may be effective for treatment of cataplexy. Tricyclics, SSRIs, and venlafaxine may be effective treatment for sleep paralysis and hypnagogic hallucinations.
- The European Academy of Neurology (EAN) 2011 guidelines on management of narcolepsy in adults (*Billiard et al 2011*) recommend modafinil as the first-line treatment for EDS associated with narcolepsy when EDS is the most disturbing symptom. Sodium oxybate is recommended when EDS, cataplexy, and poor sleep coexist. The guideline notes that the combination of modafinil and sodium oxybate may be more effective than sodium oxybate alone. Methylphenidate may be an option if the response to modafinil is inadequate; sodium oxybate is not recommended. Naps are best scheduled on a patient-by-patient basis.
- While armodafinil has been shown in clinical studies to be effective for EDS in narcolepsy, its specific place in therapy is not discussed in the current guidelines.

OSA:

- The 2006 AASM practice parameters for the medical therapy of OSA (*Morgenthaler et al 2006*) provide recommendations for patients with OSA who do not adapt well to or respond to initial therapy with continuous positive airway pressure (CPAP), oral appliances, or surgical modification. Dietary weight loss in obese individuals may be beneficial and should be combined with a primary treatment for OSA. Modafinil is recommended for the treatment of residual EDS in OSA patients who have sleepiness despite effective PAP treatment and who are lacking any other identifiable cause for their sleepiness.

SWD:

- The AASM practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders (*Morgenthaler et al 2007b*) recommend planned napping before or during the night shift to improve alertness and performance in patients with SWD. Timed light exposure in the work environment and light restriction in the morning, when feasible, is indicated to decrease sleepiness and improve alertness during night shift work. Administration of melatonin prior to daytime sleep is indicated to promote daytime sleep among night shift workers. Hypnotic medications may be used to promote daytime sleep among night shift workers. Carryover of sedation to the nighttime shift with potential adverse consequences for nighttime performance and safety must be considered. Modafinil is indicated to enhance alertness during the night shift for SWD. Caffeine is indicated to enhance alertness during the night shift for SWD.

SAFETY SUMMARY

- Sodium oxybate is contraindicated in patients with succinic semialdehyde dehydrogenase deficiency and when used in combination with sedative hypnotics or alcohol.
- Sodium oxybate carries a boxed warning regarding CNS depression and misuse and abuse.
  - Respiratory depression may occur; the concurrent use of sodium oxybate with other CNS depressants may increase the risk of respiratory depression, hypotension, profound sedation, syncope, and death.
  - As a sodium salt of the Schedule I controlled substance GHB, sodium oxybate abuse or misuse may be associated with CNS AEs including seizure, respiratory depression, decreased levels of consciousness, coma, and death.
  - Because of these risks, sodium oxybate is only available through a restricted distribution program called the Xyrem REMS program using a central pharmacy that is specially certified. Prescribers and patients must also enroll in the program (*Xyrem REMS Web site*).
- Additional warnings and precautions for sodium oxybate include:
  - Patients should avoid participation in hazardous activities requiring complete mental alertness or motor coordination within the first 6 hours of dosing or after first initiating treatment until certain that sodium oxybate does not adversely affect them.
  - Monitor patients for signs of new or increased depression and suicidality, impaired motor and cognitive function, and episodes of sleepwalking.
  - Due to its high sodium content, patients with heart failure, hypertension, or impaired renal function should be routinely monitored while taking sodium oxybate.
- Common AEs with sodium oxybate were nausea, dizziness, vomiting, somnolence, enuresis, and tremor.

- Warnings and Precautions for modafinil and armodafinil include:
  - Cases of serious rash, including Stevens-Johnson Syndrome, have been reported. Discontinue therapy at the first sign of rash unless certain rash is not drug-related.
  - Angioedema and anaphylaxis reactions may occur. Discontinue therapy and immediately seek medical attention at the first signs of angioedema or anaphylaxis.
  - Multi-organ hypersensitivity reactions may occur. There are no known factors to predict the risk of occurrence or the severity of the reaction, and therapy should be discontinued in these patients.
  - Persistent sleepiness: patients should be regularly assessed for degree of sleepiness and advised against driving or other potentially dangerous activities if necessary.
  - The emergence or exacerbation of psychiatric symptoms have been reported; use particular caution in patients with a history of psychosis, depression, or mania.
  - Consider increased monitoring in patients with known cardiovascular disease.

- The most common AEs with modafinil were headache, nausea, nervousness, rhinitis, diarrhea, back pain, anxiety, insomnia, dizziness, and dyspepsia; the most common AEs with armodafinil were headache, nausea, dizziness, and insomnia.
- Drug interactions for modafinil and armodafinil:
  - Exposure to CYP 3A4/5 substrates may be decreased:
    - Effectiveness of steroidal contraceptives may be reduced; use alternative or concomitant contraceptive methods while taking and for 1 month after discontinuation of modafinil or armodafinil.
    - Blood concentrations of cyclosporine may be reduced requiring monitoring and possible dose adjustment.
  - Exposure to CYP2C19 substrates, such as omeprazole, phenytoin, and diazepam, may be increased.
  - More frequent monitoring of prothrombin times/international normalized ratio (INR) should be considered when administered with warfarin.
  - Use caution when concomitantly used with monoamine oxidase inhibitors (MAOIs).

- Solriamfetol is contraindicated with concomitant use of MAOIs, or within 14 days following discontinuation of an MAOI because of the risk of hypertensive reaction.
- Warnings and precautions of solriamfetol include blood pressure and heart rate increases and psychiatric symptoms such as anxiety, insomnia, and irritability.
- The most common AEs in either the narcolepsy or OSA populations were headache, nausea, decreased appetite, insomnia, and anxiety.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Nuvigil (armodafinil)	Tablets	Oral	*Narcolepsy or OSA*: once daily in the morning. *SWD*: once daily, approximately 1 hour prior to the start of the work shift.	The dose should be reduced in patients with severe hepatic impairment and geriatric patients.
Provigil (modafinil)	Tablets	Oral	*Narcolepsy or OSA*: once daily in the morning. *SWD*: once daily, approximately 1 hour prior to the start of the work shift.	Patients with severe hepatic impairment should reduce the dose to one-half the recommended dose. Consider a lower dose in geriatric patients.
Sunosi (solriamfetol)	Tablets	Oral	*Narcolepsy or OSA:* once daily	Renal impairment: dose adjustments required; not recommended for use in patients with end-stage renal disease.
Xyrem (sodium oxybate)	Solution	Oral	Adults: administer nightly in 2 equal divided doses: at bedtime and 2.5 to 4 hours later; titrate to effect as directed	Both doses should be prepared prior to bedtime; dilute each dose with approximately ¼ cup of water in pharmacy-provided vials. Take each dose while in bed and lie down after dosing.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Pediatrics: weight-based dose administered at bedtime and 2.5 to 4 hours later; titrate to effect as directed.	Patients with hepatic impairment should reduce the starting dose by 50%. When using concomitantly with divalproex sodium, an initial dose reduction of at least 20% is recommended.

See the current prescribing information for full details

CONCLUSION

- Narcolepsy is a chronic neurological condition that causes excessive sleepiness throughout the day. EDS can vary in severity and in the most severe cases patients suddenly fall asleep during normal activities. Patients with narcolepsy present with or without clear evidence of cataplexy (type 1 vs type 2, respectively). There is no cure for narcolepsy and current treatments focus on alleviating symptoms and improving quality of life.
- Current clinical evidence supports the use of modafinil as a first-line agent in treating EDS associated with narcolepsy. Sodium oxybate can be used as a second-line agent for EDS in narcolepsy, but is considered first-line therapy for patients diagnosed with cataplexy. While armodafinil has been shown in clinical studies to be effective in treating narcolepsy-associated EDS, the current clinical guidelines do not discuss a specific place in therapy. Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are additional treatment alternatives for EDS due to narcolepsy, while TCAs, SSRIs, and venlafaxine are second-line alternatives for patients with cataplexy. Solriamfetol has not yet been incorporated into the guidelines.
- Patients with OSA should be treated with primary CPAP therapy, and then may use modafinil as an adjunctive treatment for residual sleepiness. SWD should be treated by utilizing a planned sleep schedule, including regular naps before and during the work shift; modafinil may be used to enhance wakefulness in these patients.
- While current clinical data indicate that modafinil, armodafinil, sodium oxybate, and solriamfetol are all effective for their respective FDA-approved indications, there is a lack of head-to-head data among these agents. A treatment plan should be individualized for all patients and the risks and benefits should be evaluated before beginning any pharmacological therapy.
- Modafinil, armodafinil, and solriamfetol are oral tablets that are dosed once daily. Sodium oxybate is an oral solution that must be taken at bedtime and repeated 2.5 to 4 hours later. Currently, modafinil and armodafinil are available generically.
- Sodium oxybate carries a boxed warning for the risk of CNS depression, misuse, and abuse. Sodium oxybate is only available through the Xyrem REMS program; patients and prescribers must enroll in the program and sodium oxybate is only dispensed through a specially certified pharmacy.

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Annual Review - Established Drug Classes

INTRODUCTION

- Pain originates from somatic or visceral structures. Somatic pain is localized and typically results from injury or disease of the skin, musculoskeletal structures, and joints. Visceral pain arises from internal organ dysfunction or from functional pathology.
- Pain can be acute or chronic. Acute pain often results from injury or inflammation and may have a survival role and assist in the healing process by minimizing re-injury. In contrast, chronic pain, often defined as pain persisting for over three to six months, may be considered a disease in that it serves no useful purpose (*Cohen et al 2016*).
  - A 2016 study estimated that approximately 50 million adults in the United States have chronic pain, and approximately 20 million have high-impact chronic pain (ie, pain that limits life or work activities on most days). Each year, chronic pain contributes to an estimated $560 billion in direct medical costs, lost productivity, and disability programs (*Dahlhamer et al 2018*).
- Pain may be classified as nociceptive and neuropathic pain.
  - Nociceptive pain, including cancer pain, results from an injury or disease affecting somatic structures such as skin, muscle, tendons and ligaments, bone, and joints. It is typically treated with nonopioid analgesics or opioids.
  - Neuropathic pain results from disease or injury to the peripheral or central nervous systems (CNS) and is less responsive to opioids. It is often treated with adjuvant drugs such as antidepressants and antiepileptics. Opioids are recommended as second- or third-line agents (*Cohen et al 2016*).
- Several pharmacologic and nonpharmacologic options are currently available for the management of pain. Treatment options include pharmacologic treatment, physical medicine, behavioral medicine, neuromodulation, interventional, and surgical approaches. Pharmacologic therapy should not be the sole focus of pain treatment; however, it is the most widely utilized option (*Cohen et al 2016*).
  - Major pharmacologic categories used in the management of pain include non-opioid analgesics, tramadol, opioid analgesics (full and partial agonists), alpha-2 (α_2) adrenergic agonists, antidepressants, anticonvulsants, muscle relaxants, N-methyl-d-aspartate (NMDA) receptor antagonists, and topical analgesics. Opioids are available in both short-acting and long-acting or sustained release formulations (*Cohen et al 2016*).
  - Combining different types of treatments, including multiple types of analgesics, may provide an additive analgesic effect without increasing adverse effects (*Cohen et al 2016, The Medical Letter 2013*).
- It is important that patients receive appropriate pain treatment with careful consideration of the benefits and risks of treatment options. The use of opioid analgesics presents serious risks, including overdose and opioid use disorder. From 1999 to 2014, there were more than 165,000 deaths due to opioid analgesic overdoses in the U.S. (*Dowell et al 2016*).
- The long-acting opioids have gained increasing attention regarding overuse, abuse, and diversion. Some manufacturers have addressed concerns about abuse and misuse by developing new formulations designed to help discourage the improper use of opioid medications.
  - In January 2013, the Food and Drug Administration (FDA) released draft guidance for industry regarding abuse deterrent opioids. This document was finalized in April 2015. The guidance explains the FDA's current direction regarding studies conducted to demonstrate that a given formulation has abuse deterrent properties. The guidance also makes recommendations about how those studies should be performed and evaluated (*FDA Industry Guidance 2015*). The 2015 guidance does not address generic opioids. Subsequently in November 2017, the FDA issued a final guidance to support industry in the development of generic versions of abuse-deterrent opioids (*FDA Industry Guidance 2017*).
  - In 2013, reformulated OxyContin (oxycodone) became the first long-acting opioid to be approved with labeling describing the product's abuse deterrent properties consistent with the FDA's guidance for industry (*Hale et al 2016*).
  - Since the approval of reformulated OxyContin, several other long-acting opioids have been approved with abuse deterrent labeling, including, Arymo ER (morphine), Embeda (morphine and naltrexone), Hysingla ER (hydrocodone), Morphabond (morphine), Targiniq ER (oxycodone and naloxone), Troxyca ER (oxycodone and naltrexone), Vantrela

ER (hydrocodone), and Xtampza ER (oxycodone) (*Drugs@FDA 2019, Hale et al 2016*). However, Targiniq ER, Troxyca ER, and Vantrela ER were never launched and were recently discontinued (*Drugs@FDA 2019*). Branded Arymo ER was also recently discontinued by the manufacturer, Egalet (*Arymo ER website 2019*).

- A number of federal agencies have recently implemented measures to combat drug abuse and misuse. The Centers for Medicare & Medicaid Services (CMS) has issued guidance in an effort to improve drug utilization review controls in Part D prescription plans. The U.S. Office of Disease Prevention and Health Promotion offers an interactive training tool, "Pathways to Safer Opioid Use," which teaches healthcare providers how to implement opioid-related recommendations from the adverse events action plan. Additionally, the National Institute on Drug Abuse (NIDA), a component of the National Institutes of Health (NIH), has a number of studies and initiatives to educate providers and patients about opioid addiction and treatment. On July 13, 2017, the National Academies of Science, Engineering, and Medicine (NASAM) also released a consensus report, commissioned by the FDA, which outlined the state of the science regarding prescription opioid abuse and misuse, as well as the evolving role that opioids play in pain management. (*CMS 2019, Office of Disease Prevention and Health Promotion 2019, NASAM 2017, NIDA 2015*).
- In December 2018, the U.S. Department of Health & Human Services (HHS) recommended prescribing or co-prescribing naloxone to all patients who are at risk for opioid overdose, including: patients receiving opioids at a dosage of 50 milligram morphine equivalents (MME) per day or greater; patients with respiratory conditions who are prescribed opioids; patients who have been prescribed benzodiazepines along with opioids; and patients prescribed opioids who have a non-opioid substance use disorder, report excessive alcohol use, or have a mental health disorder (*HHS 2018*).
- In March 2016, the Centers for Disease Control and Prevention (CDC) issued a guideline for prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care. The guideline addresses when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, follow-up, and discontinuation; and assessing risks and addressing harms of opioid use. The guideline encourages prescribers to follow best practices for responsible opioid prescribing due to the risks of opioid use (*Dowell et al 2016*).
- Methadone is FDA-approved for detoxification and maintenance treatment of opioid addiction.
  - Methadone products when used for the treatment of opioid addiction in detoxification or maintenance programs, shall be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs shall dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (42 CFR 8.12) (*Prescribing information: Dolophine 2018, methadone oral solution 2018, Methadose 2018*).
- Included in this review are the long-acting opioids, which are primarily utilized in the management of moderate to severe chronic pain in patients requiring a continuous, around-the-clock opioid analgesic for an extended period of time. Long-acting opioids are available in a variety of different dosage forms, and currently several agents are available generically (*Drugs@FDA 2019*).
  - All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of transdermal and buccal buprenorphine, a partial opioid agonist, which is a Schedule III controlled substance (*Drugs@FDA 2019*).
- Since some agents are available under multiple brand names, many tables in this review are arranged by generic name.
- Medispan class: Opioid Agonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single Entity Agents	
Arymo ER†¶, Avinza¶, Kadian, Morphabond†, MS Contin (morphine sulfate)	✔
Belbuca, Butrans (buprenorphine)	✔
Dolophine, Methadose (methadone)	✔
Duragesic (fentanyl)	✔
Exalgo# (hydromorphone)	✔
Hysingla ER†, Zohydro ER§ (hydrocodone bitartrate)	-
levorphanol	✔
Nucynta ER (tapentadol)	-

Drug	Generic Availability
Opana ER* (oxymorphone)	✔
OxyContin†, Xtampza ER† (oxycodone)	✔
Combination Products	
Embeda† (morphine sulfate/naltrexone)	-

*Generic products of the pre-reformulated Opana ER are available. The branded versions of Opana ER (pre- and post-reformulation) are no longer available on the market.
†Approved as an abuse deterrent (AD) formulation, which is consistent with the FDA's 2015 guidance for industry, *Abuse-Deterrent Opioids – Evaluation and Labeling.*
‡OxyContin had various patents extending out to 2027. Patent litigation on OxyContin reached an agreement between manufacturers. In late 2014, a number of generic products launched.
§In February 2015, a new formulation of Zohydro ER was FDA-approved with AD properties; however, it has not been deemed to meet the FDA requirements for labeling as an AD opioid. In February 2019, Pernix, the manufacturer of Zohydro ER, filed for bankruptcy. Pernix intends to continue to operate with no disruption to the availability of products and patient support services *(Pernix Press Release 2019)*.
¶Avinza branded products were discontinued by Pfizer in July 2015. Egalet discontinued the promotion and manufacture of Arymo ER branded products effective September 28, 2018.
#Availability of branded Exalgo is unclear, but generic products are available.
(*Drugs@FDA 2019, FDA Industry Guidance 2015, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Single Entity Agents										Combination Products
	buprenorphine	fentanyl	hydrocodone	hydromorphone	levorphanol	methadone	morphine	oxycodone	oxymorphone	tapentadol	morphine sulfate/ naltrexone
Pain Management											
Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in adults.	✔		✔			✔ *	✔	✔	✔	✔	✔
Management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate in opioid-tolerant pediatric patients ≥ 11 years of age who are already receiving and tolerate a minimum daily opioid dose of at least 20 mg oxycodone orally or its equivalent.								✔ †			
Management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.					✔						
Management of pain in opioid-tolerant patients, severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.		✔ ‡		✔ ‡							
Management of neuropathic pain associated with diabetic peripheral neuropathy (DPN) in adults severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate										✔	
Opioid Addiction											
Detoxification treatment of opioid addiction (heroin or other morphine-like drugs)						✔					
Maintenance treatment of opioid addiction (heroin or other morphine-like drugs), in conjunction with social and medical services						✔					
Limitations of Use											
Limitations of Use: Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release (ER) opioid formulations, reserve this agent for use in patients for whom alternative treatment options (e.g., non-opioid analgesics	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔

Indication	Single Entity Agents										Combination Products
	buprenorphine	fentanyl	hydrocodone	hydromorphone	levorphanol	methadone	morphine	oxycodone	oxymorphone	tapentadol	morphine sulfate/ naltrexone
or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.											
Limitations of Use: Not indicated as an as-needed (prn) analgesic.	✔	✔	✔	✔		✔	✔	✔	✔	✔	✔

*Methadone tablets and oral solution only
†OxyContin only
‡Patients considered opioid tolerant are those who are receiving, for one week or longer, at least 60 mg oral morphine per day, 25 mcg transdermal fentanyl per hour, 30 mg oral oxycodone per day, 8 mg oral hydromorphone per day, 25 mg oral oxymorphone per day, 60 mg oral hydrocodone per day, or an equianalgesic dose of another opioid.

(Prescribing information: Arymo ER 2018, Belbuca 2018, Butrans 2018, Dolophine 2018, Duragesic 2018, Embeda 2018, Exalgo 2018, Hysingla ER 2018, Kadian 2018, levorphanol 2018, methadone oral solution 2018, Methadose 2018, Morphabond 2018, MS Contin 2018, Nucynta ER 2018, OxyContin 2018, oxymorphone extended-release 2018, Xtampza ER 2018, Zohydro ER 2018)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- As a class, the long-acting opioids are a well-established therapy for the treatment of moderate to severe pain. In general, opioids are used for the treatment of non-cancer and cancer pain; however, data establishing their effectiveness in the treatment of neuropathic pain are available. Head-to-head trials of long-acting opioids do exist and for the most part the effectiveness of the individual agents, in terms of pain relief, appears to be similar. Small differences between the agents exist in side effect profiles, and associated improvements in quality of life or sleep domains (*Agarwal et al 2007, Aiyer et al 2017, Allan et al 2001, Allan et al 2005, Bao et al 2016, Bekkering et al 2011, Bruera et al 2004, Buynak et al 2010, Caldwell et al 2002, Caraceni et al 2011, Chou et al 2015, Clark et al 2004, Conaghan et al 2011, Felden et al 2011, Finkel et al 2005, Finnerup et al 2015, Gimbel et al 2003, Gordon et al [a], 2010, Gordon et al [b], 2010, Karlsson et al 2009, Hale et al 2007, Hale et al 2010, Katz et al 2010, King et al 2011, Kivitz et al 2006, Langford et al 2006, Ma et al 2008, Melilli et al 2014, Mercadante et al 2010, Mesgarpour et al 2014, Morley et al 2003, Musclow et al 2012, Nicholson et al 2017, Park et al 2011, Pigni et al 2011, Quigley et al 2002, Rauck et al 2014, Schwartz et al 2011, Slatkin et al 2010, Sloan et al 2005, Watson et al 2003, Whittle et al 2011, Wiffen et al 2013, Wild et al 2010*).
- Some systematic reviews and meta-analyses recommend opioids as a potential treatment option for various forms of non-cancer and cancer-related pain; however, other meta-analyses in non-cancer pain have not found a clinically meaningful difference between opioids, other non-opioid pain medications, and placebo. No single opioid is recommended over the others (*Busse et al 2018, Chou et al 2015, Finnerup et al 2015, Mesgarpour et al 2014, Stewart et al 2018*).
  - The Agency for Healthcare Research and Quality (AHRQ) conducted a systematic review (N=39 studies, 40 publications) of the effectiveness and risks of long-term (>3 months) opioid therapy for chronic pain and included both randomized and observational studies. Findings indicated that three randomized, head-to-head trials of various long-acting opioids found no differences in one-year outcomes related to pain or function. One good-quality case-control study found current opioid use to be associated with increased risk for hip, humerus, or wrist fracture versus non-use (adjusted odds ratio [OR], 1.27; 95% confidence interval [CI], 1.21 to 1.33). The risk was highest with one prescription (OR, 2.7; 95% CI, 2.34 to 3.13) and decreased with higher numbers of prescriptions, with no increased risk with more than 20 cumulative prescriptions. One fair-quality cohort study found that a cumulative opioid supply of at least 180 days over a 3.5-year period was associated with an increased risk for myocardial infarction versus no long-term opioid therapy (adjusted incidence rate ratio, 2.66; 95% CI, 2.3 to 3.08) (*Chou et al 2015*).
  - A systematic review and meta-analysis of 96 randomized controlled trials examined the use of opioids in chronic non-cancer pain. Opioid use was associated with reduced pain compared to placebo (weighted mean difference [WMD], -0.69 cm on a 10-cm visual analog scale; 95% confidence interval [CI], -0.82 to -0.56 cm; $p < 0.001$), as well as improved physical functioning as measured by the 36-item Short Form physical component score (SF-36 PCS; WMD, 2.04 points on a 100-point scale; 95% CI, 1.41 to 2.68 points; $p < 0.001$). However, the minimally important difference (pain, 1 cm; SF-36 PCS, 5 points) was not reached for either parameter. Opioids were also associated with increased vomiting vs placebo (5.9% vs. 2.3%). When opioids were compared to nonsteroidal anti-inflammatory drugs (NSAIDs), similar improvements in pain and physical functioning were observed (pain WMD for opioids vs NSAIDs, -0.60 cm; 95% CI, -1.54 to 0.34; physical functioning WMD for opioids vs NSAIDs, -0.90 points; 95% CI, -2.69 to 0.89) (*Busse et al 2018*). Similarly, another systematic review and meta-analysis of 29 studies found that opioids and other commonly used classes of pain medication produced similar percent reductions in osteoarthritis pain (opioids, 35.4%; oral NSAIDs, 34.3%; topical NSAIDs, 40.9%; acetaminophen, 32.5%; cyclooxygenase-2 [COX-2] inhibitors, 36.9%) (*Stewart et al 2018*).
  - The Special Interest Group on Neuropathic Pain of the International Association for the Study of Pain conducted a systematic review and meta-analysis of randomized, double-blinded studies of oral and topical therapy for neuropathic pain and required a number needed to treat (NNT) for 50% pain relief as the primary measure. For tapentadol ER, the review identified one negative study and one positive enrichment study with a potential bias and a high NNT of 10.2 (95% CI, 5.3 to 185.5) in 67% of the patients responding to the open phase. Thirteen trials were identified with strong opioids, in which oxycodone (10 to 120 mg/day) and morphine (90 to 240 mg/day) were used mainly in peripheral neuropathic pain. The final quality of evidence was moderate. Ten trials were positive with a combined NNT of 4.3 (95% CI, 3.4 to 5.8) and a number needed to harm of 11.7 (95% CI, 8.4 to 19.3). Maximum effectiveness seemed to be associated with 180 mg morphine or equivalent (*Finnerup et al 2015*).
  - Another systematic review evaluated long-acting opioids in the treatment of moderate to severe cancer pain. The review included only double-blinded, randomized controlled trials for efficacy assessments; open-label and controlled

observational studies were allowed for safety assessments. A total of five RCTs and four observational studies met criteria for inclusion. Similar pain intensity improvements were demonstrated for oxycodone ER, oxycodone/naloxone ER, hydromorphone ER, and oxycodone ER. However, the average equivalent dose of oxycodone ER was significantly different from hydromorphone ER. The Morphine ER and hydromorphone ER groups had similar improvements in average cancer pain in the past 24 hours and "current pain in the morning;" however, the "worst pain in the past 24 hours" and "current pain in the evening" were significantly lower in the hydromorphone ER group. The quality of life scores were comparable between oxycodone ER and oxycodone/naloxone ER as well as morphine ER and hydromorphone ER in two trials. The rate of discontinuation due to lack of efficacy was similar among patients treated with morphine ER, hydromorphone ER, oxycodone ER or oxycodone/naloxone ER and ranged from 1.1% (oxycodone/naloxone ER) to 6.5% (hydromorphone ER). The risk of experiencing serious adverse events was comparable in patients treated with morphine ER or hydromorphone ER, morphine ER or fentanyl ER, and morphine ER or oxycodone ER. Overall, the reviewers concluded that there was no difference in efficacy and risk of harms among ER opioids in the treatment of cancer-related pain based on current evidence (*Mesgarpour et al 2014*).

- A recent pragmatic, 12-month, randomized trial (N=240) compared opioid vs non-opioid medications on pain-related function, pain intensity, and adverse effects in patients with moderate to severe chronic back pain or hip or knee osteoarthritis pain despite analgesic use *(Krebs et al 2018)*.
  - Each intervention had its own prescribing strategy that included multiple medication options in 3 steps. In the opioid group, the first step was immediate-release morphine, oxycodone, or hydrocodone/acetaminophen. For the nonopioid group, the first step was acetaminophen or an NSAID. Medications were changed, added, or adjusted within the assigned treatment group according to individual patient response.
  - Groups did not significantly differ on pain-related function over 12 months (p = 0.58); mean 12-month Brief Pain Inventory (BPI) interference was 3.4 for the opioid group and 3.3 for the nonopioid group (difference, 0.1 [95% CI, −0.5 to 0.7]). Pain intensity was significantly better in the nonopioid group over 12 months (p = 0.03); mean 12-month BPI severity was 4.0 for the opioid group and 3.5 for the nonopioid group (difference, 0.5 [95% CI, 0.0 to 1.0]). Adverse medication-related symptoms were significantly more common in the opioid group over 12 months (p = 0.03); mean medication-related symptoms at 12 months were 1.8 in the opioid group and 0.9 in the nonopioid group (difference, 0.9 [95% CI, 0.3 to 1.5]).
- Arymo ER and Morphabond were approved based on bioequivalence to MS Contin. In lieu of conducting new nonclinical studies and clinical studies of the safety and efficacy, the manufacturers relied on previous findings of efficacy and safety for MS Contin (*FDA Summary Review: Arymo ER 2017, Morphabond 2018*).
- The efficacy of buprenorphine buccal films was evaluated in three 12-week, double-blind (DB), placebo-controlled (PC) trials in opioid-naïve and opioid-experienced patients with moderate-to-severe chronic low back pain. In the trials, the DB treatment phase was preceded by an OL dose titration period. Patients were eligible for randomization into the 12-week DB treatment phase if they were able to titrate to a tolerable and effective buprenorphine dose. The primary efficacy variable was the patients' pain scores (based on a 0 to 10 numeric rating scale). Two of these studies demonstrated efficacy in patients with low back pain. One trial did not show a statistically significant pain reduction for Belbuca compared to placebo, and the results of this trial are not included in the Prescribing Information (*Belbuca Prescribing Information 2018, Gimbel et al 2016, Rauck et al 2016*).
  - In one study of opioid-naïve patients, pain scores increased more in the placebo group vs. the buprenorphine group during the DB phase; mean (standard deviation [SD]) changes from baseline to week 12 were 0.94 (1.85) and 1.59 (2.04) in the buprenorphine and placebo groups, respectively, with a significant between-group difference (-0.67, 95% confidence interval [CI]: -1.07 to -0.26; p = 0.0012). A higher proportion of buprenorphine patients (62%) had at least a 30% reduction in pain score from prior to OL titration to study endpoint when compared to patients who received placebo (47%) (*Rauck et al 2016*).
  - In another study, opioid-experienced patients experienced a higher increase in their pain scores in the placebo vs. buprenorphine group after randomization. The difference between groups in the mean change from baseline to week 12 was -0.98 (95% CI: -1.32 to -0.64; p < 0.001). A significantly larger percentage of patients receiving buprenorphine than placebo had pain reductions ≥ 30% and ≥ 50% (p < 0.001 for both) (*Gimbel et al 2016*).

CLINICAL GUIDELINES

- Clinical guidelines do not state a preference for the use of one long-acting opioid over another for the use in moderate to severe pain (*Attal et al 2010, Bril et al 2011, Chou et al 2009, Hochberg et al 2012, Manchikanti et al 2017, Qaseem 2017, Paice et al 2016, The Medical Letter 2013*). However, opioid rotation is recommended if a patient experiences

adverse effects from one agent (*Chou et al 2009*). In addition, methadone safety guidelines from the 2014 American Pain Society recommend buprenorphine as an alternative to methadone for the treatment of opioid addiction in patients with risk factors or known QTc prolongation (*Chou et al 2014*).

- In March 2016, the CDC issued a guideline for prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care. The guideline addresses when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, follow-up, and discontinuation; and assessing risk and addressing harms of opioid use. Recommendations in the CDC guideline include the following (*Dowell et al 2016*):
  - Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate (category A, evidence 3).
  - Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety (category A, evidence 4).
  - Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy (category A, evidence 3).
  - When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of ER/long-acting opioids (category A, evidence 4).
  - Clinicians should prescribe opioids at the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to ≥ 50 MME/day, and should avoid increasing dosage to ≥ 90 MME/day or carefully justify a decision to titrate dosage to ≥ 90 MME/day (category A, evidence 3).
  - Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than seven days will rarely be needed (category A, evidence 4).
  - Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids (category A, evidence 4).
  - Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥ 50 MME/day), or concurrent benzodiazepine use, are present (category A, evidence 4).
  - Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months (category A, evidence 4).
  - When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs (category B, evidence 4).
  - Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible (category A, evidence 3).
  - Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder (category A, evidence 2).

Category of Recommendations:
  - Category A: Applies to all persons; most patients should receive the recommended course of action.

- Category B: Individual decision making needed; different choices will be appropriate for different patients. Clinicians help patients arrive at a decision consistent with patient values and preferences and specific clinical situations.

Evidence Type:

- Type 1: Randomized clinical trials or overwhelming evidence from observational studies.
- Type 2: Randomized clinical trials with important limitations, or exceptionally strong evidence from observational studies.
- Type 3: Observational studies or randomized clinical trials with notable limitations.
- Type 4: Clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations.

- In February 2017, the American College of Physicians published clinical practice guidelines for noninvasive treatments of acute, subacute, and chronic low back pain. The guidelines state that clinicians should only consider opioids as an option in patients who have failed other treatments (e.g., non-pharmacological treatment, NSAIDs, tramadol, duloxetine) and only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients (*Qaseem et al 2017*).
  - There is moderate-quality evidence that show strong opioids (tapentadol, morphine, hydromorphone, and oxymorphone) are associated with a small short-term improvement in pain scores (about 1 point on a pain scale of 0 to 10) and function compared with placebo. There is moderate-quality evidence that show no differences among different long-acting opioids for pain or function, and low-quality evidence shows no clear differences in pain relief between long- and short-acting opioids.

- In February 2017, the American Society of Interventional Pain Physicians (ASIPP) also published new practice guidelines for responsible, safe, and effective prescription opioids for chronic non-cancer pain. Similar to other guidelines, they do not recommend one opioid agent over the others. They do provide the following recommendations and conclusions for long-term opioid therapy (*Manchikanti et al 2017*):
  - Initiate opioid therapy with low dose, short-acting drugs, with appropriate monitoring (Evidence: Level II; Strength of Recommendation: Moderate).
  - Consider up to 40 MME as low dose, 41 to 90 MME as a moderate dose, and greater than 91 MME as high dose (Evidence: Level II; Strength of Recommendation: Moderate).
  - Avoid long-acting opioids for the initiation of opioid therapy (Evidence: Level I; Strength of Recommendation:
  - Strong).
  - Recommend methadone only for use after failure of other opioid therapy and only by clinicians with specific training in its risks and uses, within FDA recommended doses (Evidence: Level I; Strength of Recommendation: Strong).
  - Understand and educate patients of the effectiveness and adverse consequences (Evidence: Level I; Strength of Recommendation: Strong).
  - Similar effectiveness for long-acting and short-acting opioids with increased adverse consequences of long-acting opioids (Evidence: Level I-II; Strength of recommendation: Moderate to strong).
  - Recommend long-acting or high dose opioids only in specific circumstances with severe intractable pain (Evidence: Level I; Strength of Recommendation: Strong).

- The guidelines from the American College of Physicians and the American Society of Interventional Pain Physicians state that buprenorphine has lower quality evidence and is a third-line opioid for the treatment of pain (*Manchikanti et al 2017, Qaseem et al 2017*).
- Guidelines from the Society of Critical Care Medicine do not specifically address the use of long-acting opioids in intensive care unit patients; however, they recommend a multimodal approach to analgesia, using non-opioid medications as adjunctive therapy in order to decrease opioid use and optimize pain control (*Devlin et al 2018*). Similarly, an expert consensus guideline on opioid prescribing in surgical procedures from the American College of Surgeons does not make recommendations on long-acting opioid use in this setting, but recommends the maximization of non-opioid analgesia (ie, ibuprofen). It also provides recommendations on the number of oxycodone 5 mg tablets to prescribe after surgery, depending on the type of surgical procedure performed (*Overton et al 2018*).

SAFETY SUMMARY

- On July 9, 2012, the FDA approved a Risk Evaluation and Mitigation Strategy (REMS) program for ER and long-acting opioids; on September 18, 2018, this REMS was modified to include all immediate-release opioids as well. This program, now known as the Opioid Analgesic REMS program, strongly encourages healthcare providers to complete an approved training program on opioid analgesics. The goal of the REMS is to ensure that benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse.
- All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of buprenorphine buccal and transdermal systems, which are Schedule III controlled substances.
- Most long-acting opioids are associated with boxed warnings regarding the potential for abuse and misuse, life-threatening respiratory depression, neonatal opioid withdrawal syndrome, an interaction with alcohol, and accidental ingestion risks. Dolophine and methadone products have additional boxed warnings regarding life-threatening QT prolongation. Duragesic, Hysingla ER, OxyContin, Xtampza ER, and Zohydro ER also have a Boxed Warning for an interaction with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers). An additional Boxed Warning for Duragesic cautions against exposure to heat as it may cause increased fentanyl release.
- Key contraindications across the class include acute or severe bronchial asthma, significant respiratory depression, and known or suspected paralytic ileus.
- There are multiple warnings and precautions with each agent. Key safety concerns associated with the opioid analgesics include respiratory depression, driving and operating machinery, hypotension, interactions with other CNS depressants, neonatal opioid withdrawal syndrome, use in special populations, and use in those with gastrointestinal conditions.
- The frequency of adverse reactions varies to some degree with each agent; however, overall adverse reactions are similar within the class. The most common adverse events in adults include nausea, vomiting, constipation, and somnolence.
- OxyContin is approved in patients aged ≥ 11 years. The most frequent adverse events in pediatric patients were vomiting, nausea, headache, pyrexia, and constipation.
- In March 2016, the FDA issued a drug safety communication warning about several safety issues with opioids and describing new class-wide labeling requirements. The warnings include the following (*FDA Drug Safety Communication 2016*):
  - Opioids can interact with antidepressants and migraine medications to cause serotonin syndrome.
  - Taking opioids may rarely lead to adrenal insufficiency.
  - Long-term opioid use may be associated with decreased sex hormone levels and symptoms such as reduced interest in sex, impotence, or infertility.
- In August 2016, the FDA announced that it is requiring class-wide changes to drug labeling, including patient information, in order to help inform health care providers and patients of the serious risks associated with the combined use of certain opioid medications and benzodiazepines (*FDA Drug Safety Communication 2016*).
  - Among the changes, the FDA is requiring boxed warnings and patient-focused Medication Guides for prescription opioid analgesics, opioid-containing cough products, and benzodiazepines – nearly 400 products in total – with information about the serious risks associated with using these medications concomitantly. Risks include extreme sleepiness, respiratory depression, coma, and death.
- On March 14, 2017, the FDA Drug Safety Risk Management and Anesthetic and Analgesic Drug Products Advisory Committees voted 18 to 8, that the benefits of reformulated Opana ER (which did not originally gain the labeling describing potential abuse deterrent properties) no longer outweigh its risks. This vote followed an FDA analysis of epidemiological data that indicated that there was a shift in the pattern of Opana ER abuse from the nasal to the injection route after the product was reformulated (*FDA Advisory Committee 2017*). Following the FDA's official withdrawal request, the manufacturer (Endo) announced the voluntary market withdrawal of reformulated Opana ER (*Endo Press Release 2017*).
- On September 20, 2017, the FDA advised clinicians that opioid addiction medications, such as methadone and buprenorphine, should not be withheld from patients receiving concurrent benzodiazepines or other CNS depressants (*FDA Drug Safety Communication 2017*). Even though combination therapy with these agents increases the risk of serious side effects, the harm caused by untreated opioid addiction can outweigh these risks.

DOSING AND ADMINISTRATION

- Certain strengths are appropriate only for patients who are considered treatment-experienced. Please see a detailed description within the prescribing information for each agent regarding when a patient is considered opioid-tolerant and which strengths are appropriate in these patients.
- See prescribing information for detailed conversion recommendations as there are no established conversions from other opioid agents. When converting from one agent to another, it is better to underestimate need and monitor for breakthrough pain.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Arymo ER§, Avinza†, Kadian*, Morphabond, MS Contin (morphine sulfate)	ER capsules and tablets	Oral	Arymo ER, Morphabond, MS Contin: Every 8 to 12 hours Avinza: Once daily Kadian: Once daily	• Renal dose adjustment is required. • Hepatic dose adjustment is required.
Butrans, Belbuca (buprenorphine)	Transdermal system (Butrans) Buccal film (Belbuca)	Topical Oral	Administration every 7 days Every 12 hours	• Not evaluated in patients with severe hepatic impairment and should be administered with caution (Butrans). • The maximum dose is 900 mcg every 12 hours. Do not exceed this dose due to the potential for QTc interval prolongation. If pain is not adequately managed on a 900 mcg dose, consider an alternate analgesic (Belbuca). • For severe hepatic impairment, reduce the starting and incremental dose by half (Belbuca).
Dolophine, Methadose (methadone)	Oral solution, dispersible tablet, tablets	Oral	Every 8 to 12 hours (for management of pain)	• Due to the large variability in half-life (eg, 8 to 59 hours), dose adjustments may vary greatly. Dose increases may be no more frequent than every three to five days; however, some may require up to 12 days. • Due to the metabolism of methadone, patients with liver impairment may be at risk of accumulating methadone after multiple dosing.
Duragesic (fentanyl)	Transdermal system	Topical	Administration every 72 hours (Some patients may not achieve adequate analgesia using this dosing interval and may require	• Avoid use in patients with severe renal impairment. • Avoid use in patients with severe hepatic impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			systems be applied at 48 hours)	
Exalgo¶ (hydromorphone)	ER tablets	Oral	Once daily	• Moderate renal impairment: start 50% of the usual dose. • Severe renal impairment: start 25% of the usual dose. • Moderate hepatic impairment: start 25% of the usual dose.
Hysingla ER Zohydro ER (hydrocodone bitartrate)	ER capsules and tablets	Oral	Hysingla ER: Once daily Zohydro ER: Every 12 hours	• For severe hepatic impairment, reduce the Hysingla ER dose to 1/2 the usual initial dose and start Zohydro ER at the lowest dose of 10 mg every 12 hours. • Hysingla ER: In moderate to severe renal impairment (including end stage renal disease), reduce the initial dose to 1/2 the usual initial dose.
Levorphanol	Tablets	Oral	Every 6 to 8 hours	
Nucynta ER (tapentadol)	ER tablets	Oral	Twice daily	• Not recommended in patients with severe renal impairment. • Not recommended in patients with severe hepatic impairment. • In patients with moderate hepatic impairment, initiate at 50 mg every 24 hours and do not exceed 100 mg/day.
Opana ER (oxymorphone)‡	ER tablets	Oral	Every 12 hours	• Contraindicated in moderate and severe hepatic impairment.
OxyContin; Xtampza ER (oxycodone)	ER capsules and tablets	Oral	Every 12 hours	• In hepatic impairment, initiate dose at 1/3 to 1/2 the recommended initial dose.
Combination Products				
Embeda (morphine sulfate/ naltrexone)	ER capsules	Oral	Once daily	• Renal dose adjustment may be required in severe renal impairment. • Hepatic dose adjustment may be required in severe hepatic impairment.

*Available only as brand name Kadian
†All Avinza branded products have been removed from the market.
‡Generic products of the pre-reformulated Opana ER are available. The branded versions of Opana ER (pre- and post-reformulation) are no longer available on the market.
§Egalet discontinued the promotion and manufacture of Arymo ER branded products effective September 28, 2018.
¶Availability of branded Exalgo is unclear, but generic products are available.

CONCLUSION

- Opioids have been the mainstay of pain treatment for a number of years, and there is well-documented evidence of their effectiveness. Oral morphine is the standard for comparison for all other opioid agents currently available. There are several long-acting opioid agents available, which are FDA-approved for the treatment of moderate to severe pain in patients requiring around-the-clock analgesia (*Cohen et al 2016*).
  - Levorphanol is indicated for moderate to severe pain where an opioid analgesic is appropriate; however, the FDA-approved indication does not stipulate that patients require around-the-clock, daily dosing for use.
  - Nucynta ER is the only long-acting agent in this class also indicated for neuropathic pain which requires daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.
  - OxyContin has been FDA-approved as an option in pediatric patients, aged ≥ 11 years, for daily, around-the-clock, long term opioid treatment and for which alternative treatment options are inadequate. Unlike adults, pediatric patients must have responded to a minimum opioid daily dose of ≥ 20 mg oxycodone for 5 consecutive days prior to initiating treatment with OxyContin. Although study efficacy and safety data are not rigorous, OxyContin has been prescribed off-label for years within the pediatric population (*FDA Summary: OxyContin 2015*).
- All of the long-acting opioids are classified as Schedule II controlled substances by the FDA, with the exception of transdermal and buccal buprenorphine, which is a Schedule III controlled substance.
- Since 2013, a number of abuse deterrent formulations have come to the market. Although various manufacturers have introduced formulations with properties to deter misuse potential; there are only a few agents that have completed studies supporting the potential to deter abuse and misuse. The only long-acting opioids that meet all requirements and are currently available include OxyContin (oxycodone hydrochloride extended release), Embeda (morphine sulfate/naltrexone), Hysingla ER (hydrocodone bitartrate extended release), Morphabond (morphine sulfate extended release), and Xtampza ER (oxycodone extended release) (*FDA Industry Guidance 2015*). Branded Arymo ER was recently discontinued by the manufacturer, Egalet (*Arymo ER website 2019)*.
- All long-acting opioids are part of the Opioid Analgesic REMS program. In general, all of the long-acting opioids are similar in terms of adverse events, warnings, and contraindications. Methadone-containing products warn of the potential for QTc prolongation and risks associated with an interaction with CYP3A4 inhibitors (or discontinuation of CYP3A4 inducers) is cited within Duragesic, Hysingla ER, OxyContin, Xtampza ER, and Zohydro ER labeling. The main differences among the individual agents and formulations are due to dosing requirements and generic availability.
  - Several generic long-acting opioids exist, including hydromorphone; oxymorphone; levorphanol; fentanyl transdermal systems; methadone tablets, solution, and concentrate; morphine sulfate ER tablets and capsules; and oxycodone.
- Head-to-head trials demonstrate similar efficacy among the agents in the class. Systematic reviews and treatment guidelines from several professional organizations support and recommend opioids as a potential treatment option for various forms of non-cancer and cancer-related pain; however, some meta-analyses in non-cancer pain have not found a clinically meaningful difference between opioids, other non-opioid pain medications, and placebo. No single opioid is recommended over the others (*Busse et al 2018, Chou et al 2015, Finnerup et al 2015, Mesgarpour et al 2014, Stewart et al 2018*).
- Methadone safety guidelines from the 2014 American Pain Society recommend buprenorphine as an alternative to methadone for the treatment of opioid addiction in patients with risk factors or known QTc prolongation (*Chou et al 2014*). Other current clinical guidelines do not state a preference for the use of one long-acting opioid over another for use in moderate to severe pain (*Attal et al 2010, Bril et al 2011, Chou et al 2009, Hochberg et al 2012, Manchikanti et al 2012, Qaseem et al 2017*). However, opioid rotation is recommended if a patient experiences adverse effects from one agent (*Chou et al 2009*). A guideline from the CDC has been published that addresses the use of chronic pain outside of active cancer treatment, palliative care, and end-of-life care; this guideline emphasizes the use of nonpharmacologic and nonopioid therapies when possible, and notes that clinicians should consider opioid therapy only if the expected benefits for both pain and function are anticipated to outweigh risks to the patient (*Dowell et al 2016*).

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Therapeutic Class Overview
Opioids, Short Acting

INTRODUCTION

- Pain originates from somatic or visceral structures. Somatic pain is localized and typically results from injury or disease of the skin, musculoskeletal structures, and joints. Visceral pain arises from internal organ dysfunction or from functional pathology.
- Pain can be acute or chronic. Acute pain often results from injury or inflammation and may have a survival role and assist in the healing process by minimizing re-injury. In contrast, chronic pain, often defined as pain persisting for longer than 3 to 6 months, may be considered a disease in that it serves no useful purpose (*Cohen et al 2016*).
  - A 2016 study estimated that approximately 50 million adults in the United States have chronic pain, and approximately 20 million have high-impact chronic pain (ie, pain that limits life or work activities on most days). Each year, chronic pain contributes to an estimated $560 billion in direct medical costs, lost productivity, and disability programs (*Dahlhamer et al 2018*).
- Pain may be classified as nociceptive or neuropathic pain.
  - Nociceptive pain, including cancer pain, results from an injury or disease affecting somatic structures such as skin, muscle, tendons and ligaments, bone, and joints. It is typically treated with non-opioid analgesics or opioids.
  - Neuropathic pain results from disease or injury to the peripheral or central nervous systems (CNS). It is often treated with adjuvant drugs such as antidepressants and antiepileptics. Opioids are recommended as second- or third-line agents (*Cohen et al 2016*).
- Several pharmacologic and nonpharmacologic options are currently available for the management of pain. Treatment options include pharmacologic treatment, physical medicine, behavioral medicine, neuromodulation, interventional approaches, and surgery. Pharmacologic therapy should not be the sole focus of pain treatment; however, it is the most widely utilized option (*Cohen et al 2016*).
  - Combining different types of treatments, including multiple types of analgesics, may provide an additive analgesic effect without increasing adverse effects (*Cohen et al 2016, The Medical Letter 2013*).
- Major pharmacologic categories used in the management of pain include non-opioid analgesics, tramadol, opioid analgesics (full and partial agonists), alpha-2 (α_2) adrenergic agonists, antidepressants, anticonvulsants, muscle relaxants, N-methyl-d-aspartate (NMDA) receptor antagonists, and topical analgesics. Opioids are available in both short-acting and long-acting or sustained-release formulations (*Cohen et al 2016*).
- Short-acting opioid analgesics are available as single entities and in combination with acetaminophen, aspirin, butalbital, caffeine, carisoprodol, ibuprofen, and naloxone. Acetaminophen, aspirin, and ibuprofen are non-opioid analgesics. Butalbital is a barbiturate, which has anxiolytic and muscle relaxant properties. Caffeine is an analgesic adjuvant, as well as a CNS stimulant. Carisoprodol is a centrally-acting muscle relaxant (*Micromedex 2.0 2019*). Naloxone, when administered orally at the dose available in the combination tablet (0.5 mg) has no pharmacologic activity; however, when administered parenterally at the same dose, it is an effective antagonist to pentazocine and an antagonist to pure opioid analgesics (*Pentazocine and naloxone prescribing information 2016*). The presence of naloxone in this dosage form is intended to prevent the effect of pentazocine if the combination agent is misused by injection.
- In January 2011, the Food and Drug Administration (FDA) recommended that manufacturers of combination products limit the amount of acetaminophen to no more than 325 mg in each dosage form (ie, tablet or capsule) to reduce the risk of liver damage from too much acetaminophen (*FDA Safety Communication 2011*). All products with dosage forms with acetaminophen exceeding 325 mg have since been removed from the market (*FDA Safety Communication 2014*).
- The Controlled Substances Act (CSA) places substances with accepted medical uses into 1 of 4 schedules, with the substances with the highest potential for harm and abuse in Schedule II, and substances with progressively less potential for harm and abuse in Schedules III through V. Substances that are considered Schedule I do not have an accepted medical use.
  - All single-entity agents within this review are Schedule II (C-II) controlled substances except for butorphanol, which is Schedule IV (C-IV).
  - Oxycodone and hydrocodone combination products are C-II controlled substances. The codeine and dihydrocodeine tablet combination products are Schedule III (C-III) controlled substances and liquid products are Schedule V (C-V) controlled substances. Pentazocine/naloxone is a C-IV controlled substance.

- It is important that patients receive appropriate pain treatment with careful consideration of the benefits and risks of treatment options. The use of opioid analgesics presents serious risks, including overdose and opioid use disorder. From 1999 to 2014, there were more than 165,000 deaths due to opioid analgesic overdoses in the United States (*Dowell et al 2016*).
- In March 2016, the Centers for Disease Control and Prevention (CDC) issued a guideline for prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care. The guideline addresses when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, follow-up, and discontinuation; and assessing risks and addressing harms of opioid use. The guideline encourages prescribers to follow best practices for responsible opioid prescribing due to the risks of opioid use (*Dowell et al 2016*).
- In December 2018, the U.S. Department of Health & Human Services (HHS) recommended prescribing or co-prescribing naloxone to all patients who are at risk for opioid overdose, including: patients receiving opioids at a dosage of 50 milligram morphine equivalents (MME) per day or greater; patients with respiratory conditions who are prescribed opioids; patients who have been prescribed benzodiazepines along with opioids; and patients prescribed opioids who have a non-opioid substance use disorder, report excessive alcohol use, or have a mental health disorder (*HHS 2018*).
- This review focuses on short-acting opioid agonists and their use in the treatment of pain. This review does not include injectables, although some medications may be available in this formulation. In addition, immediate-release fentanyl products, tapentadol, and tramadol, are covered in other publications and are not covered in this review.
- The agents included in this review are listed in Table 1 and divided by single entity agents and combination products.
- Medispan Class: Opioid Agonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single Entity Agents	
codeine sulfate*	✔
Demerol (meperidine hydrochloride)	✔
Dilaudid (hydromorphone hydrochloride)	✔
morphine sulfate*	✔
Opana (oxymorphone hydrochloride)	✔
Oxaydo†, Roxicodone, RoxyBond (oxycodone hydrochloride)	✔
butorphanol*	✔
Combination Products	
Apadaz (benzhydrocodone/acetaminophen)	✔ ‡
ASCOMP with Codeine, Fiorinal with Codeine #3 (codeine/butalbital/aspirin/caffeine)	✔
Tylenol with Codeine (acetaminophen/codeine)	✔
codeine/carisoprodol/aspirin*	✔
Endocet, Nalocet, Percocet, Primlev (oxycodone hydrochloride/acetaminophen)	✔
Fioricet with Codeine (codeine/butalbital/acetaminophen/caffeine)	✔
Hycet*, Lorcet, Lorcet HD, Lorcet Plus, Lortab, Norco, Verdrocet, Vicodin, Vicodin ES, Vicodin HP, Xodol*, Zamicet (hydrocodone bitartrate/acetaminophen)	✔
Ibudone (hydrocodone hydrochloride/ibuprofen)	✔
oxycodone hydrochloride/aspirin*	✔
oxycodone hydrochloride/ibuprofen*	✔
pentazocine/naloxone*	✔
Dvorah, Trezix (dihydrocodeine bitartrate/acetaminophen/caffeine)	✔

*Branded product no longer commercially available
†A generic for Oxaydo is not anticipated until 2025.
‡An authorized generic is commercially available.

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications for Single Entity Agents

Indication	butorphanol	codeine	hydromorphone	meperidine	morphine	oxycodone	oxymorphone
Management of mild to moderate pain where treatment with an opioid is appropriate and for which alternative treatments are inadequate		✔					
Management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate	✔		✔	✔	✔	✔	✔

(Prescribing information: butorphanol 2018, codeine 2018, Demerol 2018, Dilaudid 2018, morphine sulfate oral solution 2018, morphine sulfate tablets 2017, Opana 2018, Oxaydo 2018, Roxicodone 2018, RoxyBond 2018)

Table 3. Food and Drug Administration Approved Indications for Combination Products

Indication	acetaminophen/ codeine	benzhydrocodone /acetaminophen	codeine/ butalbital/ acetaminophen/ caffeine	codeine/ butalbital/ aspirin/caffeine	codeine/ carisoprodol/ aspirin	dihydrocodeine/ acetaminophen/ caffeine	hydrocodone/ acetaminophen	hydrocodone/ ibuprofen	oxycodone/ acetaminophen	oxycodone/ aspirin	oxycodone/ ibuprofen	pentacozine/ naloxone
Relief of discomfort associated with acute, painful musculoskeletal conditions in adults					✔							
Relief of mild to moderate pain	✔											
Relief of tension or muscle contraction headache			✔	✔								
Short-term (< 7 days) management of acute to moderate pain											✔	
Short-term (< 10 days) management of acute pain								✔				
Short-term (≤ 14 days) management of acute pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate		✔										
Management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate						✔	✔		✔	✔		✔

(Prescribing information: Apadaz 2018, codeine/carisoprodol/aspirin 2018, Dvorah 2018, Fioricet with Codeine 2018, Fiorinal with codeine 2018, Ibudone 2017, Nalocet 2018, oxycodone/aspirin 2018, oxycodone/ibuprofen 2017, pentazocine/naloxone 2016, Percocet 2018, Primlev 2018, Trezix 2017, Tylenol with codeine 2018, Vicodin 2017)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Overall, clinical trials have demonstrated opioids to be more efficacious than placebo for both pain and functional outcomes in patients with nociceptive or neuropathic pain (*Furlan et al 2006*). However, some meta-analyses in non-cancer pain have not found a clinically meaningful difference between opioids, other non-opioid pain medications, and placebo (*Busse et al 2018, Stewart et al 2018*).
  - A systematic review and meta-analysis of 96 randomized controlled trials examined the use of opioids in chronic non-cancer pain. Opioid use was associated with reduced pain compared to placebo (weighted mean difference [WMD], -0.69 cm on a 10-cm visual analog scale; 95% confidence interval [CI], -0.82 to -0.56 cm; $p < 0.001$), as well as improved physical functioning as measured by the 36-item Short Form physical component score (SF-36 PCS; WMD, 2.04 points on a 100-point scale; 95% CI, 1.41 to 2.68 points; $p < 0.001$). However, the minimally important difference (pain, 1 cm; SF-36 PCS, 5 points) was not reached for either parameter. Opioids were also associated with increased vomiting vs placebo (5.9% vs 2.3%). When opioids were compared to nonsteroidal anti-inflammatory drugs (NSAIDs), similar improvements in pain and physical functioning were observed (pain WMD for opioids vs NSAIDs, -0.60 cm; 95% CI, -1.54 to 0.34; physical functioning WMD for opioids vs NSAIDs, -0.90 points; 95% CI, -2.69 to 0.89) *(Busse et al 2018).* Similarly, another systematic review and meta-analysis of 29 studies found that opioids and other commonly used classes of pain medication produced similar percent reductions in osteoarthritis pain (opioids, 35.4%; oral NSAIDs, 34.3%; topical NSAIDs, 40.9%; acetaminophen, 32.5%; cyclooxygenase-2 [COX-2] inhibitors, 36.9%) *(Stewart et al 2018).*
- Systematic reviews and meta-analyses have demonstrated similar safety and levels of analgesia between hydromorphone, morphine, oxycodone and oxymorphone in the management of cancer, neuropathic, rheumatoid arthritis, osteoarthritis, non-cancer, and acute pain (*Bekkering et al 2011, Caraceni et al 2011, Felden et al 2011, McNicol et al 2005, McNicol et al 2013, Pigni et al 2011, Quigley et al 2002, Reid et al 2006, Wiffen et al 2013, Whittle et al 2011*).
- The results of randomized controlled trials have generally demonstrated a comparable level of analgesia between codeine/acetaminophen, hydrocodone/acetaminophen, hydrocodone/ibuprofen and oxycodone/acetaminophen in the management of pain (*Litkowski et al 2005, Marco et al 2005, Palangio et al 2000[a], Palangio et al 2000[b], Rodriguez et al 2007, Smith et al 2004*).
- Head-to-head trials involving butalbital-containing products and oxycodone/aspirin are not available.
- In April 2017, the FDA approved RoxyBond, a new immediate-release oxycodone formulation. It was approved via the 505(b)(2) pathway with no new clinical efficacy studies. RoxyBond is the first immediate-release opioid analgesic approved with labeling describing its abuse-deterrent properties consistent with the FDA's 2015 Guidance for Industry. The labeling states that there is *in vitro* data demonstrating that RoxyBond has physicochemical properties expected to make abuse via injection difficult. Data from a clinical abuse potential study, along with support from *in vitro* data, also indicate that RoxyBond has physicochemical properties that are expected to reduce abuse by the intranasal route of administration. However, abuse by the intranasal, oral, and intravenous route is still possible (*Roxybond FDA Advisory Committee Briefing Document 2017, RoxyBond Prescribing information 2018).*
  - The manufacturer of Oxaydo (oxycodone) also conducted abuse deterrent studies; however the FDA labeling states that there is no evidence that Oxaydo has reduced abuse liability compared to immediate-release oxycodone (*Oxaydo Prescribing information 2018*).
- In February 2018, the FDA approved Apadaz (benzhydrocodone/acetaminophen) via the 505(b)(2) pathway with no new clinical efficacy studies. Benzhydrocodone is an inactive prodrug of hydrocodone and is converted rapidly to hydrocodone by enzymes in the intestinal tract. While Apadaz may have some theoretical benefit in preventing drug manipulation and deterring opioid abuse, there was insufficient *in vitro* and human abuse potential trial data to support an abuse deterrent claim in the labeling *(Apadaz FDA Advisory Committee Briefing Document 2016, Apadaz Prescribing information 2018).*
- A literature search failed to retrieve a significant amount of clinical trial information regarding the safety and effectiveness of pentazocine/naloxone and butorphanol. Specifically, no clinical trial information was obtained for pentazocine/naloxone.
- Butorphanol nasal solution has demonstrated effectiveness and safety in the management of several etiologies of pain including dental pain, postoperative uvulopalatopharyngoplasty pain, postepisiotomy pain, and anal surgery. Open-label trials have demonstrated that administration of butorphanol nasal solution reduces pain and is well tolerated (*Ladov et al 2000, Madani 2000*). Randomized, placebo-controlled trials demonstrating the effectiveness of butorphanol nasal solution have provided inconsistent results (*Joyce et al 1993, Wermeling et al 2005*). In one study, female patients with moderate to severe postepisiotomy pain achieved superior pain relief with butorphanol nasal solution compared to

placebo; however, no difference was observed in another trial evaluating dental pain. Specifically, no significant differences in summed pain intensity difference (SPID) values through 6 hours post-dose and Total Pain Relief values at 6 hours post-dose were observed between butorphanol nasal solution and placebo (*Wermeling et al 2005*). Additionally, when compared to intramuscular meperidine, treatment with butorphanol nasal solution achieved comparable pain relief but had higher incidences of somnolence, dizziness, and nausea (*Mai et al 2009*). Butorphanol nasal spray also provided superior pain relief to the combination of butalbital, caffeine, aspirin, and codeine, after the first 2 hours when given for migraine pain (*Goldstein et al 1998*).

CLINICAL GUIDELINES

- Clinical guidelines have been published that address back pain, cancer pain, neuropathic pain and osteoarthritis pain. These guidelines make recommendations for the specific place in therapy for opioids as a class but do not make any recommendations for the use of one agent over another (*American Academy of Orthopaedic Surgeons [AAOS] 2013, Attal et al 2010, Bril et al 2011, Pop-Busui et al 2017, Chou et al 2007, Chou et al 2009, Hochberg et al 2012, MacFarlane et al, 2017, Manchikanti et al 2017, Qaseem 2017, The Medical Letter 2013*). Additional guidelines are available on codeine use in patients with various cytochrome P450 (CYP) 2D6 phenotypes (*Crews et al 2014*).

- In March 2016, the CDC issued a guideline for prescribing opioids for chronic pain outside of active cancer treatment, palliative care, and end-of-life care. The guideline addresses when to initiate or continue opioids for chronic pain; opioid selection, dosage, duration, follow-up, and discontinuation; and assessing risk and addressing harms of opioid use. Recommendations in the CDC guideline include the following (*Dowell et al 2016*):
  - Non-pharmacologic therapy and non-opioid pharmacologic therapy are preferred for chronic pain. Clinicians should consider opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks to the patient. If opioids are used, they should be combined with non-pharmacologic therapy and non-opioid pharmacologic therapy, as appropriate (category A, evidence 3).
  - Before starting opioid therapy for chronic pain, clinicians should establish treatment goals with all patients, including realistic goals for pain and function, and should consider how therapy will be discontinued if benefits do not outweigh risks. Clinicians should continue opioid therapy only if there is clinically meaningful improvement in pain and function that outweighs risks to patient safety (category A, evidence 4).
  - Before starting and periodically during opioid therapy, clinicians should discuss with patients known risks and realistic benefits of opioid therapy and patient and clinician responsibilities for managing therapy (category A, evidence 3).
  - When starting opioid therapy for chronic pain, clinicians should prescribe immediate-release opioids instead of extended-release/long-acting (ER/LA) opioids (category A, evidence 4).
  - When opioids are started, clinicians should prescribe the lowest effective dosage. Clinicians should use caution when prescribing opioids at any dosage, should carefully reassess evidence of individual benefits and risks when increasing dosage to ≥50 morphine milligram equivalents (MME)/day, and should avoid increasing dosage to ≥90 MME/day or carefully justify a decision to titrate dosage to ≥90 MME/day (category A, evidence 3).
  - Long-term opioid use often begins with treatment of acute pain. When opioids are used for acute pain, clinicians should prescribe the lowest effective dose of immediate-release opioids and should prescribe no greater quantity than needed for the expected duration of pain severe enough to require opioids. Three days or less will often be sufficient; more than 7 days will rarely be needed (category A, evidence 4).
  - Clinicians should evaluate benefits and harms with patients within 1 to 4 weeks of starting opioid therapy for chronic pain or of dose escalation. Clinicians should evaluate benefits and harms of continued therapy with patients every 3 months or more frequently. If benefits do not outweigh harms of continued opioid therapy, clinicians should optimize other therapies and work with patients to taper opioids to lower dosages or to taper and discontinue opioids (category A, evidence 4).
  - Before starting and periodically during continuation of opioid therapy, clinicians should evaluate risk factors for opioid-related harms. Clinicians should incorporate into the management plan strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose, such as history of overdose, history of substance use disorder, higher opioid dosages (≥50 MME/day), or concurrent benzodiazepine use, are present (category A, evidence 4).
  - Clinicians should review the patient's history of controlled substance prescriptions using state prescription drug monitoring program (PDMP) data to determine whether the patient is receiving opioid dosages or dangerous combinations that put him or her at high risk for overdose. Clinicians should review PDMP data when starting opioid

therapy for chronic pain and periodically during opioid therapy for chronic pain, ranging from every prescription to every 3 months (category A, evidence 4).
- When prescribing opioids for chronic pain, clinicians should use urine drug testing before starting opioid therapy and consider urine drug testing at least annually to assess for prescribed medications as well as other controlled prescription drugs and illicit drugs (category B, evidence 4).
- Clinicians should avoid prescribing opioid pain medication and benzodiazepines concurrently whenever possible (category A, evidence 3).
- Clinicians should offer or arrange evidence-based treatment (usually medication-assisted treatment with buprenorphine or methadone in combination with behavioral therapies) for patients with opioid use disorder (category A, evidence 2).

Category of Recommendations:
- Category A: Applies to all persons; most patients should receive the recommended course of action.
- Category B: Individual decision making needed; different choices will be appropriate for different patients. Clinicians help patients arrive at a decision consistent with patient values and preferences and specific clinical situations.

Evidence Type:
- Type 1: Randomized clinical trials or overwhelming evidence from observational studies.
- Type 2: Randomized clinical trials with important limitations, or exceptionally strong evidence from observational studies.
- Type 3: Observational studies or randomized clinical trials with notable limitations.
- Type 4: Clinical experience and observations, observational studies with important limitations, or randomized clinical trials with several major limitations.

- In February 2017, the American College of Physicians (ACP) published clinical practice guidelines for noninvasive treatments of acute, subacute, and chronic low back pain. The guidelines state that clinicians should only consider opioids as an option in patients who have failed other treatments (eg, non-pharmacological treatment, nonsteroidal anti-inflammatory drugs [NSAIDs], tramadol, duloxetine) and only if the potential benefits outweigh the risks for individual patients and after a discussion of known risks and realistic benefits with patients (*Qaseem et al 2017*).
  - There is moderate-quality evidence that show strong opioids (tapentadol, morphine, hydromorphone, and oxymorphone) are associated with a small short-term improvement in pain scores (about 1 point on a pain scale of 0 to 10) and function compared with placebo. There is moderate-quality evidence that show no differences among different long-acting opioids for pain or function, and low-quality evidence shows no clear differences in pain relief between long- and short-acting opioids.

- In February 2017, the American Society of Interventional Pain Physicians (ASIPP) also published new practice guidelines for responsible, safe, and effective prescription opioids for chronic non-cancer pain. Similar to other guidelines, they do not recommend one opioid agent over the others. They do provide the following recommendations and conclusions for long-term opioid therapy (*Manchikanti et al 2017*):
  - Initiate opioid therapy with low dose, short-acting drugs, with appropriate monitoring (Evidence: Level II; Strength of Recommendation: Moderate).
  - Consider up to 40 MME as low dose, 41 to 90 MME as a moderate dose, and greater than 91 MME as high dose (Evidence: Level II; Strength of Recommendation: Moderate).
  - Avoid long-acting opioids for the initiation of opioid therapy (Evidence: Level I; Strength of Recommendation: Strong).
  - Understand and educate patients of the effectiveness and adverse consequences (Evidence: Level I; Strength of Recommendation: Strong).
  - There is similar effectiveness for long-acting and short-acting opioids with increased adverse consequences of long-acting opioids (Evidence: Level I-II; Strength of recommendation: Moderate to strong).
  - Recommend long-acting or high dose opioids only in specific circumstances with severe intractable pain (Evidence: Level I; Strength of Recommendation: Strong).

- Clinical guidelines provide little information about the role of partial opioid agonists in the treatment of pain (*Chou et al 2009, Hegmann 2014, Medical Letter 2013*). Unlike full agonists, the partial agonists have a ceiling on their analgesic effects, and may precipitate withdrawal if given to patients dependent on full opioid agonists (*Medical Letter 2013*).

- The two recently published clinical practice guidelines from the ACP and the ASIPP do not discuss the place in therapy of pentazocine and butorphanol.
- Guidelines from the Society of Critical Care Medicine note that opioids are a mainstay of pain management in most intensive care unit settings: however, they recommend a multimodal approach to analgesia, using non-opioid medications as adjunctive therapy in order to decrease opioid use and optimize pain control. Opioids used for procedural pain management should be used at the lowest effective dose (*Devlin et al 2018*). Similarly, an expert consensus guideline on opioid prescribing in surgical procedures from the American College of Surgeons recommends the maximization of non-opioid analgesia (ie, ibuprofen). It also provides recommendations on the number of oxycodone 5 mg tablets to prescribe after surgery, depending on the type of surgical procedure performed. The maximum recommended number of tablets for any surgical procedure covered in the guideline is 20 tablets, but in some procedures, it is recommended that no opioids be prescribed upon discharge (*Overton et al 2018*).

SAFETY SUMMARY

- In general, opioids are contraindicated in patients with a hypersensitivity to any component or the active ingredient. They should not be administered to patients with significant respiratory depression, acute or severe bronchial asthma, or suspected or documented paralytic ileus.
- Short-acting opioids that contain acetaminophen, codeine, dihydrocodeine, and ibuprofen carry boxed warnings.
  - Acetaminophen has been associated with acute liver failure, at times resulting in liver transplant and death. Most of the cases of liver injury were associated with the use of acetaminophen at doses that exceeded 4000 mg per day, and often involved more than one acetaminophen-containing product.
  - Respiratory depression and death have occurred in children who received codeine following tonsillectomy and/or adenoidectomy and had evidence of being ultra-rapid metabolizers of codeine due to a CYP 2D6 polymorphism. The use of codeine is contraindicated for postoperative pain control in pediatric patients undergoing tonsillectomy or adenoidectomy.
  - Cardiovascular risk may be increased with the use of NSAIDs, including serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk.
  - Gastrointestinal risk is increased with the use of NSAIDs including serious gastrointestinal adverse events (e.g., bleeding, ulceration, and perforation of the stomach or intestines), which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events.
- Adverse events may limit the use of opioid analgesics. The most frequently reported adverse events are light-headedness, dizziness, sedation, nausea, and vomiting (*Micromedex 2.0 2019*).
- In March 2016, the FDA announced label changes and enhanced warnings for all opioids (*FDA Safety Communication 2016*):
  - Among the changes for immediate-release opioids, the FDA is requiring a new boxed warning about the serious risks of misuse, abuse, addiction, overdose, and death. The boxed warning includes a precaution that chronic maternal use of opioids during pregnancy can result in neonatal opioid withdrawal syndrome. Updated indications clarify that immediate-release opioids should be reserved for pain severe enough to require opioid treatment and for which alternative treatment options are inadequate or not tolerated. Updates to the dosing information provide clearer instructions regarding drug administration and patient monitoring, including initial dosage, dosage changes during therapy, and a warning not to abruptly stop treatment in a physically dependent patient. Similar labeling changes were required for ER/LA opioids in 2013.
  - In addition, updated labeling is required for all opioids to include safety information about the risk of adrenal insufficiency; androgen deficiency; and drug interactions with antidepressants and migraine medications that can result in serotonin syndrome. The FDA has issued a drug safety communication describing these risks (*FDA Safety Communication 2016*).
- In August 2016, the FDA announced the addition of boxed warnings to opioid-containing products regarding the serious risks including death when used in combination with benzodiazepines or other drugs that depress the CNS, including alcohol (*FDA Safety Communication 2016*).
  - The FDA recommends that for patients who require concomitant treatment with opioids and benzodiazepines or other CNS depressants due to inadequate treatment alternatives, the dosage and duration of each drug should be limited to the lowest dose possible required for therapeutic effect.

- In September 2017, the FDA notified manufacturers of immediate-release opioid analgesics intended for use in the outpatient setting that these medications will be subject to more stringent requirements under a Risk Evaluation and Mitigation Strategy (REMS), similar to the requirements already in place for extended-release/long-acting opioid analgesics (*Gottlieb 2017*). On September 18, 2018, the long-acting opioid REMS was modified to include all immediate-release opioids as well. This program, now known as the Opioid Analgesic REMS program, strongly encourages healthcare providers to complete an approved training program on opioid analgesics. The goal of the REMS is to ensure that benefits of opioid analgesics outweigh the risks of addiction, abuse, and misuse *(FDA REMS 2018)*.
- The administration of pentazocine and butorphanol is not recommended in patients who are dependent on opioids.
- Naloxone when administered orally at the dose available in the combination tablet (0.5 mg) has no pharmacologic activity; however, when administered parenterally at the same dose, it is an effective antagonist to pentazocine and an antagonist to pure opioid analgesics. The presence of naloxone in this dosage form is intended to prevent the effect of pentazocine if the combination agent is misused by injection.
- Other warnings are similar to other opioids and include risk of abuse, misuse, diversion, respiratory depression, and adverse events in patients with acute head injury.
- Pentazocine and butorphanol should not be used with other substances that may cause CNS depression such as alcohol and sedatives.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single Entity Agents				
codeine sulfate	Tablets	Oral	Every 4 hours as needed	
Demerol, (meperidine hydrochloride)	Solution, tablets	Oral	Every 3 to 4 hours as needed	
Dilaudid (hydromorphone hydrochloride)	Solution, tablets	Oral	Solution: Every 3 to 6 hours as required Tablet: Every 4 to 6 hours as needed	
morphine sulfate	Solution, tablet	Oral	Every 4 hours as needed for pain	
Opana (oxymorphone hydrochloride)	Tablets	Oral	Every 4 to 6 hours as needed	• Contraindicated in moderate and severe hepatic impairment
Oxaydo, Roxicodone, RoxyBond (oxycodone hydrochloride)	Capsules, oral concentrate, solution, tablets, abuse-deterrent tablets	Oral	Every 4 to 6 hours as needed	
Butorphanol	Nasal solution	Intranasal	1 mg administered as 1 spray in 1 nostril; if adequate pain relief is not achieved within 60 to 90 minutes, an additional 1 mg dose may be given; the initial dose sequence may be repeated in 3 to 4 hours as required	
Combination Products				
Apadaz (benzhydrocodone/ acetaminophen)	Tablets	Oral	Every 4 to 6 hours as needed	
ASCOMP with codeine, Fiorinal with codeine #3	Capsules	Oral	Every 4 hours	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
(codeine/ butalbital/ aspirin/caffeine)				
Tylenol-codeine (codeine/ acetaminophen)	Solution, tablets	Oral	Every 4 hours as needed	
codeine/ carisoprodol/ aspirin	Tablets	Oral	Four times daily as needed	• Maximum duration of use is up to 2 or 3 weeks.
Endocet, Nalocet, Percocet, Primlev (oxycodone hydrochloride/ acetaminophen)	Solution, tablets	Oral	Every 6 hours as needed	
Fioricet with codeine (codeine/ butalbital/ acetaminophen/ caffeine)	Capsules	Oral	Every 4 hours as needed	
Hycet*, Lorcet, Lorcet HD, Lorcet Plus, Lortab, Norco, Verdrocet, Vicodin, Vicodin ES, Vicodin HP, Xodol*, Zamicet (hydrocodone bitartrate/acetaminophen)	Solution, tablets	Oral	Every 4 to 6 hours as needed	
Ibudone (hydrocodone hydrochloride/ibuprofen)	Tablets	Oral	Every 4 to 6 hours as needed	
oxycodone hydrochloride and aspirin	Tablets	Oral	Every 6 hours as needed	• Avoid use with severe renal impairment. • Avoid use with severe hepatic impairment.
oxycodone hydrochloride and ibuprofen	Tablets	Oral	Every 6 hours as needed	
pentazocine/naloxone	Tablet	Oral	Every 3 to 4 hours	
Dvorah, Trezix (dihydrocodeine bitartrate/ acetaminophen/ caffeine)	Capsules, tablets	Oral	Every 4 hours as needed	

(*Micromedex 2.0 2019*)

*Branded product no longer commercially available.

See the current prescribing information for full details

CONCLUSION

- Pain is one of the most common and debilitating patient complaints, with persistent pain having the potential to lead to functional impairment and disability, psychological distress, and sleep deprivation (*Cohen et al 2016*).
- Opioids have been the mainstay of pain treatment for a number of years, and there is well-documented evidence of their effectiveness. Oral morphine is the standard for comparison for all other opioid agents currently available. There are several short-acting opioids that are available as single entity agents and combination products for the treatment of pain (*Cohen et al 2016*).
- As a class, opioid analgesics encompass a group of naturally occurring, semisynthetic, and synthetic drugs that stimulate opioid receptors and effectively relieve pain without producing loss of consciousness. These agents primarily

produce intense analgesia via their full and partial agonist actions at mu receptors, which are found in large numbers within the CNS (*Cohen et al 2016, Micromedex 2.0 2019*).

- Short-acting opioid analgesics are available as single entities and in combination with acetaminophen, aspirin, butalbital, caffeine, naloxone, and ibuprofen. Acetaminophen, aspirin, and ibuprofen are non-opioid analgesics. Butalbital is a barbiturate, which has anxiolytic and muscle relaxant properties. Caffeine is an analgesic adjuvant, as well as a CNS stimulant. Carisoprodol is a centrally-acting muscle relaxant (*Micromedex 2.0 2019*). Naloxone, when administered orally at the dose available in the combination tablet (0.5 mg) has no pharmacologic activity; however, when administered parenterally at the same dose, it is an effective antagonist to pentazocine and an antagonist to pure opioid analgesics (*Pentazocine and naloxone prescribing information 2016*).
- Overall, clinical trials have demonstrated opioids to be more efficacious than placebo for both pain and functional outcomes in patients with nociceptive pain, neuropathic pain, or fibromyalgia (*Furlan et al 2006*). However, some meta-analyses in non-cancer pain have not found a clinically meaningful difference between opioids, other non-opioid pain medications, and placebo (*Busse et al 2018, Stewart et al 2018*).
- Systematic reviews and meta-analyses have demonstrated similar safety and level of analgesia between hydromorphone, morphine, oxycodone, and oxymorphone in the management of cancer, neuropathic, rheumatoid arthritis, osteoarthritis, non-cancer, and acute pain (*Bekkering et al 2011, Caraceni et al 2011, Felden et al 2011, McNicol et al 2005, McNicol et al 2013, Pigni et al 2011, Quigley et al 2002, Reid et al 2006, Wiffen et al 2013, Whittle et al 2011*).
- The results of randomized controlled trials have generally demonstrated a comparable level of analgesia between codeine/acetaminophen, hydrocodone/acetaminophen, hydrocodone/ibuprofen, and oxycodone/acetaminophen in the management of pain (*Litkowski et al 2005, Marco et al 2005, Palangio et al 2000[a], Palangio et al 2000[b], Rodriguez et al 2007, Smith et al 2004*).
- As a rule, opioids are contraindicated in patients with a hypersensitivity to the active ingredient or any component, respiratory depression, acute or severe bronchial asthma, or suspected or documented paralytic ileus. Opioids have an associated abuse potential and can cause cardiovascular effects, respiratory depression and significant CNS depression, especially when used with other CNS depressants. The most frequently reported adverse events are light-headedness, dizziness, sedation, nausea, and vomiting (*Micromedex 2.0 2019*).
- Clinical guidelines have been published that address back pain, cancer pain, neuropathic pain, and osteoarthritis pain. These guidelines make recommendations for the specific place in therapy for opioids as a class but do not make any recommendations for the use of one agent over another *(AAOS 2013, Attal et al 2010, Bril et al 2011, Pop-Busui et al 2017, Chou et al 2007, Chou et al 2009, Hochberg et al 2012, MacFarlane et al, 2017, Manchikanti, 2017, Qaseem 2017, The Medical Letter 2013*). Additional guidelines are available on codeine use in patients with various CYP 2D6 phenotypes (*Crews et al 2014*). A guideline from the CDC has recently been published that addresses the use of chronic pain outside of active cancer treatment, palliative care, and end-of-life care; this guideline emphasizes the use of non-pharmacologic and non-opioid therapies when possible, and notes that clinicians should consider opioid therapy only if the expected benefits for both pain and function are anticipated to outweigh risks to the patient (*Dowell et al 2016*). Guidelines from the Society of Critical Care Medicine note that opioids are a mainstay of pain management in most intensive care settings: however, they recommend a multimodal approach to analgesia, using non-opioid medications as adjunctive therapy in order to decrease opioid use and optimize pain control. Opioids used for procedural pain management should be used at the lowest effective dose (*Devlin et al 2018*). Similarly, an expert consensus guideline on opioid prescribing in surgical procedures from the American College of Surgeons recommends the maximization of non-opioid analgesia (ie, ibuprofen), and provides recommendations on the number of oxycodone 5 mg tablets to prescribe after surgery, depending on the type of surgical procedure performed (*Overton et al 2018*).
- Limited clinical information regarding the safety and effectiveness of opioid partial agonists within this review is available within the literature, and data are particularly lacking for pentazocine/naloxone. Some clinical trial data are available to demonstrate the effectiveness and safety of butorphanol nasal solution. Clinical guidelines provide little information about the role these agents play in the treatment of pain (*Chou et al 2009, Dowell et al 2016, Hegmann et al 2014, Manchikanti et al 2017, Medical Letter 2013, Qaseem et al 2017*). Unlike full agonists, the partial agonists have a ceiling on their analgesic effects, and may precipitate withdrawal if given to patients dependent on full opioid agonists (*Medical Letter 2013*).

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Therapeutic Class Overview
Inhaled Aminoglycosides

INTRODUCTION

- Cystic fibrosis (CF) is the most common fatal genetic disease, affecting approximately 29,000 patients in the United States (U.S.) (*Hamed et al 2017, National Institutes of Health 2013*). It is caused by mutations in the *CFTR* gene, which encodes for the CFTR protein. This protein acts as an ion channel regulating salt and fluid homeostasis, and defects are associated with thickened secretions, obstruction, and damage to several organs (*Ong et al 2016*). Respiratory manifestations are a significant feature of the disease, and respiratory failure is the most common cause of death in patients who do not receive a lung transplant (*Elborn 2016*).
  - CF is an autosomal recessive disorder; 2 copies of an abnormal gene must be present for the disease to develop (*Elborn 2016*). Patients may have 2 copies of the same mutation (homozygous) or 2 different mutations (heterozygous) (*Ong et al 2016*). Approximately 2000 mutations have been identified in the *CFTR* gene, and more than 200 of these mutations have been confirmed to cause CF (*Quon et al 2016*). In general, these mutations either reduce the amount of CFTR protein that reaches the cell membrane surface or reduce the function of CFTR as a chloride channel (*Egan 2016*).
  - There are 6 known classes of mutations that can cause CF. Classes I through III are associated with minimal CFTR function and most patients with these mutations have a severe CF phenotype (pancreatic insufficient and more severe lung disease). In contrast, class IV and V mutations are associated with some residual CFTR function and a milder phenotype (pancreatic sufficient and improved pulmonary outcomes and survival). Reports on the risk level for class VI mutations vary (*Egan 2016, Elborn 2016, Sosnay et al 2016*).
- Treatment of CF has traditionally been limited to addressing disease manifestations in specific organs (*Quon et al 2016*).
  - Inhaled dornase alfa, hypertonic saline, and mannitol have been used to enhance airway mucociliary clearance, while oral macrolide antibiotics and high dose ibuprofen have been used to reduce inflammation (*Quon et al 2016*).
  - Inhaled antibiotics have been commonly used to treat persistent airway infection with *Pseudomonas aeruginosa*, which contributes to lung damage in patients with CF; a reduction of bacterial load in the lungs decreases inflammation and the deterioration of lung function (*Smith et al 2018*).
  - More recently, CFTR modulators have been made available that act on the basic defect(s) in CFTR function; these include Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), and Symdeko (tezacaftor/ivacaftor) (*Drugs@FDA 2018, Elborn 2016*). However, not all CF patients are eligible for treatment with CFTR modulators, and these products are used in conjunction with traditional therapies in patients who are eligible.
  - The 2013 CF Foundation (CFF) guidelines recommend the inhaled antibiotics for patients > 6 years of age with CF to improve lung function, improve quality of life, and/or reduce exacerbations, including chronic inhaled tobramycin for patients with mild, moderate, or severe disease with persistent colonization of *P. aeruginosa* (*Mogayzel et al 2013*).
- This review includes the inhaled aminoglycoside antibiotic, tobramycin, indicated for the treatment of CF patients with *P. aeruginosa*. Inhaled tobramycin is available in a variety of formulations and may be administered via nebulization or dry powder inhalation.
- Medispan classes: Anti-Infective Agents – Aminoglycosides (tobramycin)

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Bethkis (tobramycin)	-
Kitabis Pak (tobramycin)	-
Tobi (tobramycin)	✔
Tobi Podhaler (tobramycin)	-

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drug*	Management of CF patients with *P. aeruginosa*†
Bethkis (tobramycin)	✔ (age ≥ 6 years)
Kitabis Pak (tobramycin)	✔ (age ≥ 6 years)
Tobi (tobramycin)	✔ (age ≥ 6 years)
Tobi Podhaler (tobramycin)	✔ (age ≥ 6 years)

Abbreviations: CF = cystic fibrosis, FEV_1 = forced expiratory volume in 1 second, $ppFEV_1$ = percent predicted FEV_1
* For Bethkis, safety and efficacy have not been demonstrated in patients with $ppFEV_1$ < 40% or > 80%; for Tobi Podhaler, safety and efficacy have not been demonstrated in patients with $ppFEV_1$ < 25% or > 80%; and for Kitabis Pak and Tobi, safety and efficacy have not been demonstrated in patients with $ppFEV_1$ < 25% or > 75%.
† Safety and efficacy have not been demonstrated in patients colonized with *Burkholderia cepacia.*

(*Prescribing information: Bethkis 2017, Kitabis Pak 2014, Tobi 2015, Tobi Podhaler 2015*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- A systematic review and meta-analysis of 18 trials (N = 3042), including 12 trials with tobramycin, evaluated the effects of long-term inhaled antibiotic therapy in patients with CF on clinical outcomes, quality of life, and adverse events (*Smith et al 2018*).
  - There was no subgroup analysis of individual drugs or combinations due to the small number of trials, different duration of trials, different methods of expressing outcome results, and absence of variance in results.
  - Results showed that treatment with inhaled antibiotics improved lung function (4 trials; n = 814) and reduced the frequency of exacerbations (3 trials; n = 946) vs placebo. There were insufficient data to determine an effect on nutritional outcomes, survival, or quality of life.
    - Of the 8 trials that compared different inhaled antibiotics, 1 trial (N = 273; *Assael et al 2013*) demonstrated that aztreonam improved lung function significantly more than tobramycin, but the method of defining the outcome was different vs the remaining trials, and patients were exposed to tobramycin for a long period. No significant differences were found in the remaining trials with regard to lung function.
  - Important adverse events related to the treatment were uncommon, but were less common with tobramycin vs other antibiotics.
  - Overall, the analysis determined that treatment with inhaled anti-pseudomonal antibiotics likely improved lung function and reduced exacerbation rates; however, the pooled estimates of the level of benefit were very limited. The best evidence was for inhaled tobramycin.
- A systematic review of 7 trials (N = 744) evaluated whether antibiotic treatment of early *P. aeruginosa* infection in patients with CF resulted in clinical improvements, and whether treatment with any particular antibiotic strategy (ie, combinations of inhaled, oral or intravenous antibiotics) was superior compared to other strategies or placebo (*Langton Hewer et al 2017*).
  - Most trials included inhaled tobramycin as a comparator.
  - The analysis determined that nebulized antibiotics, alone or in combination with oral antibiotics, were better vs no treatment for early infection with *P. aeruginosa*, and eradication may be sustained for up to 2 years.
  - There was insufficient evidence to determine whether antibiotic treatment for the eradication of early *P. aeruginosa* decreased mortality or morbidity, improved quality of life, or was associated with adverse events vs placebo or standard treatment.
  - Overall, there was insufficient evidence to state which antibiotic strategy should be used for the eradication of early *P. aeruginosa* infection in patients with CF.

- A network meta-analysis of 11 randomized controlled trials evaluated the effectiveness of inhaled antibiotics, including Bethkis , Tobi , tobramycin inhalation powder (TIP), and aztreonam, for the treatment of chronic *P. aeruginosa* lung infection in patients with CF (*Littlewood et al 2012*).
  - The analysis concluded that the studied antibiotics had comparable efficacies for the treatment of chronic *P. aeruginosa* lung infection in CF, as measured by improvements in change from baseline in percent predicted forced expiratory volume in 1 second (ppFEV$_1$), *P. aeruginosa* sputum density, and acute exacerbations.
  - The analyses suggested that all treatments improved clinical outcomes vs placebo. Treatment with the inhaled tobramycin formulations provided potentially clinically meaningful improvement in lung function over inhaled aztreonam, but differences were not statistically significant.
  - Prior exposure to an active drug was identified as a key factor affecting outcomes, yet, this was not typically reported in trials as a predictive factor. Most trials involved the first use of the active drug, and therefore had a population who was naïve to the active drug.
- Multiple clinical trials have shown that the efficacy of tobramycin inhalation solution (TIS) was significantly better vs placebo, as demonstrated by improved FEV$_1$, reduced sputum *P. aeruginosa* density, decreased relative risk of hospitalization for respiratory and other reasons, and decreased use of other antibiotics (*Chuchalin et al 2007, Lenoir et al 2007, Máiz et al 2013, Mazurek et al 2011, Murphy et al 2004, Ramsey et al 1999, Quittner and Buu 2002*).
  - Reported improvements in health-related quality of life (HRQoL) were significantly more likely in patients treated with TIS vs placebo, and ppFEV$_1$ was a significant predictor of HRQoL improvement (*Quitner and Buu 2002*).
  - A safety and efficacy trial determined that treatment with Bethkis nebulization solution 300 mg/4 mL demonstrated similar improvement in ppFEV$_1$ over 8 weeks of treatment compared with Tobi 300 mg/5 mL nebulization solution (*Mazurek et al 2014*). Lung function improvement with Bethkis continued throughout a 48-week extension phase, and was also associated with a favorable tolerability profile.
- TIP delivered via the Tobi Podhaler has been shown to have similar efficacy vs TIS; long-term safety and efficacy studies have shown that treatment with TIP was well tolerated with no unexpected adverse events and had sustained efficacy in patients with CF (*Hamed et al 2017, Máiz et al 2013, Sommerwerck et al 2016*).
  - The Phase 3 EVOLVE and EDIT clinical trials demonstrated that treatment with Tobi Podhaler significantly improved ppFEV$_1$ vs placebo at 28 days, and also reduced sputum *P. aeruginosa* density, respiratory-related hospitalizations, and antipseudomonal antibiotic use (*Galeva et al 2013, Konstan et al 2011a*). Improvements in lung function and a decrease in sputum *P. aeruginosa* density from baseline were sustained in patients treated with up to 7 cycles of TIP over a period of at least 1 year (*Hamed et al 2017, Konstan et al 2016*).
  - The Phase 3 open-label EAGER trial demonstrated similar increases in ppFEV$_1$ and mean reduction in sputum *P. aeruginosa* density over 24 weeks (3 cycles) of treatment with TIP vs TIS (*Konstan et al 2011b*).
- A systematic review of 6 trials (N = 208) evaluated the effectiveness of inhaled antibiotics for the treatment of pulmonary exacerbations in patients with CF (*Ryan et al 2012*). The effectiveness of these agents for long-term suppression of respiratory infection has suggested there may also be benefit for treatment of exacerbations, with the strongest evidence supporting inhaled tobramycin. However, the review found no high level evidence to support the use of inhaled antibiotics for exacerbations, as the included trials were inadequate for a valid analysis.
  - An inhaled aminoglycoside may be useful when an intravenous aminoglycoside is contraindicated due to renal impairment or risk of drug-induced hearing loss.

CLINICAL GUIDELINES

- **Cystic Fibrosis Foundation (CFF) – CF pulmonary guidelines: chronic medications for maintenance of lung health** (*Mogayzel et al 2013*)
  - The guideline provided several new recommendations when published in 2013, in addition to reaffirming several recommendations from a previous (2007) version of the guideline. Guideline recommendations specific to inhaled antibiotics and treatment of *P. aeruginosa* are included in Table 3.
  - For these guidelines, the severity of lung disease is defined by ppFEV$_1$ as follows: normal, > 90% ppFEV$_1$; mildly impaired, 70 to 89% ppFEV$_1$; moderately impaired, 40 to 69% ppFEV$_1$; and severely impaired, < 40% ppFEV$_1$.
  - Level of evidence and strength of recommendations is based on the U.S. Preventive Services Task Force system.

Table 3. Summary of recommendations from the CFF for chronic medications in CF treatment

Treatment	Recommendation	Certainty of net benefit	Estimate of net benefit	Strength of Recommendation*
2007 recommendations, reaffirmed in 2013 without changes				
Inhaled tobramycin – moderate-to-severe disease	For individuals with CF, 6 years of age and older, with moderate-to-severe lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CFF strongly recommends the chronic use of inhaled tobramycin to improve lung function and quality of life, and reduce exacerbations.	High	Substantial	A
Inhaled tobramycin – mild disease	For individuals with CF, 6 years of age and older, with mild lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CFF recommends the chronic use of inhaled tobramycin to reduce exacerbations.	Moderate	Moderate	B
Azithromycin with *P. aeruginosa*	For individuals with CF, 6 years of age and older, with *P. aeruginosa* persistently present in cultures of the airways, the CFF recommends the chronic use of azithromycin to improve lung function and reduce exacerbations.	High	Moderate	B
Other inhaled antibiotics	For individuals with CF, 6 years of age and older, with *P. aeruginosa* persistently present in cultures of the airways, the CFF concludes that the evidence is insufficient to recommend for or against the chronic use of other inhaled antibiotics (ie, carbenicillin, ceftazidime, colistin, gentamicin) to improve lung function and quality of life, or reduce exacerbations.	Low	--	I
Oral antipseudomonal antibiotics	For individuals with CF, 6 years of age and older, with *P. aeruginosa* persistently present in cultures of the airways, the CFF concludes that the evidence is insufficient to recommend for or against the routine use of chronic oral antipseudomonal antibiotics to improve lung function and quality of life, or reduce exacerbations.	Low	--	I
2013 new or modified recommendations				
Inhaled aztreonam – moderate-to-severe disease	For individuals with CF, 6 years of age and older, with moderate-to-severe lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CFF strongly recommends the chronic use of inhaled aztreonam to improve lung function and quality of life.	High	Substantial	A
Inhaled aztreonam – mild disease	For individuals with CF, 6 years of age and older, with mild lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CFF recommends the chronic use of inhaled aztreonam to improve lung function and quality of life.	Moderate	Moderate	B

* A: The committee strongly recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is substantial. B: The committee recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is moderate, or there is moderate

certainty that the net benefit is moderate to substantial. I: The committee concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

- **CFF - Clinical practice guidelines from the CFF for preschoolers with CF** (*Lahiri et al 2016*)
  - This guideline focuses on the care of preschool children 2 to 5 years of age with CF. It includes recommendations in the areas of routine surveillance for pulmonary disease, therapeutics, and nutritional and gastrointestinal care. Table 4 highlights recommendations relevant to inhaled antibiotics and treatment of *P. aeruginosa*.
  - Level of evidence and strength of recommendations is based on the U.S. Preventive Services Task Force system.

Table 4. Summary of recommendations from the CFF for medication use in preschoolers age 2 to 5 with CF

Topic	Recommendation	Grade or consensus		
		Certainty of net benefit	Estimate of net benefit	Strength of Recommendation*
Exacerbations	The CFF recommends the use of oral, inhaled, and/or intravenous antibiotics to treat pulmonary exacerbations.	Consensus Recommendation		
Chronic *Pseudomonas* infection	The CFF recommends that children who remain persistently infected with *P. aeruginosa* be treated chronically with alternate-month inhaled antipseudomonal antibiotics.	Moderate	Moderate	B

* B: The committee recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial.

- **CFF - CF pulmonary guideline: pharmacologic approaches to prevention and eradication of initial *P. aeruginosa* infection** (*Mogayzel et al 2014*)
  - This guideline focuses on the prevention of *P. aeruginosa* infection, the treatment of initial *P. aeruginosa* infection, and the use of bronchoscopy to obtain routine airway cultures in individuals with CF. Guideline recommendations specific to inhaled antibiotics and prevention of *P. aeruginosa* are included in Table 5.
  - Level of evidence and strength of recommendations is based on the U.S. Preventive Services Task Force system.

Table 5. Summary of recommendations from the CFF for pharmacologic approaches to eradication and prevention of initial *P. aeruginosa* infection

Treatment	Recommendation	Certainty of net benefit	Estimate of net benefit	Strength of Recommendation*
Inhaled antibiotics	The CFF strongly recommends inhaled antibiotic therapy for the treatment of initial or new growth of *P. aeruginosa* from an airway culture. The favored antibiotic regimen is inhaled tobramycin (300 mg twice daily) for 28 days.	High	Substantial	A
Prophylactic antipseudomonal antibiotics	The CFF recommends against the use of prophylactic antipseudomonal antibiotics to prevent the acquisition *P. aeruginosa*.	Moderate	Zero	D

* A: The committee strongly recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is substantia. D: The committee recommends against the therapy. There is moderate or high certainty that the service has no net benefit or that the harms outweigh the benefits. Clinicians should discourage the use of this therapy.

SAFETY SUMMARY

- The inhaled tobramycin agents are contraindicated in patients with hypersensitivity or allergy to components of the product(s).
- Key warnings and precautions are similar among the inhaled tobramycin products, and generally include:
  - Bronchospasm: Can occur with inhalation of tobramycin.
  - Ototoxicity: Tinnitus and hearing loss have been reported in patients receiving tobramycin inhalation.

- Nephrotoxicity: Has been associated with aminoglycosides as a class.
- Neuromuscular disorders: Aminoglycosides may aggravate muscle weakness because of a potential curare-like effect on neuromuscular function.
- Fetal harm: can occur when aminoglycosides are administered to a pregnant woman

- Adverse events associated with the inhaled tobramycin agents include:
  - Common adverse events (> 5%) occurring more frequently in Bethkis-treated patients: decreased FEV, rales, increased red blood cell sedimentation rate, and dysphonia.
  - Common adverse events (> 5%) in patients treated with Kitabis Pak and Tobi inhalation solution: cough, pharyngitis, and increased sputum.
  - Common adverse events (≥ 10%) in patients treated with Tobi Podhaler: cough, lung disorder, productive cough, dyspnea, pyrexia, oropharyngeal pain, dysphonia, hemoptysis, and headache.
    - Cough was the most common adverse event and was reported more frequently with Tobi Podhaler vs nebulized tobramycin (48% vs 31%, respectively) in clinical trials.

DOSING AND ADMINISTRATION

Table 6. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments*
Bethkis	Inhalation nebulization solution: 300 mg/4 mL ampules	Oral inhalation	Twice daily in repeated cycles of 28 days on drug, followed by 28 days off	Dose should be administered over an approximately 15-minute period, using the Pari LC Plus Reusable Nebulizer and DeVilbiss PulmoAide compressor.
Kitabis Pak	Inhalation nebulization solution: 300 mg/5 mL ampules	Oral inhalation	Twice daily in repeated cycles of 28 days on drug, followed by 28 days off	Dose should be administered over an approximately 15-minute period, using the Pari LC Plus Reusable Nebulizer and DeVilbiss PulmoAide compressor. Kitabis Pak is a co-packaging of tobramycin inhalation solution with a Pari LC Plus Reusable Nebulizer.
Tobi	Inhalation nebulization solution: 300 mg/5 mL ampules	Oral inhalation	Twice daily in repeated cycles of 28 days on drug, followed by 28 days off	Dose should be administered over an approximately 15-minute period, using the Pari LC Plus Reusable Nebulizer and DeVilbiss PulmoAide compressor.
Tobi Podhaler	Inhalation powder: 28 mg capsules	Oral inhalation	Four capsules twice daily in repeated cycles of 28 days on drug, followed by 28 days off	Capsules are for use with the Podhaler device only. The contents of each capsule are administered through a deep inhalation with a single breath; the patient must inhale 2 times from each capsule.

* Doses for all agents should be taken as close to 12 hours apart as possible; but not less than 6 hours apart; dose is not adjusted for age or weight.

See the current prescribing information for full details

- In general, aerosolized antibiotics require a compressor and nebulizer, and approximately 15 minutes per dose for administration. Nebulizers require regular cleaning after each use to prevent device contamination; lack of regular cleaning may potentially lead to transport of pathogens to the lower airways (*Blau et al 2007, Lester et al 2004*).

- Phase 1 and Phase 3 studies of treatment with tobramycin administered via the Tobi Podhaler reported an administration time of 4 to 6 minutes in patients with CF (*Geller et al 2007, Konstan et al 2011a*). The Tobi Podhaler device does not require disinfection (*Hamed et al 2017, Vazquez-Espinosa et al 2016*).

CONCLUSION

- Inhaled antibiotics have been commonly used to treat persistent airway infection with *P. aeruginosa*, which contributes to lung damage in patients with CF. Treatment with inhaled antibiotics reduces bacterial load in the lungs, and decreases inflammation and the deterioration of lung function.
- Current clinical evidence has supported the efficacy of the various inhaled tobramycin formulations for the management of CF patients with *P. aeruginosa*, and efficacy appears comparable among agents.
- Chronic use of inhaled tobramycin is recommended in patients with CF aged 6 years and older, with mild or moderate-to-severe lung disease and *P. aeruginosa*, to improve lung function and quality of life, and reduce exacerbations.
  - Inhaled antibiotic therapy is strongly recommended for initial or new growth of *P. aeruginosa*, with inhaled tobramycin as the favored regimen.
- Safety concerns with inhaled tobramycin agents include bronchospasm, ototoxicity, nephrotoxicity, and neuromuscular disorders.
  - In clinical trials, cough was reported more frequently with the Tobi Podhaler inhalation powder vs nebulized tobramycin or placebo.
- All inhaled tobramycin agents are administered twice daily. Bethkis, Kitabis Pak, and Tobi are administered via a 15-minute nebulization, and use of the nebulizer requires additional steps for cleaning and set-up. In contrast, Tobi Podhaler inhalation powder takes less time to administer, is given via a total of 8 breath-activated inhalations (2 inhalations of the contents of 4 dry powder capsules), and does not require disinfection.

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INTRODUCTION

- The hepatitis C virus (HCV) is an enveloped ribonucleic acid (RNA) virus that is primarily transmitted through exposure to infected blood (*Centers for Disease Control and Prevention [CDC] 2018*).
  - Approximately 75 to 85% of people infected with HCV will develop chronic infection.
  - The CDC estimates that 2.4 million persons in the United States (U.S.) have chronic hepatitis C (CHC).
  - Chronic HCV infection can lead to the development of active liver disease, including cirrhosis and liver cancer. It is one of the most common indications for liver transplant (*CDC 2018*).
- There are 6 major genotypes of HCV, numbered 1 to 6. Genotypes are further divided into subtypes, designated by a letter (*Gower et al 2014*).
  - Genotype 1 is the most prevalent HCV genotype globally (~46% of cases), followed by genotype 3 (~22 to 30% of cases). Genotypes 2, 4, and 6 represent 22.8% of cases combined; genotype 5 represents less than 1% of cases worldwide (*Messina et al 2015, Gower et al 2014*).
  - In the U.S., the prevalence of genotype 1a, 1b, 2, 3, 4, and 6 is 46.2%, 26.3%, 10.7%, 8.9%, 6.3%, and 1.1%, respectively (*Gower et al 2014*).
- Due to the slow evolution of chronic infection, it is difficult to directly demonstrate whether treatment prevents complications of liver disease; therefore, response to treatment is defined by surrogate virologic parameters. The primary goal of therapy for hepatitis C is eradication of the virus. There are a number of different terms in use that are relevant to monitoring response to therapy:
  - Rapid virologic response (RVR): undetectable viral load at week 4
  - Early virologic response (EVR): at least a 2-log reduction in viral load by week 12 (partial EVR) or undetectable viral load by week 12 (complete EVR)
  - End-of-treatment response (ETR): undetectable viral load at the end of treatment
  - Sustained virologic response (SVR): continued undetectable viral load 12 weeks after the completion of therapy (*Hepatitis C Support Project [HCSP] Fact Sheet 2018*).
- Obtaining an SVR is associated with a 97 to 100% chance of being HCV RNA negative during long-term follow-up. Furthermore, achieving an SVR is associated with decreased mortality, rates of hepatocellular carcinoma, liver-related complications, and the need for liver transplant. Thus, success at obtaining SVR is an important treatment goal and a common primary endpoint in the clinical trials of antiviral medications. Some trials report SVR at 12 weeks (SVR12) in addition to or instead of at 24 weeks (SVR24). There is a high degree of concordance between SVR12 and SVR24, and SVR12 is also considered an appropriate endpoint (*Chen et al 2013*).
- Over recent years, research has focused on oral HCV agents that act directly on viral targets. These direct-acting antivirals (DAAs) are stratified into 4 major categories: NS3/4A protease inhibitors, NS5B nucleoside polymerase inhibitors, NS5B nonnucleoside polymerase inhibitors, and NS5A inhibitors (*Liang et al 2013*).
  - The first DAA-containing regimens were single-ingredient DAAs that needed to be used in combination with peginterferon (PegIFN)/ribavirin (RBV). However, several IFN-free combination products and regimens have been approved since 2014. Some of these regimens also remove the need for RBV in select populations.
- This review provides information on the DAAs, including: Daklinza, Epclusa, Harvoni, Mavyret, Sovaldi, Viekira Pak, Vosevi, and Zepatier.
  - In May 2018, AbbVie announced the discontinuation of Viekira XR (ombitasvir/paritaprevir/ritonavir and dasabuvir) and Technivie (ombitasvir/paritaprevir/ritonavir). These discontinuations were voluntary, and not due to any safety, efficacy, or quality issues. These products will no longer be available, effective January 1, 2019 (*FDA Drug Shortages 2019*).
- Medispan Class: Hepatitis C Agents

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Daklinza (daclatasvir)*	--
Epclusa (sofosbuvir/velpatasvir)	✔
Harvoni (ledipasvir/sofosbuvir)	✔
Mavyret (glecaprevir/pibrentasvir)	--
Sovaldi (sofosbuvir)	--
Viekira Pak (ombitasvir/paritaprevir/ritonavir and dasabuvir)	--
Vosevi (sofosbuvir/velpatasvir/voxilaprevir)	--
Zepatier (elbasvir/grazoprevir)	--

*As of December 2018, the manufacturer has ceased distribution of 90 mg tablets of Daklinza; distribution of 30 and 60 mg tablets is expected to end as of June 2019 (*FDA Drug Shortages 2019*).

(*Drugs@FDA 2019*, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Daklinza (daclatasvir)	Epclusa (sofosbuvir-velpatasvir)	Harvoni* (ledipasvir/sofosbuvir)	Mavyret (glecaprevir-pibrentasvir)	Sovaldi* (sofosbuvir)	Viekira Pak (ombitasvir/paritaprevir/ritonavir/dasabuvir)	Vosevi† (sofosbuvir-velpatasvir-voxilaprevir)	Zepatier (elbasvir/grazoprevir)
Genotype 1	✔	✔	✔	✔	✔	✔	✔	✔
Genotype 2		✔		✔	✔		✔	
Genotype 3	✔	✔		✔	✔		✔	
Genotype 4		✔	✔	✔	✔		✔	✔
Genotype 5		✔	✔	✔			✔	
Genotype 6		✔	✔	✔			✔	

* Harvoni and Sovaldi are the only agents approved in pediatric patients; Harvoni is indicated for the treatment of pediatric patients 12 years of age and older or weighing at least 35 kg with HCV genotype 1, 4, 5, or 6 infection without cirrhosis or with compensated cirrhosis; Sovaldi is indicated for the treatment of chronic HCV genotype 2 or 3 infection in pediatric patients 12 years of age and older or weighing at least 35 kg without cirrhosis or with compensated cirrhosis for use in combination with ribavirin.
† Only approved in patients with genotypes 1, 2, 3, 4, 5, or 6 with prior failure to an NS5A inhibitor-containing regimen or patients with genotypes 1a or 3 previously treated with a sofosbuvir-containing regimen without an NS5A inhibitor.

(*Prescribing information: Daklinza 2017, Epclusa 2017, Harvoni 2017, Mavyret 2018, Sovaldi 2018, Viekira Pak 2018, Vosevi 2017, Zepatier 2018*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Daklinza

- The clinical safety and efficacy of daclatasvir in combination with sofosbuvir and with or without RBV was evaluated in 3 pivotal phase 3 trials.
  - ALLY-1 was a multicenter (MC), open-label (OL) study in patients (genotype 1 to 6 included) with advanced cirrhosis (n = 60) or patients with HCV recurrence post-liver transplant (N = 53). Patients received daclatasvir plus sofosbuvir plus RBV for 12 weeks. In the advanced cirrhosis cohort, 82% of genotype 1 patients achieved SVR12 (SVR12 in overall cohort: 83%). In the post-transplant cohort, 95% of genotype 1 patients achieved SVR12 (SVR12 in overall cohort: 94%) (*Poordad et al 2016*).

- ALLY-2 was a MC, OL, randomized study (n = 153) in patients (genotype 1 to 6 included) with HCV/human immunodeficiency virus (HIV) co-infection. Among patients who received 12 weeks of daclatasvir plus sofosbuvir therapy, 96% and 97% of treatment-naïve HCV genotype 1 and treatment-experienced HCV genotype 1a patients achieved SVR12, respectively. All treatment-naïve and treatment-experienced patients with genotype 1b (23/23), genotype 2 (13/13), genotype 3 (10/10), or genotype 4 (3/3) infection achieved SVR12 (*Wyles et al 2015*).
- ALLY-3 was a MC, OL study in genotype 3 patients (n = 152), including those with compensated cirrhosis. Patients received daclatasvir plus sofosbuvir for 12 weeks. The SVR12 rates were 90% in treatment-naïve patients and 86% in treatment-experienced patients, with an overall SVR12 rate of 89%. SVR12 rates were higher in patients without cirrhosis (96%) than in patients with cirrhosis. In cirrhotic treatment-naïve and treatment-experienced patients, the SVR12 rate was 58% and 69%, respectively (*Nelson et al 2015*).

- ALLY-3C was a phase 3, OL, MC, single-arm study that examined the efficacy of daclatasvir plus sofosbuvir plus RBV for 24 weeks in patients (n = 78) with HCV genotype 3 and compensated cirrhosis. SVR12 was achieved in 87% of patients; SVR12 rates were 93% and 79% for treatment-naïve and treatment-experienced patients, respectively (*Poordad et al 2018*).
- ALLY-3+ was a phase 3, OL, MC study that compared 12 weeks (n = 24) vs 16 weeks (n = 26) of daclatasvir plus sofosbuvir plus RBV in patients with advanced fibrosis or cirrhosis. SVR12 was 88% in the 12-week treatment group and 92% in the 16-week group, giving an overall rate in all treated patients of 90%. All patients with advanced fibrosis achieved SVR12 (*Leroy et al 2016*).
- Several recent real world and observational studies have also found daclatasvir plus sofosbuvir, with or without RBV, to be highly effective and well tolerated for the treatment of genotype 1 or 3 infection (*Alonso et al 2016, Pol et al 2017, Welzel et al 2016*).

Epclusa

- The clinical safety and efficacy of Epclusa was evaluated in 4 pivotal phase 3 trials.
  - ASTRAL-1 was a double-blind (DB), placebo-controlled (PC), MC, randomized trial in previously treated or untreated patients who were chronically infected with HCV genotype 1, 2, 4, 5, or 6. Overall, the rate of SVR among patients who received 12 weeks of Epclusa was 99% (618/624) (95% confidence interval [CI], 98 to > 99), which was significantly superior to the prespecified performance goal of 85% ($p < 0.001$). None of the 116 patients in the placebo group had an SVR (*Feld et al 2015*).
  - ASTRAL-2 was an OL, active-control (AC), MC, randomized trial comparing Epclusa for 12 weeks (n = 134) vs sofosbuvir plus RBV for 12 weeks (n = 132) in patients with genotype 2 infection. The rate of SVR12 was 99% (133/134) (95% CI, 96 to 100) among those who had received Epclusa as compared with 94% (124/132) (95% CI, 88 to 97) among those who had received sofosbuvir plus RBV (*Foster et al 2015*).
  - ASTRAL-3 was an OL, AC, MC, randomized trial comparing Epclusa for 12 weeks (n = 277) vs sofosbuvir plus RBV for 24 weeks (n = 275) in patients with genotype 3 infection. The rate of SVR12 was 95% (95% CI, 92 to 98) among those who had received Epclusa, as compared with 80% (95% CI, 75 to 85) among those who had received sofosbuvir plus RBV. The overall SVR rate with Epclusa was significantly superior to that with sofosbuvir plus RBV. The strata-adjusted absolute difference was 14.8% (95% CI, 9.6 to 20.0, $p < 0.001$) (*Foster et al 2015*).
  - ASTRAL-4 was an OL, MC, randomized trial comparing Epclusa with or without RBV for 12 weeks or Epclusa for 24 weeks in patients infected with HCV genotypes 1 through 6 and with decompensated cirrhosis. Rates of SVR12 were 83% (95% CI, 74 to 90) in patients who received Epclusa for 12 weeks, 94% (95% CI, 87 to 98) among those who received Epclusa plus RBV for 12 weeks, and 86% (95% CI, 77 to 92) among those who received Epclusa for 24 weeks. Post-hoc analyses did not detect any significant differences in rates of SVR among the 3 treatment groups (*Curry et al 2015*).
- A randomized, OL trial conducted in Spain compared 12 weeks of Epclusa to 12 weeks of Epclusa plus RBV in patients (n = 204) with HCV genotype 3 and compensated cirrhosis. SVR12 rates were 91% and 96% in the Epclusa and Epclusa plus RBV groups, respectively (*Esteban et al 2018*).
- A meta-analysis of 6 randomized controlled trials (n = 1427) found that 12 weeks of Epclusa treatment resulted in SVR12 rates of 98.2%, 99.4%, 94.7%, 99.6%, 97.1%, and 98.8% in HCV genotypes 1, 2, 3, 4, 5, and 6, respectively (*Ahmed H et al 2018[a]*).

Harvoni

Adults

- The efficacy and safety of Harvoni were evaluated in 4 trials in genotype 1 HCV monoinfected patients, 1 trial in genotype 1 or 4 HCV/HIV-1 co-infected patients, 3 trials in genotype 4, 5, or 6 HCV monoinfected patients and 2 trials in genotype 1 or 4 HCV infected pre-transplant patients with decompensated cirrhosis (Child-Pugh B and C) or post-liver transplant.
  - ION-1 was a randomized, OL trial in treatment-naïve patients (n = 865) with genotype 1 HCV with or without cirrhosis. Patients were randomized to receive Harvoni for 12 or 24 weeks, with or without RBV. In the trial, SVR12 rates of 97 to 99% were achieved (*Afdhal et al 2014[a]*).
  - ION-2 was a randomized, OL trial in patients (n = 440) with genotype 1 HCV with or without cirrhosis who failed prior therapy with an IFN-based regimen, with or without a protease inhibitor. Patients were randomized to receive Harvoni for 12 or 24 weeks, with or without RBV. SVR12 rates of up to 99% were achieved (*Afdhal et al 2014[b]*).
  - ION-3 was a randomized, OL trial in treatment-naïve patients (n = 647) with non-cirrhotic HCV genotype 1 infection. Patients randomized to treatment with Harvoni for 8 or 12 weeks or Harvoni plus RBV for 8 weeks demonstrated SVR12 rates of 93 to 95% (*Kowdley et al 2014*).
  - ION-4 was an OL, MC trial in 335 patients evaluating 12 weeks of Harvoni in treatment-naïve and treatment-experienced cirrhotic or non-cirrhotic HIV/HCV co-infected patients. SVR12 rates were high overall (96%) with comparable rates to the HCV monoinfected population (*Naggie et al 2015*).
  - SIRIUS was a DB, MC, French study in which patients with cirrhosis who did not respond to PegIFN and RBV plus telaprevir or boceprevir, were randomized to placebo for 12 weeks followed by Harvoni plus RBV for 12 weeks (n = 77) or Harvoni plus placebo for 24 weeks (n = 78). The overall SVR12 rates were 96% and 97% for Harvoni plus RBV for 12 weeks and Harvoni plus placebo for 24 weeks, respectively (*Bourlière et al 2015*).
  - Study 1119 was an OL study evaluating Harvoni for 12 weeks in patients with genotype 4 (n = 44) or 5 infection (n = 41), with or without compensated cirrhosis. The study was conducted at 5 sites in France. There were high SVR12 rates (≥ 89%) with 12 weeks of Harvoni in all patient subgroups and similar rates for genotype 4 vs genotype 5 infection (*Abergel et al 2016*).
  - In an OL, randomized study, Harvoni for 12 weeks was compared to sofosbuvir plus RBV for 24 weeks in a cohort of Egyptian patients (n = 200) with treatment-naïve genotype 4 HCV. SVR12 was higher with Harvoni (99% vs 80% with sofosbuvir plus RBV) (*Ahmed OA et al 2018*). Another OL randomized study in Egyptian patients (n = 255) compared Harvoni and Harvoni plus RBV for 8 or 12 weeks. SVR12 rates were 95% and 90% among patients receiving 8 weeks of Harvoni and Harvoni plus RBV, respectively. The SVR12 rate for patients receiving 12 weeks of Harvoni (with or without RBV) was 98% (*Shiha et al 2018*).
  - ELECTRON-2 was an OL trial that enrolled patients from 2 centers in New Zealand. The trial evaluated Harvoni for 12 weeks in patients with genotype 6 infection (n = 25). The rate of SVR12 was 96%. The single patient who did not reach SVR12 was a patient who withdrew consent during week 8 of treatment and therefore did not receive the full course of treatment (*Gane et al 2015*).
  - SOLAR-1 and SOLAR-2 were OL, MC trials that evaluated 12 and 24 weeks of treatment with Harvoni in combination with RBV in patients with genotype 1 and 4 infection who had undergone liver transplantation and/or who had decompensated liver disease. The 2 trials were identical in study design. The SVR12 rates observed with 24 weeks of Harvoni plus RBV were similar to the SVR12 rates observed with 12 weeks of treatment. In pre-transplant patients with decompensated cirrhosis, the SVR12 rate for Harvoni plus RBV for 12 weeks was 87% (80/92). In post-transplant patients (with or without cirrhosis), the SVR12 was 93% (194/208) (*Charlton et al 2015; Manns et al 2016*).

Pediatric

- A phase 2, OL, MC study (n = 100) evaluated Harvoni for 12 weeks in patients aged 12 to 17 years with chronic HCV genotype 1 infection. Overall, 98% of patients reached SVR12. No patient had virologic failure; 2 patients who did not achieve SVR12 were lost to follow-up either during or after treatment (*Balistreri et al 2016*).
- A phase 2, OL, MC study evaluated the efficacy of Harvoni for 12 weeks (n = 89) in patients aged 6 to 11 years with chronic HCV, primarily genotype 1, infection. Treatment was given for 24 weeks for IFN-experienced patients with HCV genotype 1 and cirrhosis (n = 1); or IFN-experienced with HCV genotype 3 with or without cirrhosis (n = 2). Among patients treated for 12 weeks, SVR12 was achieved in 99% of patients (88/89); the SVR12 rate was 100% (3/3) for patients given Harvoni for 24 weeks. One patient with genotype 1a and cirrhosis who was treatment-naïve experienced virologic relapse 4 weeks after a 12-week course of treatment (*Murray et al 2018*).

Mavyret

- The efficacy of Mavyret in patients who were treatment-naïve or treatment-experienced to combinations of PegIFN, RBV and/or sofosbuvir (PRS) with genotype 1, 2, 4, 5, or 6 infection without cirrhosis was studied in 5 trials using 8- or 12-week durations: ENDURANCE-1, ENDURANCE-2, ENDURANCE-4, SURVEYOR-1 (Part 2), and SURVEYOR-2 (Part 2 and Part 4).
  - ENDURANCE-1 was a randomized, MC, OL trial comparing the efficacy of 8 and 12 weeks of treatment with Mavyret in patients with genotype 1 infection with or without HIV-1 co-infection. The SVR rate was 99% (348/351) and 99.7% (351/352) in the Mavyret 8- and 12-week arms, respectively (*Mavyret prescribing information 2018, Zeuzem et al 2018*).
  - ENDURANCE-4, SURVEYOR-1, and SURVEYOR-2 were OL, MC trials evaluating the safety and efficacy of Mavyret in treatment-naïve or PRS treatment-experienced patients. ENDURANCE-4 and SURVEYOR-1 evaluated 12 weeks of Mavyret in patients with genotypes 5 and 6. The overall SVR rate was 100% (57/57). SURVEYOR-2 evaluated 8 weeks of Mavyret in patients with genotypes 2, 4, 5, or 6; the SVR rate was 98% (193/197), 93% (43/46), 100% (2/2), and 100% (10/10), respectively (*Asselah et al 2017, Asselah et al 2018[a], Mavyret prescribing information 2018*).
  - ENDURANCE-2 was a randomized, DB, placebo-controlled, MC study assessing the efficacy of Mavyret for 12 weeks in non-cirrhotic patients with genotype 2 HCV (n = 196). The SVR12 rate in the treatment group was 99% (*Asselah et al 2018[a]*).
- The efficacy of Mavyret in patients who were treatment-naïve or PRS treatment-experienced with genotype 1, 2, 4, 5, or 6 with compensated cirrhosis was studied in the OL, single-arm EXPEDITION-1 trial. Patients were treated with 12 weeks of Mavyret. The overall SVR rate was 99% (145/146). (*Forns et al 2017*).
- The efficacy of Mavyret in patients without cirrhosis or with compensated cirrhosis who were treatment-naïve or PRS treatment-experienced with genotype 3 infection was studied in ENDURANCE-3 and in SURVEYOR-2 (Part 3).
  - ENDURANCE-3 was a randomized, OL, AC trial in treatment-naïve patients. Patients were randomized (2:1) to either Mavyret for 12 weeks or to the combination of Sovaldi and Daklinza for 12 weeks; subsequently the trial included a third non-randomized arm with Mavyret for 8 weeks. The SVR rate for 8 weeks of Mavyret, 12 weeks of Mavyret, and 12 weeks of Sovaldi plus Daklinza was 94.9% (149/157), 95.3% (222/233), and 96.5% (111/115), respectively. The treatment difference for 12 weeks of Mavyret vs 12 weeks of Sovaldi plus Daklinza was -1.2% (95% CI, -5.6% to 3.1%). The treatment difference for 8 weeks vs 12 weeks of Mavyret was -0.4% (95% CI, -5.4% to 4.6%) (*Mavyret prescribing information 2018, Zeuzem et al 2018*).
  - SURVEYOR-2 (Part 3) was an OL trial randomizing PRS treatment-experienced patients with genotype 3 infection without cirrhosis to 12 or 16 weeks of treatment. In addition, the trial evaluated the efficacy of Mavyret in genotype 3 infected patients with compensated cirrhosis in 2 dedicated treatment arms using 12-week (treatment-naïve only) and 16-week (PRS treatment-experienced only) durations. The SVR rate was 98% (39/40) in treatment-naïve patients with cirrhosis who were treated with 12 weeks of Mavyret. The SVR rate was 96% (66/69) in PRS treatment-experienced patients, with or without cirrhosis, who were treated with 16 weeks of Mavyret (*Mavyret prescribing information 2018, Wyles et al 2017*).
  - A pooled analysis of 5 trials in patients (n = 693) with HCV genotype 3 found that treatment with Mavyret for 8 or 12 weeks achieved SVR12 in 95% of treatment-naïve patients without cirrhosis; treatment-naïve patients with cirrhosis who were treated for 12 weeks had an SVR12 rate of 97%. Treatment-experienced patients without cirrhosis achieved SVR12 rates of 90% and 96% with 12 and 16 weeks of Mavyret treatment, respectively. Treatment-experienced patients with cirrhosis achieved SVR12 rates of 94% with 16 weeks of Mavyret treatment (*Flamm et al 2018*).
- ENDURANCE-5,6 was a single-arm, OL, MC trial examining the efficacy of Mavyret in patients (n = 84) with HCV genotypes 5 and 6. Patients without cirrhosis or with compensated cirrhosis were treated with 8 or 12 weeks of Mavyret, respectively. The overall SVR12 rate was 97.6%, with 95.7% and 98.4% of patients with HCV genotype 5 and 6 infections, respectively, achieving SVR12 (*Asselah et al 2018[b]*).
- EXPEDITION-2 was an OL study in HCV/HIV-1 co-infected patients (n = 153) evaluating Mavyret in HCV genotypes 1 through 6 with or without compensated cirrhosis for 8 or 12 weeks, respectively. Treatment-naïve and treatment-experienced patients were both included. The overall SVR12 rate was 98% (*Rockstroh et al 2018*).
- EXPEDITION-4 was an OL, single-arm, MC trial evaluating the safety and efficacy in patients with severe renal impairment (chronic kidney disease [CKD] Stages 4 and 5; 82% were on hemodialysis) with compensated liver disease (with and without cirrhosis). The study included patients with (19%) or without compensated cirrhosis (81%). The SVR rate was 98% (102/104). Of the 2 patients who failed, 1 discontinued the medication and the other was lost to follow-up *(Gane et al 2017, Mavyret prescribing information 2018).*

- MAGELLAN-1 was a randomized, OL trial in genotype 1- or 4-infected patients who failed a previous regimen containing an NS5A inhibitor and/or NS3/4A protease inhibitor. Due to higher rates of virologic failure and treatment-emergent drug resistance, the data did not support labeling for treatment of HCV genotype 1-infected patients who are both NS3/4A protease inhibitor and NS5A inhibitor-experienced (*Mavyret prescribing information 2018, Poordad et al 2017*).
  - In protease inhibitor-experienced patients (but NS5A inhibitor-naïve), the SVR rate was 92% (23/25) for patients treated with Mavyret for 12 weeks. In NS5A-experienced patients (but protease inhibitor-naïve), the SVR rate was 94% (16/17).
- MAGELLAN-2 was an OL trial that included treatment-naïve or treatment-experienced patients (n = 100) with chronic HCV genotype 1 through 6 who had received a liver or kidney transplant. The overall SVR12 was 98% after 12 weeks of therapy (*Reau et al 2018*). In 2018, Mavyret received approval for use in liver and kidney transplant recipients (*Mavyret prescribing information 2018*).
- In a pooled analysis of 9 trials in patients (n = 2041) with HCV genotypes 1 through 6 without cirrhosis, treatment with Mavyret for 8 or 12 weeks resulted in SVR12 rates of 98% and 99%, respectively (*Puoti et al 2018*).

Sovaldi

Adults

- The clinical safety and efficacy of sofosbuvir were evaluated in 6 pivotal phase 3 trials.
  - NEUTRINO was a single-arm, OL study of Sovaldi in combination with IFN and RBV in patients infected with HCV genotype 1, 4, 5, or 6. SVR was achieved in 90% of patients at 12 weeks (*Lawitz et al 2013*).
  - FISSION was a randomized, OL, AC, non-inferiority study in patients with HCV genotype 2 or 3. Patients received treatment with Sovaldi plus RBV for 12 weeks or PegIFN plus RBV for 24 weeks. An SVR was reported in 67% of patients in both treatment groups at 12 weeks after the end of treatment (*Lawitz et al 2013*).
  - In POSITRON, HCV genotype 2 or 3 patients who had previously discontinued IFN therapy due to adverse events, who had a concurrent medical condition precluding therapy with an IFN, or who decided against treatment with an IFN-containing regimen were randomized to receive treatment with Sovaldi and RBV or matching placebos. Rates of SVR at 12 weeks were significantly higher in the Sovaldi treatment group compared to placebo (78 vs 0%, respectively; $p < 0.001$) (*Jacobson et al 2013*).
  - In FUSION, patients who did not achieve SVR with prior IFN therapy (relapsers or nonresponders) were randomized to receive treatment with Sovaldi and RBV for 12 or 16 weeks. Rates of SVR were 50% with 12 weeks of treatment, as compared with 73% with 16 weeks of treatment (*Jacobson et al 2013*).
  - The VALENCE trial evaluated Sovaldi in combination with RBV for the treatment of genotype 2 or 3 HCV infection in treatment-naïve patients or patients who did not achieve SVR with prior IFN-based treatment, including those with compensated cirrhosis. Rates of SVR were 93% in genotype 2 patients and 84% in genotype 3 patients (*Zeuzem et al 2014[a]*).
  - PHOTON-1 was an OL trial evaluating treatment with 12 or 24 weeks of Sovaldi in combination with RBV in genotype 1, 2, or 3 CHC patients co-infected with HIV-1. Genotype 2 and 3 patients were either treatment-naïve or experienced, whereas genotype 1 patients were treatment-naïve. Rates of SVR were similar to those observed in patients with HCV mono-infection across all genotypes (*Sulkowski et al 2014*).

Pediatric

- Study 1112 was an OL trial evaluating treatment with Sovaldi in combination with RBV in pediatric patients 12 years of age and older with genotype 2 or 3 HCV infection. Patients with HCV genotype 2 or 3 infection in the trial were treated with Sovaldi and weight-based RBV for 12 or 24 weeks, respectively. The majority of patients were treatment-naïve (83%), and 73% were infected by vertical transmission; 40% were assessed as not having cirrhosis (the remainder did not have a cirrhosis determination). SVR12 rates were 100% (13/13) for patients with genotype 2 and 97% (38/39) for genotype 3. The single patient who did not achieve SVR was lost to follow-up after achieving SVR4 (*Wirth et al 2017*).

Vosevi

- The efficacy of Vosevi was evaluated in 2 pivotal trials in DAA-experienced patients.
  - POLARIS-1 was a randomized, DB, PC trial that evaluated 12 weeks of treatment with Vosevi compared with 12 weeks of placebo in DAA-experienced patients with genotype 1, 2, 3, 4, 5, or 6 HCV infection without cirrhosis or with compensated cirrhosis who previously failed a regimen containing an NS5A inhibitor. Overall, 51% of patients had been previously treated with ledipasvir (the NS5A component of Harvoni). The remaining patients were treated with

other NS5A inhibitors. The overall SVR rate was 96% (253/263). The SVR rate was 99% (140/142) and 93% (113/121) in patients without cirrhosis and with cirrhosis, respectively (*Bourlière et al 2017*).
  - POLARIS-4 was a randomized, OL trial that evaluated 12 weeks of treatment with Vosevi and 12 weeks of treatment with Epclusa in patients with genotype 1, 2, 3, or 4 HCV infection without cirrhosis or with compensated cirrhosis who had previously failed an HCV DAA-containing regimen that did not include an NS5A inhibitor. In the trial, prior DAA regimens contained sofosbuvir (85%) with the following: PegIFN and RBV or just RBV (69%), HCV NS3/4A protease inhibitor (boceprevir, simeprevir, or telaprevir; 15%) and investigational DAA (< 1%). The SVR12 rate was 98% (178/182) (95% CI, 95 to 99; significantly superior to the prespecified performance goal of 85% [p < 0.001]) for patients receiving Vosevi for 12 weeks. The SVR12 rate was 90% (136/151) (95% CI, 84 to 94, not significantly superior to the prespecified performance goal of 85% [p = 0.09]) for patients receiving Epclusa for 12 weeks. One patient had viral breakthrough and 14 patients relapsed (*Bourlière et al 2017*).

Viekira Pak

- Efficacy and safety of Viekira Pak were evaluated in 8 pivotal clinical trials with chronic HCV genotype 1 infection:
  - Treatment-naïve genotype 1a and 1b (SAPPHIRE-I)
  - Treatment-experienced genotype 1a and 1b (SAPPHIRE-II)
  - Treatment-experienced genotype 1b (PEARL-II)
  - Treatment-naïve genotype 1b (PEARL-III)
  - Treatment-naïve genotype 1a (PEARL-IV)
  - Treatment-naïve and -experienced genotype 1a and 1b with cirrhosis (TURQUOISE-II)
  - Treatment-naïve and -experienced genotype 1b with cirrhosis (TURQUOISE-III).
  - Treatment-naïve and -experienced genotype 1b with cirrhosis (TURQUOISE-IV)
- SAPPHIRE-I and SAPPHIRE-II were MC, randomized, DB, PC trials. Patients were randomized to Viekira Pak plus RBV for 12 weeks or placebo. Patients in the placebo treatment arm received placebo for 12 weeks, after which they received OL Viekira Pak plus RBV for 12 weeks (*Feld et al 2014, Zeuzem et al 2014[b]*).
  - In SAPPHIRE-I (n = 631), SVR12 was achieved in 96.2% (95% CI, 94.5 to 97.9) of patients receiving Viekira Pak with RBV. This rate was non-inferior and superior to the historical control rate with telaprevir plus PegIFN/RBV.
  - In SAPPHIRE-II (n = 394), SVR12 was achieved in 96.3% (95% CI, 94.2 to 98.4) of patients receiving Viekira Pak with RBV. This rate was non-inferior and superior to the historical control rate among patients who had previously been treated with PegIFN/RBV and who received retreatment with telaprevir plus PegIFN/RBV.
- In PEARL-II (n = 186), patients without cirrhosis were randomized to receive OL Viekira Pak with or without RBV for 12 weeks of treatment (*Andreone et al 2014*).
  - Rates of SVR12 were 96.6% (95% CI, 92.8 to 100) with Viekira Pak plus RBV and 100% (95% CI, 95.9 to 100) with Viekira Pak alone. Rates of SVR in both treatment groups were non-inferior and superior to the historical rate for telaprevir plus PegIFN/RBV in comparable treatment-experienced patients.
  - Non-inferiority of treatment with Viekira Pak alone compared to Viekira Pak plus RBV was met (treatment difference in SVR12 rates, 3.4% [95% CI, -0.4 to 7.2]).
- PEARL-III and PEARL-IV were MC, DB, PC trials. Patients without cirrhosis were randomized to receive Viekira Pak with or without RBV for 12 weeks of treatment (*Ferenci et al 2014*).
  - In PEARL-III (n = 419), treatment with Viekira Pak resulted in SVR12 rates of 99.5% (95% CI, 98.6 to 100) with RBV and 99% (95% CI, 97.7 to 100) without RBV in patients with genotype 1b infection.
  - In PEARL-IV (n = 305), treatment with Viekira Pak resulted in SVR12 rates of 97% (95% CI, 93.7 to 100) with RBV and 90.2% (95% CI, 86.2 to 94.3) without RBV in patients with genotype 1a infection.
- The OL TURQUOISE-II trial (n = 380) enrolled patients with compensated cirrhosis (Child-Pugh A) or liver scarring with few to no outward symptoms who were either treatment-naïve or PegIFN/RBV treatment-experienced. Patients were randomized to receive Viekira Pak in combination with RBV for 12 or 24 weeks of treatment. Patients who previously failed therapy with a treatment regimen that included a DAA were excluded (*Poordad et al 2014*).
  - Patients who received 12 weeks of treatment had an SVR12 response of 91.8% (97.5% CI, 87.6 to 96.1).
  - Those patients who received 24 weeks of treatment achieved an SVR12 rate of 95.9% (97.5% CI, 92.6 to 99.3).
  - Rates of SVR12 in the 12- and 24-week treatment groups were non-inferior and superior to the historical rate with telaprevir plus PegIFN/RBV among patients with HCV genotype 1 infection and cirrhosis. The difference in the rates of SVR between the 2 treatment groups was not significant.

- The OL TURQUOISE-III trial (n = 60) enrolled genotype 1b patients with compensated cirrhosis who were either treatment-naïve or PegIFN/RBV treatment-experienced. Patients were randomized to receive Viekira Pak for 12 weeks. SVR12 was achieved in all patients enrolled in the study (*Feld et al 2016*).
- The OL TURQUOISE-IV trial (n = 36) enrolled genotype 1b patients in Russia and Belarus with compensated cirrhosis who were either treatment-naïve or PegIFN/RBV treatment-experienced. Patients received Viekira Pak plus RBV for 12 weeks. SVR12 was achieved in all patients enrolled in the study (*Isakov et al 2018*).
- Safety and efficacy of Viekira Pak were also evaluated in liver transplant patients and in patients with HCV genotype 1 co-infected with HIV-1.
  - CORAL-I was a phase 2, OL trial in HCV genotype 1 liver transplant recipients who were at least 12 months post transplantation with mild fibrosis (Metavir score < F2). Patients received treatment with Viekira Pak with RBV for 24 weeks. Of the 34 patients enrolled, 33 achieved an SVR12, for a rate of 97% (95% CI, 85 to 100) (*Kwo et al 2014*).
  - TURQUOISE-I was a phase 3, randomized, OL trial in 63 patients with treatment-naïve or -experienced HCV genotype 1 infection who were co-infected with HIV-1. Patients on a stable antiretroviral therapy regimen were treated for 12 or 24 weeks with Viekira Pak in combination with RBV. SVR12 rates were 91% for patients with HCV genotype 1a infection and 100% for those with genotype 1b infection (*Wyles et al 2014*).

Zepatier

- The safety and efficacy of Zepatier were evaluated in 7 pivotal clinical trials including patients with genotype 1 or 4 infection. A small number of patients with other HCV genotypes were also included in the clinical trials; however, Zepatier is only indicated for genotypes 1 and 4.
  - C-EDGE TN was a DB, PC, MC, randomized study in treatment-naïve patients with genotype 1, 4, or 6 infection. Of the 316 patients receiving Zepatier for 12 weeks, 95% (95% CI, 92 to 97) achieved SVR12. SVR12 was achieved in 97% (95% CI, 90 to 100) of cirrhotic patients and 94% (95% CI, 90 to 97) of noncirrhotic patients (*Zeuzem et al 2015*).
  - C-EDGE CO-INFECTION was an OL, MC trial in treatment-naïve patients with genotype 1, genotype 4, and genotype 6 infection who were co-infected with HIV. All patients (n = 218) received Zepatier for 12 weeks. In the overall population, 96% achieved SVR12 (95% CI, 92.9 to 98.4), exceeding the historical reference rate of 70% (*Rockstroh et al 2015*).
  - C-SURFER was a DB, PC, MC, randomized study, evaluating Zepatier for 12 weeks in patients with genotype 1 infection with CKD stage 4 to 5. Of the 122 patients receiving Zepatier, 6 were excluded from the modified full analysis set population for reasons other than virologic failure. Of the 116 remaining patients, 115 achieved SVR12, a rate better than the historical control rate of 45% ($p < 0.001$) (*Roth et al 2015*).
  - C-SCAPE was an OL, randomized study that evaluated the efficacy of Zepatier for 12 weeks, with or without RBV, in patients with genotype 4, 5, or 6 infection. In patients with genotype 4 infection, SVR12 was achieved in 100% (10/10) of patients receiving Zepatier with RBV vs 90% (9/10) in patients receiving Zepatier alone (*Brown et al 2015, Brown et al 2018*).
  - C-EDGE TE was an OL, MC, randomized study evaluating 12 or 16 weeks of Zepatier, with or without RBV in patients with genotype 1, 4, or 6 HCV infection and previous treatment with Peg IFN/RBV. SVR12 was achieved in 92.4% (97/105) receiving Zepatier alone for 12 weeks, 94.2% (98/104) receiving Zepatier plus RBV for 12 weeks, 92.4% (97/105) receiving Zepatier alone for 16 weeks, and 97.2% (103/106) receiving Zepatier plus RBV (*Kwo et al 2017*).
  - C-SALVAGE was an OL, MC study evaluating Zepatier plus RBV for 12 weeks in patients (n = 79) with genotype 1 infection who failed a regimen containing PegIFN/RBV and another DAA. SVR12 was achieved in 96% (95% CI, 89.3 to 99.2) of patients. The 3 patients not achieving SVR12 had a past history of virologic failure (*Forns et al 2015*).
  - C-CORAL was a randomized, DB, PC study evaluating Zepatier for 12 weeks in treatment-naïve patients (n = 489) with genotype 1, 4, or 6 HCV infection. SVR12 was achieved in 94.4% of patients receiving Zepatier. SVR12 rates of 98.2%, 91.9%, and 66.7% were seen in patients with genotype 1b, 1a, and 6 infections, respectively (*Wei et al 2018*).
- A meta-analysis of 8 trials (n = 1297) found an overall SVR rate of 96.6% with Zepatier treatment in patients with genotype 1 HCV (*Ahmed H et al 2018[b]*).
- In a pooled analysis of clinical trial data, treatment-naïve and treatment-experienced patients with genotype 4 HCV infection (n = 155) had SVR12 rates of 96.4% (treatment-naïve) and 88.6% (treatment-experienced) after 12 or 16 weeks of Zepatier with or without RBV (*Asselah et al 2018[c]*).

CLINICAL GUIDELINES

- In order to provide healthcare professionals with timely guidance, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) have developed a web-based process for the rapid formulation and dissemination of evidence-based, expert-developed recommendations for hepatitis C management (*AASLD-IDSA 2018*).
  - Recommended regimens are those that are favored for most patients in a given group, based on optimal efficacy, favorable tolerability and toxicity profiles, and duration.
  - The guidance also lists alternative regimens, which are those that are effective but, relative to recommended regimens, have potential disadvantages, limitations for use in certain patient populations, or less supporting data than recommended regimens. For a listing of alternative regimens, refer to the web-based guidance for full details.
- For the general genotype 1 population, the guidance recommends 4 different regimens considered to have comparable efficacy: Epclusa, Harvoni, Mavyret, and Zepatier. The level of evidence and treatment duration depend on the genotype 1 subtype, prior treatment status (naïve or experienced), and the presence of cirrhosis.
- The guidance recommends Epclusa and Mavyret for patients with genotype 2 or 3 infection.
- The guidance recommends Epclusa, Harvoni, Mavyret, and Zepatier for the treatment of genotype 4 infection. The guidance recommends Epclusa, Harvoni, and Mavyret for treatment of genotype 5 and 6.
- The guidance provides recommendations for several unique patient populations, including patients who have failed prior therapy with DAAs, co-infection with HIV/HCV, decompensated cirrhosis, recurrent HCV infection in the post-transplant setting, or renal impairment. Some key recommendations include:
  - Epclusa, Harvoni (listed as an alternative for patients with compensated cirrhosis), and Mavyret are recommended for genotype 1 patients with prior failure to HCV NS3/4A protease inhibitors. Epclusa (genotype 1b), Mavyret (regardless of genotype 1 subtype), and Vosevi (genotype 1a) are recommended for patients with prior failure to sofosbuvir-containing regimens.
  - Vosevi is recommended in genotype 1, 3, 4, 5, or 6 patients with prior failure to an NS5A inhibitor-containing regimen.
  - Sovaldi-based regimens (ie, Epclusa, Harvoni, Sovaldi plus Daklinza) are recommended for patients with decompensated cirrhosis.
  - HIV/HCV-co-infected patients should be treated and re-treated the same as patients without HIV infection, after recognizing and managing interactions with antiretroviral medications.
  - For patients with stage 4 or 5 CKD (creatinine clearance below 30 mL/min), Mavyret (regardless of genotype) and Zepatier (genotypes 1 and 4 only) are recommended. For kidney transplant recipients, Harvoni (genotypes 1 and 4 only) and Mavyret are recommended.

SAFETY SUMMARY

- Due to the DAAs used in combination therapy with PegIFN and RBV, all contraindications to those 2 medications (PegIFN and RBV) also apply to the class. This includes a contraindication for use in pregnancy due to the RBV component.
- Mavyret is contraindicated in patients with severe hepatic impairment (Child-Pugh C) and coadministration with atazanavir and rifampin.
- Viekira Pak is contraindicated in patients with:
  - Moderate to severe hepatic impairment (Child-Pugh B and C) due to the risk of potential toxicity.
  - Known hypersensitivity to ritonavir (eg, toxic epidermal necrolysis or Stevens-Johnson syndrome).
  - Concomitant use of drugs that are highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events.
  - Concomitant use of drugs that are moderate or strong inducers of CYP3A.
  - Concomitant use of drugs that are strong inducers or strong inhibitors of CYP2C8
- Vosevi is contraindicated in patients with rifampin coadministration.
- Zepatier is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C). It is also contraindicated with organic anion transporting polypeptides 1B1/3 (OATP1B1/3) inhibitors, strong inducers of CYP3A, and efavirenz.
- Daklinza is contraindicated in combination with drugs that strongly induce CYP3A.
- Key warnings and precautions for the DAAs include:

- Serious symptomatic bradycardia may occur in patients taking amiodarone and sofosbuvir in combination with another DAA (eg, Sovaldi plus Daklinza, Epclusa, Harvoni, Vosevi).
- Viekira Pak carries a risk of hepatic decompensation and hepatic failure in patients with cirrhosis.

- Overall, DAA combination therapies are well tolerated and discontinuations due to adverse events are not common.
  - The most common adverse reactions observed with each treatment regimen listed below include:
    - Daklinza in combination with Sovaldi: headache and fatigue
    - Daklinza in combination with Sovaldi and RBV: headache, anemia, fatigue, and nausea
    - Epclusa: headache and fatigue
    - Epclusa and RBV in patients with decompensated cirrhosis: fatigue, anemia, nausea, headache, insomnia, and diarrhea
    - Harvoni: fatigue, headache, and asthenia
    - Mavyret: headache and fatigue
    - Sovaldi in combination with RBV: fatigue and headache
    - Sovaldi in combination with PegIFN alfa and RBV: fatigue, headache, nausea, insomnia, and anemia
    - Viekira Pak with RBV: fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia.
    - Viekira Pak without RBV: nausea, pruritus, and insomnia
    - Vosevi: headache, fatigue, diarrhea, and nausea
    - Zepatier: fatigue, headache, and nausea.
    - Zepatier with RBV: anemia and headache

- In October 2016, the FDA announced that a new *Boxed Warning* would be added to all DAAs for HCV infection, regarding the risk of hepatitis B virus (HBV) reactivation. This *Boxed Warning* was based on case reports submitted to the FDA and from the published literature of HCV/HBV co-infected patients treated with DAAs from November 2013 to July 2016 (*FDA 2016*).
  - HBV can become reactivated in any patient who has a current or previous infection with HBV and is treated with DAAs. In a few cases, HBV reactivation in patients treated with DAAs resulted in serious liver problems or death.
  - The *Boxed Warning* was added to the labeling for all of the DAAs in February 2017. The warning directs healthcare providers to test all patients for evidence of current or prior HBV infection before initiation of HCV treatment. HCV/HBV co-infected patients should be monitored for HBV reactivation and hepatitis flare during HCV treatment and post-treatment follow-up. Appropriate patient management for HBV infection should be initiated as clinically indicated.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Route	Usual Recommended Frequency	Comments
Daklinza (daclatasvir)	Oral	One tablet once daily (60 mg dose); must be used in combination with Sovaldi	*Recommended dosage modification with CYP3A inhibitors and inducers*: • Strong CYP3A inhibitors and certain HIV antiviral agents: 30 mg once daily • Moderate CYP3A inducers and nevirapine: 90 mg once daily *Duration of therapy:* • 12 to 24 weeks (when used in combination with Sovaldi)
Epclusa (sofosbuvir/velpatasvir)	Oral	One tablet once daily	• No dosage recommendation can be given for patients with severe renal impairment or end-stage renal disease (ESRD).

Drug	Route	Usual Recommended Frequency	Comments
			Duration of therapy: • 12 weeks
Harvoni (ledipasvir/sofosbuvir)	Oral	One tablet once daily	• No dosage recommendation can be given for patients with severe renal impairment or ESRD. *Duration of therapy:* • 12 to 24 weeks
Mavyret (glecaprevir/pibrentasvir)	Oral	Three tablets daily	• Contraindicated in patients with severe hepatic impairment (Child-Pugh C). Not recommended in patients with moderate hepatic impairment (Child-Pugh B). *Duration of therapy:* • 8 to 16 weeks
Sovaldi (sofosbuvir)	Oral	One tablet once daily; must be used in combination with RBV ± PegIFN or Daklinza	• Safety and efficacy have not been established in patients with severe renal impairment. *Duration of therapy:* • 12 to 24 weeks (when used in combination with Daklinza)
Viekira Pak (ombitasvir/paritaprevir/ritonavir and dasabuvir)	Oral	Two ombitasvir, paritaprevir, ritonavir 12.5/75/50 mg tablets once daily (in the morning) and one dasabuvir 250 mg tablet twice daily (morning and evening)	• Contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C). *Duration of therapy:* • 12 to 24 weeks
Vosevi (sofosbuvir/velpatasvir/voxilaprevir)	Oral	One tablet once daily	• No dosage recommendation can be given for patients with severe renal impairment or ESRD. • Not recommended in patients with moderate or severe hepatic impairment (Child-Pugh B or C). *Duration of therapy:* • 12 weeks
Zepatier (elbasvir/grazoprevir)	Oral	One tablet once daily	• Testing patients with HCV genotype 1a infection for the presence of virus with NS5A resistance-associated polymorphisms is recommended prior to initiation of treatment with Zepatier to determine dosage regimen and duration. • Contraindicated in patients with moderate hepatic impairment

Drug	Route	Usual Recommended Frequency	Comments
			(Child-Pugh B) due to the lack of clinical safety and efficacy experience in HCV-infected Child-Pugh B patients, and in patients with severe hepatic impairment (Child-Pugh C) due to a 12-fold increase in grazoprevir exposure. *Duration of therapy:* • 12 to 16 weeks

See the current prescribing information for full details

CONCLUSION

- Hepatitis C is a disease affecting primarily the liver that results from infection with the hepatitis C virus. Long-term complications include cirrhosis and hepatocellular carcinoma. Hepatitis C is the leading indication for liver transplant.
- Success at obtaining an SVR is an important treatment goal and a common primary endpoint in the clinical trials of antiviral medications.
- PegIFN-free, DAA combination regimens, such as Epclusa, Harvoni, Mavyret, and Zepatier have become the standard of care for the treatment of genotype 1 infection. There is a lack of head-to-head trial data available comparing these regimens, but they are considered to have comparable efficacy and safety for treating the general genotype 1 population (*AASLD-IDSA 2018*).
- The only DAA fixed-dose combination products approved and recommended for the treatment of genotypes 2 and 3 infection are Mavyret and Epclusa (*AASLD-IDSA 2018*).
- Similar to genotype 1, several DAA combination regimens have demonstrated high SVR rates for genotype 4 infection. Epclusa, Harvoni, Mavyret, and Zepatier are recommended by the AASLD-IDSA guidance (*AASLD-IDSA 2018*).
- Data are limited for treatment of genotype 5 and 6 infection; however, Epclusa, Harvoni, and Mavyret are approved by the FDA and supported by the AASLD-IDSA guidance (*AASLD-IDSA 2018*).
- Of the combination products, Epclusa and Harvoni are the preferred treatment options in patients with decompensated cirrhosis (Child-Pugh B and C). Mavyret and Zepatier are recommended for patients with advanced kidney disease.

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INTRODUCTION

- Influenza is an infectious respiratory illness caused by the influenza A and influenza B viruses. Influenza epidemics occur annually in the United States, typically from late fall to early spring. Although the majority of infected individuals recover without complications, some cases of influenza result in severe illness or death *(Grohskopf et al 2018)*.
- The virus is primarily transmitted through direct contact with large-particle respiratory droplets from an infected individual's coughs and sneezes. It is also spread through contact with surfaces contaminated by infected respiratory droplets. Adults begin to shed virus 1 day prior to symptom onset, and they remain contagious for 5 to 7 days after falling ill *(Centers for Disease Control and Prevention [CDC] 2018[a])*.
- Signs and symptoms of uncomplicated influenza illness include fever, myalgia, headache, malaise, nonproductive cough, sore throat, and rhinitis. Complications of influenza infection include sinusitis, otitis media, pneumonia, sepsis, and exacerbation of chronic medical conditions. Elderly adults, young children, pregnant women, and patients with chronic medical conditions have a higher risk of developing complications from influenza *(CDC 2019[a], CDC 2019[b])*.
- Annual influenza vaccination is the most effective method for preventing seasonal influenza virus infection and its complications. Antiviral prescription medications are also available for influenza prophylaxis and treatment; however, antiviral chemoprophylaxis is not a substitute for annual influenza vaccination *(Grohskopf et al 2018)*.
- Initiation of antiviral therapy to treat influenza is recommended as early as possible for patients with confirmed or suspected influenza who are hospitalized; have severe, complicated, or progressive illness; or are at higher risk for influenza complications *(Fiore et al 2011)*.
- Three classes of antiviral medications are available and included in this review. The adamantanes include amantadine and Flumadine (rimantadine). The neuraminidase inhibitors include Rapivab (peramivir), Relenza (zanamivir), and Tamiflu (oseltamivir). Currently, the only endonuclease inhibitor on the market is Xofluza (baloxavir marboxil), which was approved by the Food and Drug Administration (FDA) in late October 2018.
- Resistance to adamantanes is high (> 99%) among currently circulating influenza A virus strains, and these agents lack activity against influenza B virus. Therefore, amantadine and rimantadine have not been recommended for treatment or chemoprophylaxis during recent influenza seasons *(CDC 2018[b])*.
- The neuraminidase inhibitors and baloxavir marboxil are active against both influenza A and influenza B viruses. Peramivir, zanamivir, oseltamivir, and baloxavir marboxil were the only antivirals recommended for the 2018-2019 influenza season in the United States *(CDC 2018[b])*.
- Circulating influenza viruses may evolve, and drug-resistant influenza virus strains have been reported. Prescribers should refer to influenza drug susceptibility patterns when selecting an antiviral agent *(CDC 2018[b])*.
- Medispan class: Antiparkinson, Dopaminergic and Influenza Agents. The only agent from the Antiparkinson, Dopaminergic category that will be included in this review is amantadine for the influenza indication.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
amantadine	✔
Flumadine (rimantadine)	✔
Rapivab (peramivir)	-
Relenza (zanamivir)	-
Tamiflu (oseltamivir)	✔
Xofluza (baloxavir marboxil)	-

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019)*

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication[1]	amantadine[2]	Flumadine (rimantadine)	Rapivab[3] (peramivir)	Relenza[4] (zanamivir)	Tamiflu[5] (oseltamivir)	Xofluza (baloxavir marboxil)
Prophylaxis and treatment of signs and symptoms of infection caused by various strains of influenza A virus	✔					
Prophylaxis and treatment of illness caused by various strains of influenza A virus in adults (17 years and older)		✔				
Prophylaxis against influenza A virus in children (1 to 16 years of age)		✔				
Treatment of acute uncomplicated influenza in patients 2 years and older who have been symptomatic for no more than 2 days			✔			
Prophylaxis of influenza in adults and pediatric patients aged 5 years and older				✔		
Treatment of uncomplicated acute illness due to influenza A and B virus in adults and pediatric patients aged 7 years and older who have been symptomatic for no more than 2 days				✔		
Prophylaxis of influenza A and B in patients 1 year and older					✔	
Treatment of acute, uncomplicated illness due to influenza A and B infection in patients 2 weeks of age and older who have been symptomatic for no more than 48 hours					✔	

Indication[1]	amantadine[2]	Flumadine (rimantadine)	Rapivab[3] (peramivir)	Relenza[4] (zanamivir)	Tamiflu[5] (oseltamivir)	Xofluza (baloxavir marboxil)
Treatment of acute uncomplicated influenza in patients 12 years and older who have been symptomatic for no more than 48 hours						✔

[1] The changing of viruses over time is a limitation of use for antivirals. The emergence of resistance mutations could decrease drug effectiveness. Other factors, such as changes in viral virulence, may also diminish the clinical benefit of antivirals. Prescribers should consider available information on influenza drug susceptibility patterns and treatment effects when selecting an antiviral.
[2] Amantadine is also indicated in the treatment of parkinsonism and drug-induced extrapyramidal reactions.
[3] Limitations of use for peramivir:
- Efficacy is based on clinical trials of naturally occurring influenza in which the predominant influenza infections were influenza A virus; a limited number of subjects infected with influenza B virus were enrolled.
- Efficacy could not be established in patients with serious influenza requiring hospitalization.

[4] Limitations of use for zanamivir:
- Not recommended for treatment or prophylaxis of influenza in individuals with underlying airways disease (such as asthma or chronic obstructive pulmonary disease) due to the risk of serious bronchospasm.
- Has not been proven effective for treatment of influenza in individuals with underlying airways disease.
- Has not been proven effective for prophylaxis of influenza in the nursing home setting.

[5] Limitations of use for oseltamivir:
- Not recommended for patients with end-stage renal disease not undergoing dialysis.

(Prescribing information: amantadine capsules 2018, amantadine oral solution 2016, amantadine tablets 2018, Flumadine 2010, Rapivab 2018, Relenza 2018, Tamiflu 2018, Xofluza 2018)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Adamantanes

- Clinical trials have demonstrated that the adamantanes are effective in both the prophylaxis and treatment of influenza A virus *(Bryson et al 1980, Crawford et al 1988, Dolin et al 1982, Hall et al 1987, Hayden et al 1989, Jackson et al 2011, Jefferson et al 2006[a], Jefferson et al 2006[b], Monto et al 1995, Reuman et al 1989)*.
- One systematic review assessed the efficacy and safety of adamantanes in healthy adults by analyzing 20 prophylaxis and 13 treatment randomized trials comparing amantadine or rimantadine with placebo. For prophylaxis, amantadine was 61% better than placebo at reducing influenza risk ($p < 0.001$). Although rimantadine was 72% better than placebo at preventing influenza, statistical significance was not achieved. There was significant heterogeneity between the prophylaxis trials, and only a small sample size was available for rimantadine compared to amantadine. For treatment, amantadine and rimantadine both reduced the duration of fever by 1 day. Both agents caused gastrointestinal side effects, but amantadine caused significantly more adverse effects in the central nervous system than rimantadine *(Jefferson et al 2006[a])*.
- The adamantanes are not currently recommended for treatment of influenza due to high levels of resistance in influenza A viruses and lack of efficacy against influenza B viruses (*CDC 2018[b], Uyeki et al 2019*).

Neuraminidase inhibitors

- The neuraminidase inhibitors have demonstrated efficacy for their respective indications. Zanamivir inhalation and oral oseltamivir are effective in both the prophylaxis and treatment of influenza A and B. Clinical trials have demonstrated a reduction in laboratory-confirmed influenza, illness, fever duration, secondary complications, and household contacts with influenza infection *(Aoki et al 2003, Chik et al 2004, Cooper et al 2003, Fry et al 2014, Halloran et al 2007, Hayden et al 1997, Hayden et al 1999, Hayden et al 2000, Hayden et al 2004, Hedrick et al 2000, Hiba et al 2011, Kaiser et al 2003, Kawai et al 2005, Kawai et al 2006, Lin et al 2006, MIST Study Group 1998, Monto et al 1999[a], Monto et al*

1999[b], Monto et al 2002, Nicholson et al 2000, Peters et al 2001, Reuman et al 1989, Singh et al 2003, Treanor et al 2000, Turner et al 2003, Wang et al 2012, Welliver et al 2001, Whitley et al 2001).

- One systematic review analyzed 20 oseltamivir and 26 zanamivir randomized, placebo-controlled trials in order to better define their efficacy and safety. In prophylaxis trials, the risk of symptomatic influenza was reduced by 3.05% in patients treated with oseltamivir compared to placebo and 1.98% in patients treated with zanamivir compared to placebo. In adults, the time to first alleviation of symptoms was reduced by 0.7 days ($p < 0.0001$) in patients receiving oseltamivir compared to placebo and 0.6 days ($p < 0.00001$) in patients receiving zanamivir compared to placebo. Oseltamivir significantly reduced the time to alleviation of symptoms in non-asthmatic children and decreased the incidence of self-reported pneumonia. Zanamivir significantly reduced the risk of bronchitis in adults with influenza. Neither treatment was a significant improvement over placebo in time to symptom alleviation in asthmatic children or risk of hospitalizations, otitis media, or sinusitis. Many studies included were at a high risk of selection bias due to inadequate reporting and a high risk of attrition bias due to selective reporting. All trials were sponsored by the manufacturers *(Jefferson et al 2014)*.
- In a systematic review of other published systematic reviews and meta-analyses, treatment of influenza with neuraminidase inhibitors (oseltamivir or zanamivir) was found to be likely effective in reducing mortality among hospitalized patients; the odds of mortality appeared especially lower when therapy was started early (within 48 hours of symptom onset). When used for treatment in the general population, these agents appear to reduce the duration of symptoms by approximately 0.5 to 1 day. Both oseltamivir and zanamivir were found likely to be effective at reducing secondary symptomatic influenza transmission when used prophylactically (*Doll et al 2017*).
- Peramivir intravenous (IV) infusion is approved for the treatment of influenza A and B in adults. The primary endpoint for the main clinical trial supporting FDA approval of peramivir was time to alleviation of symptoms. The trial evaluated 296 previously healthy adults presenting with the onset of influenza-like illness within the previous 48 hours and a positive influenza rapid antigen test. In this multicenter, double-blind, placebo-controlled clinical trial, patients were randomized to peramivir 300 mg, 600 mg, or placebo as a single IV dose. Acetaminophen use was permitted. Patients self-reported body temperature, symptoms, and resumption of activities over 14 days. The primary endpoint, the median time to alleviation of symptoms, was significantly earlier with peramivir 300 mg (59.1 hours) and 600 mg (59.9 hours) compared to placebo (81.8 hours; both $p = 0.0092$). There was no significant difference in the incidence of all adverse events in patients receiving peramivir compared to placebo. Diarrhea was the most common adverse event, occurring in 14.1%, 15.2% and 17% of the peramivir 300 mg, 600 mg, and placebo groups, respectively *(Kohno et al 2010)*.
- Studies have evaluated peramivir in hospitalized patients *(De Jong et al 2014, Ison et al 2014, Ison et al 2013)*. The Phase 3 clinical trial of peramivir in hospitalized influenza patients failed to meet its primary endpoint of reducing the time to clinical resolution compared to placebo. There are no clinical endpoints that have been validated for clinical trials of neuraminidase inhibitors treating hospitalized patients with influenza *(FDA 2014)*.
- Numerous placebo-controlled trials have demonstrated the efficacy of neuraminidase inhibitors individually, but head-to-head trials directly comparing the agents are limited. One randomized, double-blind, placebo-controlled safety trial compared the use of oseltamivir, zanamivir and placebo in 390 healthy adults for influenza chemoprophylaxis over 16 weeks. The study showed that both treatments were well tolerated compared to placebo, and there were no discontinuations due to adverse events *(Anekthananon et al 2013)*.
- A Phase 3, multinational, multicenter, double-blind, randomized, noninferiority trial compared a single dose of 300 or 600 mg IV peramivir to 5 days of oral oseltamivir in 1,091 patients with seasonal influenza. The primary endpoint, time to alleviation of influenza symptoms, had a median of 78.0 hours in patients receiving 300 mg of peramivir, 81.0 hours in patients receiving 600 mg of peramivir, and 81.8 hours in patients receiving oseltamivir. Both strengths of peramivir were noninferior to oseltamivir with a noninferiority margin of 0.170. There was no significant difference between treatments in the incidence of complications of influenza infection *(Kohno et al 2011)*.
- A meta-analysis including 2 controlled clinical trials and 5 observational trials (N = 1676) examined the comparative efficacy of IV peramivir and oral oseltamivir in the treatment of seasonal influenza. No significant differences between treatments were noted for the following outcomes: mortality, hospital length of stay, virus titer 48 hours after admission, and incidence of adverse events. However, the time to resolution of influenza symptoms or fever was shorter with peramivir than with oseltamivir treatment (mean difference, -7.17 hours; $p < 0.01$) (*Lee et al 2017*).
- Observational studies comparing the clinical efficacy of peramivir, zanamivir, and oseltamivir in treating influenza have demonstrated within-class variation in the time to alleviation of influenza symptoms. The lack of robust data from randomized, head-to-head trials prevents the recommendation of one neuraminidase inhibitor over another. Local and seasonal susceptibility trends, route of administration, and patient-specific factors such as age and compliance should be taken into account when selecting an agent for antiviral drug therapy *(Kawai et al 2008, Takemoto et al 2013)*.

- While influenza virus strains resistant to specific neuraminidase inhibitors have emerged, overall resistance remains low. According to surveillance data on seasonal influenza virus strains, the rate of resistance to oseltamivir is 1 to 3% and resistance to zanamivir is < 1% *(Li et al 2015)*.

Endonuclease inhibitor

- In a Phase 3, double-blind, randomized, placebo- and oseltamivir-controlled trial (CAPSTONE-1), 1436 patients 12 to 64 years of age with influenza-like illness were randomized in a 2:2:1 ratio to receive a single, weight-based oral dose of baloxavir marboxil, treatment-dose oseltamivir for 5 days, or matching placebo. The primary endpoint, time to alleviation of influenza symptoms, was 53.7 hours (95% confidence interval [CI], 49.5 to 58.5) with baloxavir marboxil compared with 80.2 hours (95% CI, 72.6 to 87.1) with placebo ($p < 0.001$). The median time to alleviation of symptoms was similar between baloxavir marboxil and oseltamivir (53.5 hours and 53.8 hours, respectively). Treatment-related adverse events were more common with oseltamivir (8.4%) than baloxavir marboxil (4.4%; $p = 0.009$), or placebo (3.9%) (*Hayden et al 2018*).

CLINICAL GUIDELINES

- Annual influenza vaccination is the most effective method for preventing seasonal influenza virus infection and its complications. All individuals 6 months of age and older should receive an influenza vaccination each year, unless contraindicated. Prophylactic antiviral administration is not a substitute for early influenza vaccination *(Grohskopf et al 2018)*.
- Amantadine and rimantadine are not recommended for antiviral treatment or prophylaxis of influenza in the United States due to high rates of resistance in influenza A viruses and lack of efficacy against influenza B viruses *(American Academy of Pediatrics [AAP] 2018, Fiore et al 2011, CDC 2018[b], Uyeki et al 2019)*.
- Key recommendations from the CDC include the following (*CDC 2018[b]*):
  - Widespread or routine use of antiviral medications for prophylaxis is not recommended except as one of multiple interventions to control institutional influenza outbreaks. Routine use of post-exposure chemoprophylaxis is not recommended, but may be considered in certain patients who are either not candidates for vaccination or received their annual vaccination less than 2 weeks prior to exposure. Oseltamivir and zanamivir are agents recommended for chemoprophylaxis.
  - The antivirals recommended for influenza treatment in the most recent influenza season included oseltamivir, zanamivir, peramivir, and baloxavir marboxil. Treatment of influenza with antiviral therapy is recommended as early as possible for patients with confirmed or suspected influenza who are hospitalized; have severe, complicated, or progressive illness; or are at a high risk for complications. Currently, oseltamivir is the recommended agent for hospitalized patients with influenza and those not hospitalized but with severe, complicated, or progressive influenza.
  - Populations at a high risk for influenza complications and recommended to receive antiviral treatment include children younger than 2 years old, adults age 65 and above, pregnant or postpartum women, American Indians, Alaska Natives, obese patients with a body mass index (BMI) of 40 kg/m^2 and above, patients younger than 19 years old receiving long-term treatment with aspirin, residents of nursing homes, and patients with immunosuppression, chronic disorders (eg, pulmonary, cardiovascular, renal, hepatic, hematological and metabolic), or neurologic conditions.
  - Early antiviral treatment can shorten the duration of fever and illness symptoms, and may reduce the risk of influenza-related complications such as otitis media, pneumonia, and respiratory failure. In observational studies, early treatment with oseltamivir has been reported to reduce deaths in hospitalized adults and shorten the duration of hospitalization in children. Clinical benefit is greatest when antiviral treatment is administered early, especially within 48 hours of influenza illness onset.
- Key recommendations from the Infectious Diseases Society of America include the following (*Uyeki et al 2019*):
  - Clinicians should start antiviral treatment as soon as possible for adults and children with documented or suspected influenza who are hospitalized, have severe or progressive illness, or are at high risk of complications; children < 2 years and adults ≥ 65 years of age; and women who are pregnant or within 2 weeks postpartum.
  - Clinicians can consider antiviral treatment for patients with documented or suspected influenza who are not at high risk of complications if they are outpatients with illness onset ≤ 2 days before presentation, or symptomatic outpatients who are household contacts or healthcare providers of persons at high risk of developing complications.
  - A single neuraminidase inhibitor (oseltamivir, zanamivir, or peramivir) is recommended for treatment; combination neuramidase inhibitors are not recommended.

- Otherwise healthy, ambulatory patients with uncomplicated influenza should receive a 5-day course of treatment with oral oseltamivir or inhaled zanamivir, or a single dose of intravenous peramivir; a longer course can be considered for those with immunocompromising conditions or requiring hospitalization for lower respiratory tract disease.
- Antiviral drugs should not be used for routine or widespread chemoprophylaxis outside of institutional outbreaks.
- Antiviral chemoprophylaxis can be considered for certain individuals including adults and children ≥ 3 months at very high risk for complications who are not eligible for vaccination or for whom the vaccine is expected to have low effectiveness, and those in close contact with individuals at high risk of complications who are not eligible for vaccination or chemoprophylaxis. Oral oseltamivir or inhaled zanamivir are the recommended agents for preexposure chemoprophylaxis.

SAFETY SUMMARY

- Common adverse events with adamantanes include nausea, dizziness, insomnia, headache, anorexia, dry mouth, and agitation.
- Amantadine and rimantadine should be used with caution in patients with epilepsy due to an increased risk for seizures.
- Amantadine has anticholinergic effects and is contraindicated in patients with untreated angle closure glaucoma. There have also been reports of death from overdose and suicide attempts with amantadine.
- Common adverse events with neuraminidase inhibitors include nausea, vomiting, and headache. The most common adverse effect with peramivir is diarrhea.
- All 3 neuraminidase inhibitors have labeled warnings for neuropsychiatric events such as hallucinations and delirium. Patients should be monitored for signs of abnormal behavior.
- Oseltamivir and peramivir have warnings for serious skin and hypersensitivity reactions, including Stevens-Johnson syndrome.
- Zanamivir has a warning for bronchospasm and should not be used in patients with asthma or chronic obstructive pulmonary disease. It is also contraindicated in patients with milk protein allergies.
- Common adverse events with baloxavir marboxil include diarrhea, headache, bronchitis, nausea, and nasopharyngitis.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration*

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
amantadine	Capsules, oral solution, tablets	Oral	Once daily or twice daily Adults: 200 mg once daily or 100 mg twice daily Pediatric patients: 1 to 9 years: 4.4 to 8.8 mg/kg/day not to exceed 150 mg per day 9 to 12 years: 100 mg twice daily The safety and efficacy of amantadine in newborn infants and infants below the age of 1 year have not been established.	Should be taken for 10 days following a known exposure. If using in conjunction with vaccine until antibody response, take for 2 to 4 weeks. Treatment of illness should be started within 24 to 48 hours of symptom onset and continued for 24 to 48 hours after symptoms disappear. For adult patients intolerant to 200 mg daily dose because of central nervous system or other toxicities: 100 mg daily dose Because amantadine is primarily excreted in the urine, it accumulates when renal function declines. Thus, the dose of amantadine should be reduced in patients with renal impairment and in individuals who are 65 years of age or older according to the following:

				For CrCl 30 to 50 mL/min: 200 mg 1st day, then 100 mg daily For CrCl 15 to 29 mL/min: 200 mg 1st day, then 100 mg on alternate days For CrCl < 15 mL/min and HD: 200 mg every 7 days For patients ≥ 65 years: 100 mg once daily The dose of amantadine may need reduction in patients with congestive heart failure, peripheral edema, or orthostatic hypotension.
Flumadine (rimantadine)	Tablets	Oral	Twice daily **Adults (17 years and older)** Treatment: 100 mg twice daily for 7 days Prophylaxis: 100 mg twice daily **Pediatric patients** Prophylaxis in patients 1 to 9 years: 5 mg/kg/day, not to exceed 150 mg per day 10 to 16 years: Refer to the adult dose The safety and efficacy of rimantadine in pediatric patients below the age of 1 year have not been established.	Treatment of illness should be started within 48 hours of symptoms. A suspension can be made from the tablets and is stable for 14 days. Dose adjustment in patients ≥ 65 years: 100 mg once daily Dose adjustment in patients with CrCl < 29 mL/min: 100 mg daily Dose adjustment in patients with severe hepatic dysfunction: 100 mg daily
Rapivab (peramivir)	Injection	IV	Patients ≥ 13 years: 600 mg as a single dose Patients < 13 years: 2 to 12 years: 12 mg/kg (maximum dose 600 mg) as a single dose Safety and effectiveness in pediatric patients < 2 years of age have not been established.	One time dose should be provided within 2 days of onset of influenza symptoms A single dose administered by IV infusion for a minimum of 15 minutes. Peramivir must be diluted prior to administration. Dose adjustment in adults and adolescents 13 years of age or older with CrCl = 30 to 49 mL/min: 200 mg

				Dose adjustment in pediatric patients 2 to 12 years of age with CrCl 30 to 49 mL/min: 4 mg/kg Dose adjustment in adults and adolescents 13 years of age or older with CrCl 10 to 29 mL/min: 100 mg Dose adjustment in pediatric patients 2 to 12 years of age with CrCl 10 to 29 mL/min: 2 mg/kg HD: Administer after dialysis
Relenza (zanamivir)	Inhalation powder (in blisters)	Oral inhalation via Diskhaler device	Once daily or twice daily, depending on the indication Treatment (≥ 7 years): 10 mg twice daily for 5 days Prophylaxis in household setting (≥ 5 years): 10 mg once daily for 10 days Prophylaxis in community outbreak (adults and adolescents): 10 mg once daily for 28 days	The 10 mg dose is provided by 2 inhalations (one 5 mg blister per inhalation). Patients scheduled to use an inhaled bronchodilator at the same time as zanamivir should use their bronchodilator before taking zanamivir. If zanamivir is prescribed for children, it should be used only under adult supervision and instruction, and the supervising adult should first be instructed by a healthcare professional. Due to the low systemic bioavailability of zanamivir following oral inhalation, no dosage adjustments are necessary for patients with renal impairment; however, the potential for drug accumulation should be considered.
Tamiflu (oseltamivir)	Capsules, powder for oral suspension	Oral	Once daily or twice daily, depending on the indication **Patients ≥ 13 years** Treatment: 75 mg twice daily for 5 days Prophylaxis: 75 mg once daily for at least 10 days following close contact with an infected individual and up to 6 weeks during a community outbreak. In immunocompromised patients, may be continued for up to 12 weeks. **Patients < 13 years** Treatment: • 2 weeks to < 1 year: 3 mg/kg twice daily for 5 days	Start treatment within 48 hours of symptom onset or close contact with the infected individual. Taking with food may enhance tolerability. In an emergency, a suspension can be made from capsules. Dosage adjustment is recommended for patients with a CrCl between 10 and 60 mL/minute and for patients with ESRD undergoing routine HD or CAPD. Not recommended for patients with ESRD not undergoing dialysis. No dosage adjustment for mild to moderate hepatic impairment. Safety not evaluated in patients with severe hepatic impairment.

			• 1 to 12 years: 30 to 75 mg twice daily for 5 days; specific weight-based dosing recommendations as follows: ○ ≤ 15 kg: 30 mg twice daily ○ 15.1 kg to 23 kg: 45 mg twice daily ○ 23.1 kg to 40 kg: 60 mg twice daily ○ ≥ 40.1 kg: 75 mg twice daily <u>Prophylaxis</u>: • 1 to 12 years: 30 to 75 mg once daily for 10 days; specific weight-based dosing recommendations as follows: ○ ≤ 15 kg: 30 mg once daily ○ 15.1 kg to 23 kg: 45 mg once daily ○ 23.1 kg to 40 kg: 60 mg once daily ○ ≥ 40.1 kg: 75 mg once daily • During a community outbreak, can continue for up to 6 weeks (or up to 12 weeks in immuno-compromised patients).	
Xofluza (baloxavir marboxil)	Tablets	Oral	Single, weight-based dose <u>Patients 40 kg to < 80 kg:</u> • Single dose of 40 mg <u>Patients ≥ 80 kg:</u> • Single dose of 80 mg Safety and effectiveness in pediatric patients < 12 years of age have not been established.	Initiate treatment within 48 hours of symptom onset. Take orally as a single dose with or without food; however, coadministration with dairy products, calcium-fortified beverages, polyvalent cation-containing laxatives, antacids, or oral supplements should be avoided. No dosage adjustment is recommended for CrCl ≥ 50 mL/min or mild to moderate hepatic impairment; safety has not been evaluated in severe renal or hepatic impairment.

CAPD=continuous ambulatory peritoneal dialysis; CrCl =creatinine clearance; ESRD=end stage renal disease; HD=hemodialysis
*See the current prescribing information for full details

CONCLUSION

- The first line of protection against influenza is vaccination. All individuals 6 months of age and older without contraindications should receive yearly influenza vaccination *(AAP 2018, Fiore et al 2011, Grohskopf et al 2018)*.
- Antivirals are available for the prevention and treatment of influenza. Overall, the adamantanes, the neuraminidase inhibitors, and baloxavir marboxil (an endonuclease inhibitor) have demonstrated safety and efficacy for their respective

indications. However, amantadine and rimantadine are not currently recommended due to high rates of resistance in circulating influenza virus strains *(CDC 2018[b])*.

- Zanamivir and oseltamivir are both effective in preventing influenza and are recommended in certain situations for chemoprophylaxis, but are not substitutes for annual vaccination *(CDC 2018[b], Uyeki et al 2019)*. Peramivir and baloxavir marboxil are not approved or recommended for influenza prophylaxis *(CDC 2018[b])*.
- Peramivir, zanamivir, oseltamivir, and baloxavir marboxil effectively treat influenza by reducing the duration of fever and illness. Initiation of treatment is recommended as soon as possible for patients with suspected influenza who are hospitalized, severely ill, or at high risk for influenza complications (*CDC 2018[b]*).
- Limited within-class comparisons prevent the recommendation of one neuraminidase inhibitor over another. Factors to consider when selecting an antiviral agent include the route of administration, seasonal and geographical susceptibility trends, and patient-specific factors such as age and compliance *(Takemoto et al 2013)*.
- The most common adverse events with amantadine and rimantadine are nausea, insomnia, dizziness, headache, anorexia, dry mouth, and agitation. The adamantanes are associated with an increased risk for seizures.
- The most common adverse events with zanamivir and oseltamivir are headache, nausea, and vomiting. Diarrhea is the most common adverse event with peramivir. The neuraminidase inhibitors have a labeled warning for neuropsychiatric events such as delirium and abnormal behavior leading to injury.
- The most common adverse events with baloxavir marboxil are diarrhea, headache, bronchitis, nausea, and nasopharyngitis.

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Therapeutic Class Overview
Macrolides

INTRODUCTION

- The first agent in the macrolide class, erythromycin, has been used since the 1950s to treat respiratory tract infections and skin and soft tissue infections. Limitations of its use include gastrointestinal intolerance and a short half-life, which makes multiple daily doses necessary.
- Zithromax (azithromycin) and Biaxin (clarithromycin) have broader activity, more favorable pharmacokinetics and pharmacodynamics, and are better tolerated (*Zuckerman et al 2011*). These agents have been used for the treatment of respiratory tract infections, sexually transmitted diseases, and infections caused by *Helicobacter pylori* and *Mycobacterium avium* complex (MAC).
- Dificid (fidaxomicin) is the newest agent in the macrolide category. It exhibits minimal systemic absorption, high fecal concentrations, a long post-antibiotic effect, and restricted activity against normal gut flora, providing active and selective therapy for infection with *Clostridium difficile* (*Louie et al 2009, Tannock et al 2010*).
- Ketek (telithromycin) was the first member of the related ketolide group of antibiotics; however, telithromycin is no longer available in the US market (*Clinical Pharmacology 2019, FDA Web site 2018*).
- This review will focus on the following: Macrolide class containing azithromycin, clarithromycin, erythromycin, and fidaxomicin. Injectable and ophthalmic forms of azithromycin and erythromycin will not be discussed in this review.
- Medispan Class: Macrolides

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Biaxin* (clarithromycin)	✔
Biaxin XL* (clarithromycin extended-release)	✔
Dificid (fidaxomicin)	--
E.E.S., Ery-Tab, EryPed, Erythrocin (erythromycin)	✔
Zithromax (azithromycin)	✔

*The branded product is no longer marketed.

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	azithromycin	clarithromycin	clarithromycin XL	erythromycin	Dificid (fidaxomicin)
Pharyngitis/tonsillitis due to *Streptococcus pyogenes*	✔ a	✔ a			
Helicobacter pylori infection and duodenal ulcer disease[b]		✔			
Acute maxillary sinusitis due to *Haemophilus influenzae, Moraxella catarrhalis*, or *Streptococcus pneumoniae*	✔	✔ a	✔		
Acute bacterial exacerbation of chronic bronchitis due to *Haemophilus influenzae, Haemophilus parainfluenzae, Moraxella catarrhalis*, or *Streptococcus pneumoniae*	✔ c	✔	✔		
Community-acquired pneumonia (CAP) due to *Haemophilus influenzae, Mycoplasma pneumoniae, Streptococcus pneumoniae*, or *Chlamydophila pneumoniae*.	✔ d	✔ a	✔ e		

Indication	azithromycin	clarithromycin	clarithromycin XL	erythromycin	Dificid (fidaxomicin)
Uncomplicated skin and skin structure infections due to *Staphylococcus aureus* or *Streptococcus pyogenes*	✔ f	✔ a			
Disseminated mycobacterial infections due to *Mycobacterium avium* or *Mycobacterium intracellulare*	✔ g	✔ a			
Prevention of disseminated *Mycobacterium avium* complex (MAC) disease in patients with advanced HIV infection	✔ h	✔ a			
Acute otitis media due to *Haemophilus influenzae, Moraxella catarrhalis*, or *Streptococcus pneumoniae* in children	✔	✔			
Urethritis and cervicitis due to *Chlamydia trachomatis* or *Neisseria gonorrhoeae*	✔				
Genital ulcer disease in men due *to Haemophilus ducreyi* (chancroid)	✔				
Clostridium difficile-associated diarrhea in adults (≥18 years of age)					✔
Non-gonococcal urethritis and cervicitis due to *Chlamydia trachomatis*	✔ i				
Rheumatic fever, prophylaxis of adults and children				✔	
Chlamydial infection				✔	
Diphtheria, adjunct to antitoxin in adults and children				✔	
Erythrasma in adults and children				✔	
Female gonococcal pelvic inflammatory disease in adults and children				✔	
Entamoeba histolytica-intestinal infectious disease in adults and children				✔	
Infection of skin or subcutaneous tissue in adults and children				✔	
Legionnaires disease in adults and children				✔	
Listeriosis in adults and children				✔	
Neonatal chlamydial conjunctivitis in children				✔	
Neonatal chlamydial pneumonia in children				✔	
Nongonococcal urethritis				✔	
Pertussis in adults and children				✔	
Respiratory tract infection in adults and children				✔	
Syphilis in adults and children				✔	

[a] Also indicated for children; for clarithromycin, CAP due to *Haemophilus influenzae* is not approved in children.
[b] Tablets in combination with amoxicillin and Prevacid (lansoprazole) or Prilosec (omeprazole) as triple therapy.
[c] Azithromycin is not indicated for *Haemophilus parainfluenzae*. This was previously termed as acute exacerbations of chronic obstructive pulmonary disease.
[d] Also indicated for children. Should not be used in patients with pneumonia who are judged to be inappropriate for oral therapy because of moderate to severe illness or risk factors such as any of the following: cystic fibrosis, nosocomially acquired infections, known or suspected bacteremia, requiring hospitalization, elderly or debilitated patients, or significant underlying health problems that may compromise ability to respond to illness (including immunodeficiency or functional asplenia).
[e] Also approved for *Haemophilus parainfluenzae* and *Moraxella catarrhalis.*
[f] Also approved for *Streptococcus agalactiae.*
[g] 600 mg tablet taken in combination with ethambutol.
[h] 1200 mg taken alone or in combination with rifabutin.
[i] One gram dose.

(Micromedex 2.0 2019, Prescribing information: Clarithromycin 2018, Clarithromycin extended-release 2019, Dificid 2019, E.E.S. 2018, Ery-Tab 2018, EryPed 2019, Erythrocin 2018, Zithromax 2018)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Overall, the macrolide antibiotics have demonstrated efficacy for their respective indications, and available head-to-head studies do not consistently demonstrate the superiority of one macrolide over another.
- Studies evaluating the macrolides in the treatment of acute bacterial sinusitis demonstrate similar clinical and bacteriologic response rates with azithromycin and amoxicillin, amoxicillin/clavulanate, and levofloxacin *(Henry et al 2003, Klapan et al 1999, Murray et al 2005*).
- For the treatment of acute bacterial exacerbations of chronic bronchitis, 1 trial demonstrated no significant difference between clarithromycin and erythromycin in clinical and bacteriologic response rates, and another trial showed no significant difference between 7 days of treatment with immediate-release and 5 days of treatment with extended-release clarithromycin *(Gotfried et al 2005, Swanson et al 2005).* A pooled analysis of studies in the treatment of lower respiratory tract infections, including acute bronchitis and pneumonia did not find a significant difference between azithromycin and amoxicillin or amoxicillin/clavulanate (*Laopaiboon et al 2015*). A network meta-analysis of 48 studies examined the relative efficacy and safety of various antibiotics in the treatment of bronchitis and found no difference in efficacy between macrolides and beta-lactams or quinolones (*Wang et al 2017*).
- There are not enough data to make a conclusion about the efficacy of macrolides compared to non-macrolide antibiotics for the treatment of pediatric community-acquired lower respiratory tract infections caused by *Mycoplasma pneumoniae (Gardiner et al 2015).*
- For the treatment of *C. difficile* diarrhea, fidaxomicin was shown in clinical trials to be non-inferior to vancomycin in clinical cure rates, although it was also shown to have significantly lower rates of recurrence and higher rates of global cure *(Cornely et al 2012, Crook et al 2012, Louie et al 2011).* A meta-analysis of antibiotic treatments for *C. difficile*-associated diarrhea found statistical superiority of fidaxomicin over vancomycin in achieving symptomatic cure when pooling results from 2 trials *(Nelson et al 2017).* An additional meta-analysis of treatments for recurrent *C. difficile* infection found that fidaxomicin was superior to vancomycin and metronidazole in achieving a sustained symptomatic cure (*Beinortas et al 2018*).
- Regimens for the treatment of *H. pylori* infection have demonstrated varying results. One study demonstrated significantly better eradication rates with quadruple therapy (omeprazole, bismuth, metronidazole, and tetracycline) compared to triple therapy (clarithromycin, amoxicillin, and omeprazole) *(Malfertheiner et al 2011).* Similarly, another study demonstrated significantly higher eradication rates with quadruple therapy with pantoprazole, bismuth, metronidazole, and tetracycline compared to triple therapy with clarithromycin, amoxicillin, and pantoprazole (*Zheng et al 2010*). A study which compared clarithromycin vs metronidazole-based triple therapy (both combined with esomeprazole and amoxicillin) found significantly higher eradication rates in the group that received metronidazole-based triple therapy (*Adachi et al 2017*). A recent meta-analysis of 44 randomized controlled trials comparing triple therapy (proton pump inhibitor [PPI], clarithromycin, and amoxicillin) and quadruple sequential therapy (amoxicillin plus PPI for 5 days, followed by PPI, clarithromycin and metronidazole for 5 days) showed that eradication rates were statistically significantly better for the quadruple sequential group overall ($p < 0.001$), but equivalent when triple therapy lasted for 10 or 14 days. Neither group achieved optimal efficacy of ≥ 90% eradication rate *(Nyssen et al 2016).*
- A study demonstrated no significant difference between azithromycin and clarithromycin in sterilization rates in patients with human immunodeficiency virus (HIV) and positive blood cultures for MAC disease *(Dunne et al 2001).* However, it is important to note that the study did not enroll the target number of patients, reducing the power of the study to 61%. A meta-analysis of 14 studies examining macrolide-containing regimens for the treatment of MAC found that macrolide-containing regimens have a treatment success rate of 60% (*Kwak et al 2017*). Clarithromycin has shown efficacy compared to placebo in the prevention of the development of disseminated MAC infection in patients with HIV (*Pierce et al 1996*).
- In the treatment of acute otitis media (AOM), azithromycin and clarithromycin have generally shown similar clinical efficacy when compared to other antibiotic agents including amoxicillin, amoxicillin/clavulanate, and cefdinir (*Arguedas et al 2005, Aspin et al 1994, Block et al 2005).*

- For the treatment of pertussis, azithromycin has shown efficacy in an open-label study, with up to 100% eradication rates (*Pichichero et al 2003).* A study directly comparing azithromycin, clarithromycin, and erythromycin demonstrated 100% eradication rates for all agents after 2 weeks (*Aoyama et al 1996).* Other studies comparing the macrolides for the treatment of pertussis show similar results *(Langley et al 2004, Lebel et al 2001).*
- Head-to-head studies evaluating the treatment of pharyngitis and pneumonia generally show no significant difference between agents in clinical and bacteriologic response *(Drehobl et al 2005, O'Doherty et al 1998, Schonwald et al 1990, Venuta et al 1998)*. For the treatment of multiple diseases including pharyngitis, pneumonia and skin and skin structure infections, a study demonstrated no significant difference in clinical response between immediate- and extended-release clarithromycin *(Block et al 2006).*
- For the treatment of pelvic inflammatory disease, a Cochrane review found no clear difference between azithromycin and doxycycline. A sensitivity analysis that included a single study with low risk of bias found that azithromycin was superior to doxycycline for mild to moderate pelvic inflammatory disease (*Savaris et al, 2017*).
- A Cochrane review of 14 RCTs evaluated the safety and efficacy of antibiotic treatments for genital infections with *C. trachomatis*, and found a higher rate of microbiological failure in men treated with azithromycin single-dose vs doxycycline once or twice daily for 7 days (RR, 2.45; 95% CI, 1.36 to 4.41); the effect of both treatments on clinical failure was uncertain (RR, 0.94; 95% CI, 0.43 to 2.05). Results for microbiological failure with azithromycin vs doxycycline in women were uncertain (RR, 1.71; 95% CI, 0.48 to 6.16), and no studies assessed clinical failure. Azithromycin is likely associated with fewer adverse events compared to doxycycline in both men and women (RR, 0.83; 95% CI, 0.71 to 0.98) *(Páez-Canro et al 2019)*.

CLINICAL GUIDELINES

- Per treatment guidelines, azithromycin and clarithromycin are recommended as first-line treatment for CAP, prevention of MAC in children, and treatment of MAC in children and adults *(Bradley et al 2011, Mandell et al 2007, Panel 2019[b], Uthman et al 2013)*. Both azithromycin and clarithromycin were also previously recommended for the prevention of MAC in adults; however, a recent update to the guidelines no longer recommends primary prophylaxis against disseminated MAC disease in patients with HIV who initiate ART therapy immediately. In patients whom prophylaxis is being considered, azithromycin and clarithromycin are still the preferred agents (*Panel 2019[a]*). Clarithromycin is also recommended as part of a multi-drug regimen for *H. pylori* infections (*Chey et al 2017, Jones et al 2017*).
- Macrolides are recommended as first-line treatment for pertussis, some sexually transmitted infections such as chancroid, urethritis, cervicitis, chlamydia, some skin and soft tissue infections such as impetigo (although some strains of *Staphylococcus aureus* and *Streptococcus pyogenes* may be resistant), cat scratch disease, and bacillary angiomatosis *(CDC 2005, Stevens et al 2014, Workowski 2015)*. Azithromycin should not be used in patients with cardiovascular disease due to the risk of abnormal electrical activity of the heart that may lead to a potentially fatal irregular heart rhythm; an alternative macrolide should be selected (*CDC 2017).*
- Per treatment guidelines, azithromycin in combination with ceftriaxone is recommended as first-line treatment for gonorrhea (*Workowski 2015).*
- The macrolides are recommended as an alternative treatment for Group A streptococcal pharyngitis *(Shulman et al 2012, Short et al 2017, van Driel et al 2016).* In general, children that require treatment of AOM should receive high-dose amoxicillin 90 mg/kg/day if amoxicillin has not been given in the last 30 days or the child does not have purulent conjunctivitis *(Lieberthal et al 2013*). For children with recent amoxicillin use, concurrent purulent conjunctivitis, or penicillin allergy, an antibiotic with additional beta-lactamase coverage for AOM should be prescribed. Macrolides such as erythromycin and azithromycin have limited efficacy against *Haemophilus influenzae* and *S. pneumoniae.*
- Azithromycin is recommended to be used to improve lung function and reduce exacerbations in individuals aged 6 years and older who have cystic fibrosis with *Pseudomonas aeruginosa* persistently present in cultures of the airways. In individuals without *P. aeruginosa* persistently present in cultures of the airways, the chronic use of azithromycin should be considered to reduce exacerbations *(Mogayzel et al 2013).* Treatment appears safe over a 6-month period (*Southern et al 2012*).
- For exacerbations of chronic obstructive pulmonary disease (COPD) that are due to bacterial infections, it is recommended to use amoxicillin with clavulanate, a macrolide, or tetracycline *(GOLD 2019).*
- First-line treatment for acute sinusitis is amoxicillin-clavulanate. Macrolides are no longer recommended due to increasing resistance (*Short et al 2017).*

- Fidaxomicin is a unique agent for the treatment of *C. difficile* diarrhea. Preliminary data suggest it may have efficacy in treating more resistant strains than metronidazole or vancomycin. It may also decrease the number of recurrent infections. Older guidelines mention this agent as a treatment option for severe cases of *C. difficile* diarrhea but do not explicitly recommend its use due to a lack of data (*Surawicz et al 2013, Steele et al 2015).* More recent guidelines recommend the use of either fidaxomicin or vancomycin as initial therapy for *C. difficile* diarrhea, as well as in recurrent episodes *(McDonald 2018)*.

SAFETY SUMMARY

- The most frequently reported adverse events for macrolides are gastrointestinal in nature and include nausea/vomiting, abdominal pain, abnormal taste, dyspepsia, and diarrhea/loose stools. In clinical trials, patients also reported headache, and pediatric patients reported rashes.
- The macrolides should not be used in patients reporting a sensitivity or hepatic dysfunction with previous use.
- The macrolides act on the cytochrome (CYP) P450 system; therefore, many drug interactions can occur. Some interactions include the statins, pimozide, colchicine, protease inhibitors, and calcium channel blockers.
- Prolongation of the QTc interval has been reported with use of these agents. They should not be used in patients with congenital QTc interval prolongation or in patients with proarrhythmic conditions.
- With the exception of fidaxomicin, all agents in the class can cause hepatic injury. If signs and symptoms occur, the drug should be discontinued immediately.
- A large, multicenter, randomized controlled trial that studied the effects of a 2-week course of clarithromycin on patients with stable coronary heart disease who were followed for up to 3 years found a significant increase in cardiovascular mortality associated with the use of clarithromycin (*Jespersen 2006*). A 10-year follow-up to the initial study found that clarithromycin was associated with an increased risk of all-cause mortality and cerebrovascular disease (*Winkel 2015*). Risks and benefits of clarithromycin treatment should be weighed in patients with suspected or confirmed coronary artery disease.
- Azithromycin and clarithromycin have been associated with serious allergic and skin reactions, including angioedema, anaphylaxis, acute generalized exanthematous pustulosis, Stevens-Johnson syndrome, toxic epidermal necrolysis, and drug reaction with eosinophilia and systemic symptoms (DRESS). These may recur even after discontinuation of therapy. Fatalities have been reported.
- In August 2018, the FDA issued a warning that azithromycin should not be used as a long-term prophylaxis therapy against bronchiolitis obliterans syndrome in patients after a stem cell transplant (*FDA MedWatch 2018)*. Results of a clinical trial indicated that use of azithromycin in this setting may increase the risk of cancer relapse and death.
- Azithromycin and erythromycin are Pregnancy Category B (no evidence of risk in humans, but there remains a remote possibility; animal reproductive studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women). Clarithromycin is not recommended for use in pregnant women based on animal reproduction studies that have shown an adverse effect on the fetus; current data in humans are insufficient to inform drug-associated risks. The labeling for fidaxomicin has also been updated to follow the FDA's Pregnancy and Lactation Labeling Rule Conversion, and states that there are limited data in humans to inform any drug-associated risk; however, reproduction studies in animals have not shown evidence of harm to the fetus. Safety labeling changes for erythromycin products include a precaution that observational studies have described cardiovascular malformations that have occurred in early pregnancy after exposure to erythromycin products.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Biaxin (clarithromycin)	Granules for suspension, tablet	Oral	Twice daily	The dose of clarithromycin should be reduced by 50% in patients with creatinine clearance (CrCL) < 30 mL/min; for patients with CrCL 30 to 60 mL/min taking atazanavir or ritonavir, the clarithromycin dose
Biaxin XL (clarithromycin extended release)	Extended release tablet	Oral	Once daily	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				should be reduced by 50%; for CrCL < 30 mL/min and on atazanavir or ritonavir, the clarithromycin dose should be reduced by 75%.
Dificid (fidaxomicin)	Tablet	Oral	Twice daily	
E.E.S., Ery-Tab, EryPed, Erythrocin	Delayed release capsule, suspension, delayed release tablet, film-coated tablet, tablet	Oral	Two to 4 times daily	Use caution in patients with impaired hepatic function.
Zithromax (azithromycin)	Dose packet, suspension, tablet	Oral	Once daily	

See the current prescribing information for full details

CONCLUSION

- The macrolides have been proven effective by clinical trials for many different infections; however, antibiotics are overused, and thus, many bacteria have become resistant to the macrolides as well as other antibiotics. Selection of agents for treatment of different infections is based on local susceptibility patterns.
- Per treatment guidelines (*Bradley et al 2011, Chey et al 2017, Mandell et al 2007, Panel 2019[a], Panel 2019[b]*), azithromycin and clarithromycin are recommended as first line treatment for CAP, prevention and treatment of MAC in children and treatment of MAC in adults, and clarithromycin as part of a multi-drug regimen for *H. pylori* infections.
- Macrolides are recommended as first line treatment for pertussis, some sexually transmitted infections, and some skin and soft tissue infections (*CDC 2005, Stevens et al 2014, Workowski 2015*).
- The macrolides are recommended as an alternative treatment for Group A streptococcal pharyngitis (*Shulman et al 2012, Short et al 2017, van Driel et al 2016*).
- The macrolides are often used when patients are allergic to penicillins (*Stevens et al 2014, Workowski 2015*).
- Dificid (fidaxomicin) is recommended in recent *C. difficile* treatment guidelines as an initial therapy alternative to vancomycin for *C. difficile* diarrhea, as well as in recurrent infections (*McDonald 2018*). Earlier guidelines suggest that it may have a place in therapy for severe, recurrent cases due to limited data (*Cohen et al 2010, Surawicz et al, 2013, Steele et al 2015*).
- The most common side effects seen with the macrolides are gastrointestinal including nausea/vomiting, diarrhea, and abdominal pain.
- Many drug interactions can occur with agents in this category due to their action on the CYP 450 system; caution should be used when adding a macrolide to a patient's drug regimen.

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INTRODUCTION

- Immunomodulators treat a wide variety of conditions, including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), plaque psoriasis (PsO), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC), hidradenitis suppurativa (HS), and uveitis (UV), as well as several less common conditions.
- T cells, B cells, and cytokines such as tumor necrosis factor (TNF), interleukin-1 (IL-1) and interleukin-6 (IL-6) play a key role in the inflammatory and immune process (*Choy et al 2001*). This has led to the development of biologic agents to target these areas. The Food and Drug Administration (FDA) has currently approved 5 originator TNF inhibitors: Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Remicade (infliximab), and Simponi/Simponi Aria (golimumab), as well as 7 biosimilar TNF inhibitors: Amjevita (adalimumab-atto), Erelzi (etanercept-szzs), Hyrimoz (adalimumab-adaz), Inflectra (infliximab-dyyb), Renflexis (infliximab-abda), Cyltezo (adalimumab-adbm), and Ixifi (infliximab-qbtx). Other agents targeting different cells and cytokines are also FDA-approved for RA treatment. These include Orencia (abatacept), which inhibits CD28-B7 mediated costimulation of the T-cell; Rituxan (rituximab), which targets CD20, a molecule that is found on the surface of B-cells; Actemra (tocilizumab) and Kevzara (sarilumab), which have activity directed against the IL-6 receptor; and Kineret (anakinra), which targets the IL-1 receptor. Of these agents, one biosimilar product has been approved: Truxima (rituximab-abbs). Oral agents on the market, Xeljanz and Xeljanz XR (tofacitinib) and Olumiant (baricitinib), target Janus-associated kinase (JAK) pathways. By inhibiting the JAK pathway, the ability of cytokines to produce inflammation is reduced.
- Other immunomodulators include Ilaris (canakinumab), which binds to the IL-1ß receptor and is approved to treat JIA; and Entyvio (vedolizumab), which binds to the α4β7 integrin and is approved to treat CD and UC. Otezla (apremilast), an oral, small-molecule phosphodiesterase 4 (PDE-4) inhibitor, and Stelara (ustekinumab), which targets the IL-12 and IL-23 cytokines, are each approved for the treatment of PsA and PsO; Stelara is additionally indicated for the treatment of CD. Cosentyx (secukinumab) and Taltz (ixekizumab) bind and neutralize IL-17A and are indicated for the treatment of PsO and PsA; Cosentyx is additionally indicated to treat PsA and AS. Siliq (brodalumab), an IL-17 receptor antagonist, as well as Tremfya (guselkumab) and Ilumya (tildrakizumab-asmn), both IL-23 antagonists, are indicated for selected patients with PsO.
- Certain rare conditions for which immunomodulators are indicated are mentioned in this review but are not discussed in detail; these include:
    - Ilaris for the treatment of 1) cryopyrin-associated periodic syndromes (CAPS), specifically the subtypes familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS); 2) TNF receptor associated periodic syndrome (TRAPS); 3) hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD); and 4) familial Mediterranean fever (FMF)
    - Kineret for the treatment of CAPS, specifically neonatal-onset multisystem inflammatory disease (NOMID)
    - Actemra for giant cell arteritis (GCA) and cytokine release syndrome (CRS).
- Rituxan is also approved for non–Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), granulomatosis with polyangiitis (GPA) (Wegener's granulomatosis) and microscopic polyangiitis (MPA), and pemphigus vulgaris. These indications will not be discussed in this review.
- Tysabri (natalizumab), an integrin receptor antagonist, is indicated for multiple sclerosis and CD for patients who have had an inadequate response to, or are unable to tolerate conventional therapies and TNF inhibitors; it is not included as a drug product in this review (*Tysabri prescribing information 2018*). Arcalyst (rilonacept), an interleukin-1 blocker indicated for CAPS, is also not included in this review (*Arcalyst prescribing information 2016*).
- Although FDA-approved, the launch plans for the biosimilar drugs Amjevita (adalimumab-atto), Erelzi (etanercept-szzs), Cyltezo (adalimumab-adbm), Hyrimoz (adalimumab-adaz), Ixifi (infliximab-qbtx), and Truxima (rituximab-abbs) are pending and may be delayed; therefore, these agents are not currently included in this review. The manufacturer of Ixifi to date does not have plans to launch Ixifi in the United States.
- Medispan Classes: Antineoplastic-Monoclonal Antibodies, Antipsoriatics, Antirheumatic-Enzyme Inhibitors, Anti-TNF-Alpha-Monoclonal Antibodies, Integrin Receptor Antagonists, Interleukin-1 Receptor Antagonists, Interleukin-1beta Receptor Inhibitors, Interleukin-6 Receptor Inhibitors, PDE-4 Inhibitors, Selective Costimulation Modulators, Soluble Tumor Necrosis Factor Receptor Agents, Tumor Necrosis Factor Alpha Blockers

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Biosimilar or Generic Availability	Type of Agent
Actemra (tocilizumab)	Genentech	01/08/2010	-	Human monoclonal antibody targeting the IL-6 receptor
Cimzia (certolizumab)	UCB	04/22/2008	-	TNFα inhibitor
Cosentyx (secukinumab)	Novartis	01/21/2015	-	Human monoclonal antibody to IL-17A
Enbrel (etanercept)	Amgen	11/02/1998	-*	sTNFR fusion protein, TNFα inhibitor
Entyvio (vedolizumab)	Takeda Pharmaceuticals America, Inc.	05/20/2014	-	Human monoclonal antibody binds to the α4β7 integrin
Humira (adalimumab)	AbbVie	12/31/2002	-*	TNFα inhibitor
Ilaris (canakinumab)	Novartis	06/17/2009	-	Human monoclonal antibody that binds to IL-1ß
Ilumya (tildrakizumab-asmn)	Sun Pharma Global	03/20/2018	-	Human monoclonal antibody to IL-23
Inflectra (infliximab-dyyb)	Celltrion/ Hospira/Pfizer	04/05/2016	N/A†	TNFα inhibitor
Kevzara (sarilumab)	Sanofi Genzyme Regeneron	05/22/2017	-	Human monoclonal antibody targeting IL-6 receptor
Kineret (anakinra)	Swedish Orphan Biovitrum	11/14/2001	-	IL-1 receptor antagonist
Olumiant (baricitinib)	Eli Lilly	05/31/2018	-	Small molecule Janus kinase (JAK) inhibitor
Orencia (abatacept)	Bristol Myers Squibb	12/23/2005	-	sCTLA-4-Ig recombinant fusion protein
Otezla (apremilast)	Celgene Corporation	03/21/2014	-	Small-molecule phosphodiesterase 4 inhibitor
Remicade (infliximab)	Janssen Biotech	8/24/1998	-†	TNFα inhibitor
Renflexis (infliximab-abda)	Merck	04/21/2017	N/A†	TNFα inhibitor
Rituxan (rituximab)	Genentech	11/26/1997	-*	Anti-CD20 monoclonal antibody
Siliq (brodalumab)	Valeant	02/15/2017	-	Human monoclonal antibody directed against the IL-17 receptor A (IL-17RA)
Simponi/ Simponi Aria (golimumab)	Janssen Biotech	04/24/2009 and 07/18/2013	-	TNFα inhibitor
Stelara (ustekinumab)	Janssen Biotech	09/25/2009	-	Human monoclonal antibody targeting the IL-12 and IL-23 cytokines
Taltz (ixekizumab)	Eli Lilly	03/22/2016	-	Human monoclonal antibody to IL-17A
Tremfya (guselkumab)	Janssen Biotech	07/13/2017	-	Human monoclonal antibody to IL-23 cytokine
Xeljanz / Xeljanz XR (tofacitinib)	Pfizer	11/06/2012 and 02/23/2016	-	Small molecule Janus kinase (JAK) inhibitor

*Erelzi (etanercept-szzs) has been FDA-approved as a biosimilar to Enbrel (etanercept). Amjevita (adalimumab-atto), Cyltezo (adalimumab-adbm), and Hyrimoz (adalimumab-adaz) have been FDA-approved as biosimilars to and Humira (adalimumab). Truxima (rituximab-abbs) has been FDA-approved as a biosimilar to Rituxan (rituximab), but only carries an indication for the treatment of adult patients with NHL.The specific launch dates for these products are pending and may be delayed. Further information on Erelzi, Amjevita, Cyltezo, Hyrimoz, and Truxima will be included in this review after these products have launched.
†Inflectra (infliximab-dyyb), Renflexis (infliximab-abda), and Ixifi (infliximab-qbtx) have been FDA-approved as biosimilar agents to Remicade (infliximab), however, they are not FDA-approved as interchangeable biologics.
(Drugs@FDA, 2019; Prescribing information: Actemra, 2018; Cimzia, 2018; Cosentyx, 2018; Enbrel, 2018; Entyvio, 2018; Humira, 2019; Ilaris, 2016; Ilumya 2018; Inflectra, 2018; Kevzara, 2018; Kineret, 2018; Olumiant 2018; Orencia, 2017; Otezla, 2017; Remicade, 2018; Renflexis, 2017; Rituxan, 2019; Siliq, 2017; Simponi, 2018; Simponi Aria, 2018; Stelara, 2018; Taltz, 2019; Tremfya, 2019; Xeljanz/Xeljanz XR, 2018)

Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

INDICATIONS

Table 2. Food and Drug Administration Approved Indications (see footnotes for less common indications: CAPS, CRS, FMF, GCA, HIDS/MKD, and TRAPS)

Drug	Rheumatoid Arthritis (RA)	Crohn's Disease (CD)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Ulcerative Colitis (UC)	Hidradenitis Suppurativa (HS)	Uveitis (UV)
Actemra[ŷ] (tocilizumab)	✔ *		✔ **	✔ **						
Cimzia (certolizumab)	✔	✔			✔ ‡	✔	✔			
Cosentyx (secukinumab)					✔ ‡	✔	✔			
Enbrel (etanercept)	✔ †			✔ **	✔ ‡	✔ †	✔			
Entyvio (vedolizumab)		✔						✔		
Humira (adalimumab)	✔ ‡‡	✔ ⌐		✔ ∫	✔ ‡	✔ ∫∫	✔	✔	✔ †	✔ ▼
Ilaris" (canakinumab)			✔ **							

Drug	Rheumatoid Arthritis (RA)	Crohn's Disease (CD)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Ulcerative Colitis (UC)	Hidradenitis Suppurativa (HS)	Uveitis (UV)
Ilumya (tildrakizumab-asmn)					✔ ‡					
Inflectra (infliximab-dyyb)	✔ ⊥	✔ ⌐⌐			✔ ‡‡‡	✔	✔	✔ ⊥⊥		
Kevzara (sarilumab)	✔ *									
Kineret▼▼ (anakinra)	✔ ∞									
Olumiant (baricitinib)	✔									
Orencia (abatacept)	✔ ∞∞			✔ ⌂		✔				
Otezla (apremilast)					✔ ‡	✔				

Drug	Rheumatoid Arthritis (RA)	Crohn's Disease (CD)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Ulcerative Colitis (UC)	Hidradenitis Suppurativa (HS)	Uveitis (UV)
Remicade (infliximab)	✔	✔			✔	✔	✔	✔		
Renflexis (infliximab-abda)	✔	✔			✔	✔	✔	✔		
Rituxan‴ (rituximab)	✔									
Siliq (brodalumab)					✔					
Simponi (golimumab)	✔					✔	✔	✔		
Simponi Aria (golimumab)	✔					✔	✔			
Stelara (ustekinumab)		✔			✔	✔				

Drug	Rheumatoid Arthritis (RA)	Crohn's Disease (CD)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Ulcerative Colitis (UC)	Hidradenitis Suppurativa (HS)	Uveitis (UV)
Taltz (ixekizumab)					✔ ‡	✔				
Tremfya (guselkumab)					✔ ‡					
Xeljanz/ Xeljanz XR (tofacitinib)	✔ ǂǂ					✔		✔ (Xeljanz only)		

ϒActemra is also indicated for treatment of giant cell arteritis in adults and chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome in adults and pediatric patients ≥ 2 years.
*Patients with moderately to severely active RA who have had an inadequate response (or intolerance [Kevzara]) to ≥ 1 Disease-Modifying Anti-Rheumatic Drugs (DMARDs).
**Patients 2 years and older.
†In combination with methotrexate (MTX) or used alone.
‡Indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe PsO who are candidates for systemic therapy or phototherapy, with the exception of Enbrel, which is indicated for the treatment of patients 4 years and older with chronic moderate to severe PsO who are candidates for systemic therapy or phototherapy, and Stelara, which is indicated for the treatment of patients 12 years and older with moderate to severe PsO.
‡‡Indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. Can be used alone or in combination with MTX or other DMARDs.
ǂǂǂ Indicated for the treatment of adult patients with chronic severe (ie, extensive and/or disabling) PsO who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.
∫Indicated for reducing signs and symptoms of JIA for patients 2 years of age and older. Can be used alone or in combination with MTX.
∫∫Indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA. Can be used alone or in combination with non-biologic DMARDs.
▼ Treatment of non-infectious intermediate, posterior and panuveitis in adult and pediatric patients 2 years of age or older.
↑ Treatment of moderate to severe hidrandenitis suppurative in patients 12 years of age or older.
▼▼Kineret is also indicated for the treatment of cryopyrin-associated periodic syndromes (CAPS) including neonatal-onset multisystem inflammatory disease (NOMID).
"Ilaris also indicated for the treatment of CAPS in adults and children 4 years of age and older including: familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS); tumor necrosis factor receptor associated periodic syndrome (TRAPS) in adult and pediatric patients; hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD) in adult and pediatric patients; and familial Mediterranean fever (FMF) in adult and pediatric patients.
∞Indicated for the reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active RA, in patients 18 years of age or older who have failed one or more DMARDs. Can be used alone or in combination with DMARDs other than TNF blocking agents.
∞∞Indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. May be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.
⌂ Indicated for reducing signs and symptoms in pediatric patients 2 years and older with moderate to severely active PJIA. May be used as monotherapy or with MTX.
⌐For all patients 6 years of age and older, indicated for reducing signs and symptoms and inducing and maintaining clinical remission in patients who have had an inadequate response to conventional therapy. For adults, also indicated for reducing signs and symptoms and inducing clinical remission if patients have also lost a response to or are intolerant of infliximab.

⌐⌐Indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy and for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing CD. And for patients 6 years of age and older for reducing signs and symptoms and inducing and maintaining clinical remission with moderately to severely active disease who have had an inadequate response to conventional therapy.
⌐⌐⌐Indicated for treatment of adult patients with moderately to severely active CD who have: 1) failed or were intolerant to treatment with immunomodulators or corticosteroids but never failed a TNF blocker, or 2) failed or were intolerant to treatment with ≥ 1 TNF blockers
┴In combination with MTX, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active RA.
┴┴For reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy. Also for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active disease who have had an inadequate response to conventional therapy (Remicade only). The biosimilars Inflectra and Renflexis did not receive FDA approval for pediatric UC due to existing marketing exclusivity for Remicade for this indication (not for clinical reasons).
'"Rituxan also indicated for Non–Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), granulomatosis with polyangiitis (GPA) (Wegener's Granulomatosis) and microscopic polyangiitis (MPA), and pemphigus vulgaris.
╪In combination with MTX is indicated for the treatment of adult patients with moderately- to severely- active RA who have had an inadequate response to ≥ 1TNF antagonist therapies.
╪╪Treatment of moderate to severe PsO in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.
┤ In combination with MTX, is indicated for the treatment of adult patients with moderately to severely active RA.
┤ ┤ Alone or in combination with MTX, is indicated for the treatment of adult patients with active PsA.
╪╪Indicated for the treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to MTX. It may be used as monotherapy or in combination with MTX or other nonbiologic DMARDs. Use in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.
˜Indicated in adult patients with moderately to severely active UC who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-mercaptopurine for: inducing and maintaining clinical response; improving endoscopic appearance of the mucosa during induction; inducing clinical remission; and achieving and sustaining clinical remission in induction responders.

CLINICAL EFFICACY SUMMARY

Rheumatoid arthritis (RA)

- The approval of the subcutaneous (SQ) formulation of Orencia (abatacept) was based on a double-blind, double-dummy, randomized trial demonstrating noninferiority to the intravenous (IV) formulation. The trial enrolled patients with RA who had an inadequate response to methotrexate (MTX). The proportion of patients achieving American College of Rheumatology 20% improvement (ACR 20) was not significantly different between the groups (*Genovese et al 2011*).
- Orencia (abatacept), Remicade (infliximab), and placebo were compared in a Phase 3, randomized, double-blind trial (n = 431). Enrolled patients had an inadequate response to MTX, and background MTX was continued during the trial. Although efficacy was comparable between abatacept and infliximab after 6 months of treatment, some differences in favor of abatacept were evident after 1 year of treatment. After 1 year, the mean changes from baseline in disease activity score based on erythrocyte sedimentation rate (DAS28-ESR) were -2.88 and -2.25 in the abatacept and infliximab groups, respectively (estimate of difference, -0.62; 95% confidence interval [CI], -0.96 to -0.29). Abatacept demonstrated greater efficacy vs infliximab on some (but not all) secondary endpoints, including the proportion of patients with a good European League Against Rheumatism (EULAR) response (32.0% vs 18.5%), low disease activity score (LDAS) (35.3% vs 22.4%), ACR 20 responses (72.4% vs 55.8%), and improvements in the Medical Outcomes Study short-form-36 (SF-36) physical component summary (PCS) (difference of 1.93). Overall, abatacept had a relatively more acceptable safety and tolerability profile, with fewer serious adverse events (AEs) and discontinuations due to AEs than the infliximab group (*Schiff et al 2008*).
- Treatment with Orencia (abatacept) was directly compared to treatment with Humira (adalimumab), when added to MTX, in a multicenter, investigator-blind, randomized controlled trial (n = 646) of RA patients with inadequate response to MTX. After 2 years, the proportions of patients achieving ACR 20 responses were comparable between abatacept and adalimumab treatment groups (59.7 and 60.1%, respectively; difference 1.8%; 95% CI, -5.6 to 9.2%). ACR 50 and ACR 70 responses were also similar between the 2 groups after 2 years of treatment. Rates of AEs were similar between treatment groups (*Schiff et al 2014*).
- The RAPID-1 and RAPID-2 studies compared Cimzia (certolizumab) in combination with MTX to placebo plus MTX in adults with active RA despite MTX therapy (*Keystone et al 2008, Smolen et al 2009a*). A significantly greater proportion of patients on certolizumab 400 mg plus MTX at weeks 0, 2, and 4 then 200 or 400 mg every 2 weeks attained greater ACR 20, ACR 50 and ACR 70 responses compared to patients on placebo and MTX, respectively, after 24 weeks ($p \leq 0.01$). The response rates were sustained with active treatment over 52 weeks (*Keystone et al 2008*). The Modified Total Sharp Score (mTSS) was significantly lower with certolizumab in combination with MTX compared to MTX in combination with placebo (*Keystone et al 2008, Smolen et al 2009a*). A trial evaluated Cimzia (certolizumab) monotherapy vs placebo in patients with active disease who had failed at least 1 prior DMARD. After 24 weeks, ACR 20 response rates were significantly greater with active treatment (45.5%) compared to placebo (9.3%; $p < 0.001$). Significant improvements in secondary endpoints (ACR 50, ACR 70, individual ACR component scores, and patient reported outcomes) were also associated with certolizumab therapy (*Fleischmann et al 2009*).
- More Cimzia (certolizumab)-treated patients achieved clinical disease activity index (CDAI) remission than placebo-treated patients (18.8% vs 6.1%, $p \leq 0.05$) in a randomized, double-blind, placebo-controlled trial of certolizumab over 24 weeks in 194 patients with RA who were on DMARD therapy with MTX, leflunomide, sulfasalazine and/or hydroxychloroquine for at least 6 months (*Smolen et al 2015a*).
- A randomized, double-blind, placebo-controlled trial (n = 316) conducted in Japan compared Cimzia (certolizumab) plus MTX to placebo plus MTX in MTX-naïve patients with early RA (≤ 12 months persistent disease) and poor prognostic factors: high anti-cyclic citrullinated peptide (anti-CCP) antibody and either positive rheumatoid factor and/or presence of bone erosions (*Atsumi et al 2016*). The primary endpoint was inhibition of radiographic progression (change from baseline in mTSS at week 52). The certolizumab plus MTX group showed significantly greater inhibition of radiographic progression vs MTX alone (mTSS change, 0.36 vs 1.58; $p < 0.001$). Clinical remission rates were higher in patients treated with certolizumab plus MTX vs MTX alone. The authors suggest that certolizumab plus MTX could be used as possible first-line treatment in this patient population. In a long-term extension, a higher percentage of patients treated with certolizumab plus MTX experienced inhibition of radiographic progression (change from baseline in mTSS) at week 104 vs MTX alone (84.2% vs 67.5%; $p < 0.001$) (*Atsumi et al 2017*).
- The FDA approval of Simponi (golimumab) for RA was based on 3 multicenter, double-blind, randomized, controlled trials in 1,542 patients ≥ 18 years of age with moderate to severe active disease. A greater percentage of patients from all 3 trials treated with the combination of golimumab and MTX achieved ACR responses at week 14 and week 24 vs patients treated with MTX alone (*Emery et al 2009, Keystone et al 2009, Smolen et al 2009b*). Additionally, the golimumab 50 mg groups demonstrated a greater improvement compared to the control groups in the change in

mean Health Assessment Questionnaire (HAQ) Disability Index (HAQ-DI) (*Keystone et al 2009, Smolen et al 2009b*). Response with golimumab + MTX was sustained for up to 5 years (*Keystone et al 2013a, Smolen et al 2015b*).

- Simponi Aria (golimumab) was studied in patients with RA. In 1 trial, 643 patients could receive golimumab 2 mg/kg or 4 mg/kg intravenously (IV) every 12 weeks with or without MTX, or placebo with MTX. The proportion of patients meeting the primary endpoint of ACR 50 response was not significantly different between the golimumab with or without MTX groups and the placebo group. However, significantly more patients receiving golimumab plus MTX achieved an ACR 20 response at week 14 compared with patients receiving placebo plus MTX (53 vs 28%; $p < 0.001$) (*Kremer et al 2010*). In the GO-FURTHER trial (n = 592), golimumab 2 mg/kg IV or placebo was given at weeks 0, 4 and then every 8 weeks. An increased percentage of patients treated with golimumab + MTX achieved ACR 20 response at week 14 (58.5% [231/395] of golimumab + MTX patients vs 24.9% [49/197] of placebo + MTX patients [$p < 0.001$]) (*Weinblatt et al 2013*). In an open-label extension period, treatment was continued through week 100, with placebo-treated patients crossing over to golimumab at week 16 (early escape) or week 24. Clinical response was maintained through week 100, with an ACR 20 response of 68.1%. There was a very low rate of radiographic progression throughout the study, and patients treated with IV golimumab plus MTX from baseline had significantly less radiographic progression to week 100 compared to patients who had initially received placebo plus MTX. No unexpected AEs occurred (*Bingham et al 2015*). In the GO-MORE trial, investigators treated patients with golimumab SQ for 6 months. If patients were not in remission, they could be randomized to receive golimumab SQ or IV. The percentages of patients who achieved DAS28-ESR remission did not differ between the combination SQ + IV group and the SQ golimumab group (*Combe et al 2014*).
- The efficacy and safety of Actemra (tocilizumab) were assessed in several randomized, double-blind, multicenter studies in patients age ≥ 18 years with active RA. Patients were diagnosed according to ACR criteria, with at least 8 tender and 6 swollen joints at baseline. Tocilizumab was given every 4 weeks as monotherapy (AMBITION), in combination with MTX (LITHE and OPTION) or other DMARDs (TOWARD) or in combination with MTX in patients with an inadequate response to TNF antagonists (RADIATE). In all studies, mild to moderate AEs were reported, occurring in similar frequencies in all study groups. The most common AEs in all studies were infections and gastrointestinal symptoms (*Emery et al 2008, Genovese et al 2008, Jones et al 2010, Kremer et al 2011, Smolen et al 2008*).
    - AMBITION evaluated the safety and efficacy of tocilizumab monotherapy vs MTX in patients with active RA for whom previous treatment with MTX or biological agents had not failed. A total of 673 patients were randomized to 1 of 3 treatment arms, tocilizumab 8 mg/kg every 4 weeks, MTX 7.5 mg/week and titrated to 20 mg/week within 8 weeks, or placebo for 8 weeks followed by tocilizumab 8 mg/kg. The primary endpoint was the proportion of patients achieving ACR 20 response at week 24. The results showed that tocilizumab monotherapy when compared to MTX monotherapy produced greater improvements in RA signs and symptoms, and a favorable benefit-risk ratio in patients who had not previously failed treatment with MTX or biological agents. Additionally, more patients treated with tocilizumab achieved remission at week 24 when compared to patients treated with MTX (*Jones et al 2010*).
    - LITHE evaluated 1,196 patients with moderate to severe RA who had an inadequate response to MTX. Patients treated with tocilizumab had 3 times less progression of joint damage, measured by Total Sharp Score, when compared to patients treated with MTX alone. Significantly more patients treated with tocilizumab 8 mg/kg were also found to achieve remission at 6 months as compared to MTX (33% vs 4%), and these rates continued to increase over time to 1 year (47% vs 8%) (*Kremer et al 2011*). These benefits were maintained or improved at 2 years with no increased side effects (*Fleishmann et al 2013*).
    - OPTION evaluated tocilizumab in 623 patients with moderate to severely active RA. Patients received tocilizumab 8 mg/kg, 4 mg/kg, or placebo IV every 4 weeks, with MTX at stable pre-study doses (10 to 25 mg/week). Rescue therapy with tocilizumab 8 mg/kg was offered at week 16 to patients with < 20% improvement in swollen and tender joint counts. The primary endpoint was ACR 20 at week 24. The findings showed that ACR 20 was seen in significantly more patients receiving tocilizumab than in those receiving placebo at week 24 ($p < 0.001$). Significantly more patients treated with tocilizumab achieved ACR 50 and ACR 70 responses at week 24 as well ($p < 0.001$). Greater improvements in physical function, as measured by the HAQ-DI, were seen with tocilizumab when compared to MTX (-0.52 vs -0.55 vs -0.34; $p < 0.0296$ for 4 mg/kg and $p < 0.0082$ for 8 mg/kg) (*Smolen et al 2008*).
    - TOWARD examined the efficacy and safety of tocilizumab combined with conventional DMARDs in 1220 patients with active RA. Patients remained on stable doses of DMARDs and received tocilizumab 8 mg/kg or placebo every 4 weeks for 24 weeks. At week 24, significantly more patients taking tocilizumab with DMARDs achieved an ACR 20 response than patients in the control group. The authors concluded that tocilizumab, combined with any of the DMARDs evaluated (MTX, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine, and leflunomide), was safe and effective in reducing articular and systemic

symptoms in patients with an inadequate response to these agents. A greater percentage of patients treated with tocilizumab also had clinically meaningful improvements in physical function when compared to placebo (60% vs 30%; p value not reported) (*Genovese et al 2008).*

- RADIATE evaluated the safety and efficacy of tocilizumab in patients with RA refractory to TNF antagonist therapy. A total of 499 patients with inadequate response to ≥ 1TNF antagonists were randomly assigned to 8 or 4 mg/kg tocilizumab or placebo every 4 weeks with stable MTX doses (10 to 25 mg/week) for 24 weeks. ACR 20 responses and safety endpoints were assessed. This study found that tocilizumab plus MTX is effective in achieving rapid and sustained improvements in signs and symptoms of RA in patients with inadequate response to TNF antagonists and has a manageable safety profile. The ACR 20 response in both tocilizumab groups was also found to be comparable to those seen in patients treated with Humira (adalimumab) and Remicade (infliximab), irrespective of the type or number of failed TNF antagonists (*Emery et al 2008*). In the ADACTA trial, patients with severe arthritis who could not take MTX were randomized to monotherapy with tocilizumab or adalimumab. The patients in the tocilizumab group had a significantly greater improvement in DAS28 at week 24 than patients in the adalimumab group (*Gabay et al 2013*).

- More recently, results of a randomized, double-blind trial evaluating Actemra (tocilizumab) in early RA were published (*Bijlsma et al 2016*). Patients (n = 317) had been diagnosed with RA within 1 year, were DMARD-naïve, and had a DAS28 score of ≥ 2.6. Patients were randomized to 1 of 3 groups: tocilizumab plus MTX, tocilizumab plus placebo, or MTX plus placebo. Tocilizumab was given at a dose of 8 mg/kg every 4 weeks (maximum 800 mg per dose), and MTX was given at a dose of 10 mg orally per week, increased to a maximum of 30 mg per week as tolerated. Patients not achieving remission switched from placebo to active treatments, and patients not achieving remission in the tocilizumab plus MTX group switched to a standard of care group (usually a TNF inhibitor plus MTX). The primary endpoint was the proportion of patients achieving sustained remission (defined as DAS28 < 2.6 with a swollen joint count ≤4, persisting for at least 24 weeks). The percentages of patients achieving a sustained remission on the initial regimen were 86%, 84%, and 44% in the tocilizumab plus MTX, tocilizumab monotherapy, and MTX monotherapy groups, respectively (p < 0.0001 for both comparisons vs MTX). The percentages of patients achieving sustained remission during the entire study were 86%, 88%, and 77% in the tocilizumab plus MTX, tocilizumab monotherapy, and MTX monotherapy groups, respectively (p = 0.06 for tocilizumab plus MTX vs MTX; p = 0.0356 for tocilizumab vs MTX). The authors concluded that immediate initiation of tocilizumab is more effective compared to initiation of MTX in early RA.
- The FDA approval of the SQ formulation of Actemra (tocilizumab) was based on 1 multicenter, double-blind, randomized, controlled trial in patients (n = 1262) with RA. Weekly tocilizumab SQ 162 mg was found to be non-inferior to tocilizumab IV 8 mg/kg every 4 weeks through 24 weeks. A higher incidence of injection-site reactions were reported with the SQ formulation (*Burmester et al 2014a*). In an open-label extension period, patients in both treatment arms were re-randomized to receive either IV or SQ tocilizumab through week 97. The proportions of patients who achieved ACR 20/50/70 responses, DAS28 remission, and improvement from baseline in HAQ-DI ≥ 0.3 were sustained through week 97 and comparable across arms. IV and SQ treatments had a comparable safety profile with the exception of higher injection-site reactions with the SQ formulation (*Burmester et al 2016*). A placebo-controlled trial in 656 patients further confirmed the efficacy of SQ Actemra administered every other week (*Kivitz et al 2014*).
- A phase 3 trial (MONARCH) evaluating the efficacy of Kevzara (sarilumab) monotherapy vs Humira (adalimumab) monotherapy for the treatment of patients with active RA with an inadequate response or intolerance to MTX reported superiority of sarilumab over adalimumab based on change from baseline in DAS28-ESR at week 24 (-3.28 vs -2.20; difference, -1.08; 95% CI, -1.36 to -0.79; p < 0.0001) (*Burmester et al 2017*). DAS28-ESR remission, ACR 20/50/70 response rates, and improvements in HAQ-DI scores were also more likely with sarilumab. Aside from the MONARCH trial, sarilumab has not been directly compared to any other biologic or tofacitinib. Nonetheless, 2 pivotal trials have shown the agent to be superior in achievement of ACR 50 when compared to MTX plus placebo, in both MTX inadequate responders and TNF inhibitor inadequate responder patients (*Genovese et al 2015, Fleischmann et al 2017*). Additionally, a meta-analysis of 4 randomized controlled trials (RCTs) has shown that ACR 50 response rates were significantly higher with sarilumab 200 mg and sarilumab 200 mg plus MTX when compared to MTX plus placebo (OR, 4.05; 95% CI, 2.04 to 8.33 and OR, 3.75; 95% CI, 2.37 to 5.72, respectively). Ranking probability based on the surface under the cumulative ranking curve (SUCRA) suggested that sarilumab 200 mg was most likely to achieve ACR 50 response rate, followed by sarilumab 200 mg plus MTX, sarilumab 150 mg plus MTX, adalimumab 40 mg, and MTX plus placebo (*Bae et al 2017).*
- In a Phase 3 trial, the percentage of patients who met criteria for RA disease remission was not significantly different in the Xeljanz (tofacitinib) groups (5 mg and 10 mg twice daily) vs placebo. However, significantly more patients in the tofacitinib groups did meet criteria for decrease of disease activity. The tofacitinib groups also had significant decreases in fatigue and pain (*Fleishmann et al 2012*). In another Phase 3 study, Xeljanz (tofacitinib), when

administered with background MTX, was superior to placebo with respect to all clinical outcomes. Although not directly compared to Humira (adalimumab), the clinical efficacy of tofacitinib was numerically similar to that observed with adalimumab. Safety of tofacitinib continues to be monitored for long term effects (*van Vollenhoven et al 2012*). The ORAL Scan trial showed the ACR 20 response rates at month 6 for patients receiving tofacitinib 5 mg and 10 mg twice daily were 51.5% and 61.8%, respectively, vs 25.3% for patients receiving placebo ($p < 0.0001$ for both comparisons) (*van der Heijde et al 2013*). Treatment effects were maintained through month 24 in the ORAL Scan trial, with an ACR 20 response rate of 50.5% and 58.3% for tofacitinib 5 mg and 10 mg twice daily, respectively (*van der Heijde et al 2019*). The ORAL START trial evaluated tofacitinib and MTX in 956 patients with active RA over 24 months. The primary endpoint of mean change from baseline in modified total Sharp score was significantly less with tofacitinib (0.6 for 5 mg; 0.3 for 10 mg) compared to MTX (2.1; $p < 0.001$) (*Lee et al 2014*). No radiographic progression was defined as a change from baseline in the modified total Sharp score of < 0.5 points. However, a minimal clinically important difference in modified total Sharp score is 4.6 points; this study did not meet this minimal clinical meaningful difference threshold.

- In the ORAL Step study, patients with RA who had an inadequate response to ≥ 1 TNF inhibitors were randomized to Xeljanz (tofacitinib) 5 mg or 10 mg twice daily or placebo; all patients were on MTX (*Burmester et al 2013a, Strand et al 2015a*). The primary outcome, ACR 20 response rate, was significantly higher with tofacitinib 5 mg (41.7%; 95% CI, 6.06 to 28.41; $p = 0.0024$) and 10 mg (48.1%; 95% CI, 12.45 to 34.92; $p < 0.0001$) compared to placebo (24.4%). Improvements in HAQ-DI was reported as -0.43 (95% CI, -0.36 to -0.157; $p < 0.0001$) for tofacitinib 5 mg and -0.46 (95% CI, -0.38 to -0.17; $p < 0.0001$) for tofacitinib 10 mg groups compared to -0.18 for placebo. Common AEs included diarrhea, nasopharyngitis, headache, and urinary tract infections in the tofacitinib groups.
- The approval of Olumiant (baricitinib) was based on 2 confirmatory, 24-week, phase 3 trials in patients with active RA. In RA-BEACON, enrolled patients (N = 527) had moderate to severe RA and an inadequate response or intolerance to ≥ 1 TNF antagonist(s) (*Genovese et al 2016*). Patients received baricitinib once daily or placebo along with continuing a stable dose of a conventional DMARD. The primary endpoint, ACR 20 response at week 12, was achieved by 49% and 27% of patients in the baricitinib 2 mg and placebo groups, respectively ($p \leq 0.001$). In RA-BUILD, enrolled patients (N = 684) had moderate to severe RA and an inadequate response or intolerance to ≥ 1 conventional DMARD(s) (*Dougados et al 2017*). Patients received baricitinib once daily or placebo; concomitant conventional DMARDs were permitted but not required. The primary endpoint, ACR20 response at week 12, was achieved by 66% and 39% of patients in the baricitinib 2 mg and placebo groups, respectively ($p \leq 0.001$).
- Inflectra (infliximab-dyyb) was evaluated and compared to Remicade (infliximab; European Union formulation) in PLANETRA (N=606), a double-blind, multicenter, randomized trial (*Yoo et al 2013, Yoo et al 2016, Yoo et al 2017*). The primary endpoint, ACR 20 at week 30, was achieved by 58.6% and 60.9% of patients in the Remicade and Inflectra groups, respectively (treatment difference [TD], 2%; 95% CI, -6% to 10%) (intention-to-treat population). Corresponding results in the per-protocol population were 69.7% and 73.4%, respectively (TD, 4%; 95% CI, -4% to 12%). Equivalence was demonstrated between the 2 products.
    - Secondary endpoints included several other disease activity scales and a quality-of-life scale; no significant differences were noted in any of these endpoints at either the 30-week or 54-week assessments.
    - In the extension study (n = 302) through 102 weeks, all patients received Inflectra. Response rates were maintained, with no differences between the Inflectra maintenance group and the group who switched from Remicade to Inflectra.
- Renflexis (infliximab-abda) was evaluated and compared to Remicade (infliximab; European Union formulation) in 584 patients in a double-blind, multicenter, randomized phase 3 trial (*Choe et al 2017*). The primary endpoint, ACR 20 at week 30, was achieved by 64.1% and 66.0% of patients in the Renflexis and Remicade groups, respectively (TD, -1.88%; 95% CI, -10.26% to 6.51%) (per-protocol population). Equivalence was demonstrated between the 2 products.
    - Secondary endpoints were also very similar between the 2 groups.
    - At week 54 of this trial, patients transitioned into the switching/extension phase, in which patients initially taking Remicade were re-randomized to continue Remicade or switch to Renflexis; patients initially taking Renflexis continued on the same treatment. Although slight numerical differences were observed, there was consistent efficacy over time across treatments and the proportions of patients achieving ACR responses were comparable between groups (*Renflexis FDA clinical review 2017*).
- Two studies, 1 double-blind and 1 open-label, evaluated Rituxan (rituximab) in patients who had failed treatment with a TNF blocker (*Cohen et al 2006, Haraoui et al 2011*). All patients continued to receive MTX. Both studies showed > 50% of patients achieving ACR 20 response. AEs were generally mild to moderate in severity.
- A Cochrane review (*Lopez-Olivo et al 2015*) examined Rituxan (rituximab) for the treatment of RA. Eight studies and a total of 2720 patients were included. Rituximab plus MTX, compared to MTX alone, resulted in more patients achieving ACR 50 at 24 weeks (29% vs 9%, respectively) and clinical remission at 52 weeks (22% vs 11%). In addition, rituximab plus MTX compared to MTX alone resulted in more patients having no radiographic progression

(70% vs 59% at 24 weeks, with similar results at 52 through 56 and 104 weeks). Benefits were also shown for physical function and quality of life.

- In the open-label ORBIT study (n = 295), adults with active, seropositive RA and an inadequate response to DMARDs who were biologic-naïve were randomized to either Rituxan (rituximab) (n = 144) or a TNF inhibitor (physician/patient choice of Enbrel [etanercept] or Humira [adalimumab]; n = 151) (*Porter et al 2016*). Medication doses were generally consistent with FDA-approved recommendations. Patients were able to switch over to the alternative treatment due to side effects or lack of efficacy. The primary endpoint was the change in DAS28-ESR in the per-protocol population at 12 months.
    - The changes in DAS28-ESR were -2.6 and -2.4 in patients in the rituximab and TNF inhibitor groups, respectively. The difference of -0.19 (95% CI, -0.51 to 0.13) was within the prespecified non-inferiority margin of 0.6 units. The authors concluded that initial treatment with rituximab was non-inferior to initial TNF inhibitor treatment in this patient population. However, interpretation of these results is limited due to the open-label study design and the high percentage of patients switching to the alternative treatment (32% in the TNF inhibitor group and 19% in the rituximab group). The indication for rituximab is limited to patients with an inadequate response to TNF inhibitor(s).
- A randomized, open-label trial evaluated biologic treatments in patients with RA who had had an inadequate response to a TNF inhibitor (*Gottenberg et al 2016*). Patients (n = 300) were randomized to receive a second TNF inhibitor (n = 150) or a non-TNF-targeted biologic (n = 150) of the prescriber's choice. The second TNF inhibitors, in order of decreasing frequency, included Humira (adalimumab), Enbrel (etanercept), Cimzia (certolizumab), and Remicade (infliximab), and the non-TNF biologics included Actemra (tocilizumab), Rituxan (rituximab), and Orencia (abatacept). The primary endpoint was the proportion of patients with a good or moderate EULAR response at week 24, defined as a decrease in DAS28-ESR of > 1.2 points resulting in a score of ≤ 3.2.
    - At week 24, 52% of patients in the second anti-TNF group and 69% of patients in the non-TNF group achieved a good or moderate EULAR response (p = 0.003 or p = 0.004, depending on how missing data were handled). Secondary disease activity scores also generally supported better efficacy for the non-TNF biologics; however, HAQ scores did not differ significantly between groups. Among the non-TNF biologics, the proportion of EULAR good and moderate responders at week 24 did not significantly differ between abatacept, rituximab, and tocilizumab (67%, 61%, and 80%, respectively). There were 8 patients (5%) in the second TNF inhibitor group and 16 patients (11%) in the non-TNF biologic group that experienced serious AEs (p = 0.10), predominantly infections and cardiovascular events. There were some limitations to this trial; notably, it had an open-label design, and adherence may have differed between groups because all non-TNF biologics were given as infusions under observation and most of the TNF inhibitor drugs were self-injected by patients. The authors concluded that among patients with RA inadequately treated with TNF inhibitors, a non-TNF biologic was more effective in achieving a good or moderate disease activity response at 24 weeks; however, a second TNF inhibitor was also often effective in producing clinical improvement.
- Another recent randomized trial (*Manders et al 2015*) evaluated the use of Orencia (abatacept) (n = 43), Rituxan (rituximab) (n = 46), or a different TNF inhibitor (n = 50) in patients (n =139) with active RA despite previous TNF inhibitor treatment. Actemra (tocilizumab) was not included. In this trial, there were no significant differences with respect to DAS28, HAQ-DI, or SF-36 over the 1-year treatment period, and AEs also appeared similar. A cost-effectiveness analysis was also included in this publication, but results are not reported in this review.
- A Cochrane review examined Orencia (abatacept) for the treatment of RA. ACR 50 response was not significantly different at 3 months but was significantly higher in the abatacept group at 6 and 12 months compared to placebo (relative risk [RR], 2.47; 95% CI, 2 to 3.07 and RR, 2.21; 95% CI, 1.73 to 2.82). Similar results were seen in ACR 20 and ACR 70 (*Maxwell et al 2009*).
- The safety and efficacy of Humira (adalimumab) for the treatment of RA were assessed in a Cochrane systematic review. Treatment with adalimumab in combination with MTX was associated with a RR of 1.52 to 4.63, 4.63 (95% CI, 3.04 to 7.05) and 5.14 (95% CI, 3.14 to 8.41) for ACR 20, ACR 50, and ACR 70 responses, respectively, at 6 months when compared to placebo in combination with MTX. Adalimumab monotherapy was also proven efficacious (*Navarro-Sarabia et al 2005*). In another study, patients received adalimumab 20 mg or 40 mg every other week for 1 year, and then could receive 40 mg every other week for an additional 9 years. At Year 10, 64.2%, 49%, and 17.6% of patients achieved ACR 50, ACR 70, and ACR 90 responses, respectively (*Keystone et al 2013b*).
- A Phase 3, open-label study evaluated the long-term efficacy of Humira (adalimumab) for RA. Patients receiving adalimumab in 1 of 4 early assessment studies could receive adalimumab for up to 10 years in the extension study. Of 846 enrolled patients, 286 (33.8%) completed 10 years of treatment. In patients completing 10 years, adalimumab led to sustained clinical and functional responses, with ACR 20, ACR 50, and ACR 70 responses being achieved by 78.6%, 55.5%, and 32.8% of patients, respectively. The authors stated that patients with shorter disease duration achieved better outcomes, highlighting the need for early treatment. No unexpected safety findings were observed.

This study demonstrated that some patients with RA can be effectively treated with adalimumab on a long-term basis; however, the study is limited by its open-label design, lack of radiographic data, and the fact that only patients who continued in the study were followed (*Furst et al 2015*).

- A Cochrane review was performed to compare Kineret (anakinra) to placebo in adult patients with RA. Significant improvements in both primary (ACR 20, 38% vs 23%; RR, 1.61; 95% CI, 1.32 to 1.98) and secondary (ACR 50 and ACR 70) outcomes were detected. The only significant difference in AEs noted with anakinra use was the rate of injection site reactions (71% vs 28% for placebo) (*Mertens et al 2009*).
- In another Cochrane review, Enbrel (etanercept) was compared to MTX or placebo in adult patients with RA and found that at 6 months, 64% of individuals on etanercept 25 mg twice weekly attained an ACR 20 vs 15% of patients on either MTX alone or placebo (RR, 3.8; number needed to treat [NNT], 2). An ACR 50 and ACR 70 were achieved by 39% and 15%, respectively, in the etanercept group compared to 4% (RR, 8.89; NNT, 3) and 1% (RR, 11.31; NNT, 7) in the control groups, respectively. Etanercept 10 mg twice weekly was only associated with significant ACR 20 (51% vs 11% of controls; RR, 4.6; 95% CI, 2.4 to 8.8; NNT, 3) and ACR 50 responses (24% vs 5% of controls; RR, 4.74; 95% CI, 1.68 to 13.36; NNT, 5). Seventy-two percent of patients receiving etanercept had no increase in Sharp erosion score compared to 60% of MTX patients. Etanercept 25 mg was associated with a significantly reduced total Sharp score (weighted mean difference, -10.5; 95% CI, -13.33 to -7.67). The Sharp erosion scores and joint space narrowing were not significantly reduced by either etanercept dose (*Blumenauer et al 2003*). In a trial of 353 patients with RA, patients received a triple therapy combination of sulfasalazine, hydroxychloroquine and MTX or etanercept and MTX. Triple therapy was shown to be noninferior to etanercept + MTX (*O'Dell et al 2013*).
- A more recent Cochrane review (*Singh et al 2016a*) evaluated the benefits and harms of 10 agents for the treatment of RA in patients failing treatment with MTX or other DMARDs. Agents included Xeljanz (tofacitinib) and 9 biologics (Orencia [abatacept], Humira [adalimumab], Kineret [anakinra], Cimzia [certolizumab], Enbrel [etanercept], Simponi [golimumab], Remicade [infliximab], Rituxan [rituximab], and Actemra [tocilizumab]), each in combination with MTX or other DMARDS, compared to comparator agents such as DMARDs or placebo. Data from 79 randomized trials (total 32,874 participants) were included. Key results from this review are as follows:
    - ACR 50: Biologic plus MTX/DMARD was associated with a statistically significant and clinically meaningful improvement in ACR 50 vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics. Differences between treatments in individual comparisons were small.
    - HAQ: Biologic plus MTX/DMARD was associated with a clinically and statistically significant improvement in function measured by HAQ vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics.
    - Remission: Biologic plus MTX/DMARD was associated with clinically and statistically significantly greater proportion of patients achieving RA remission, defined by DAS < 1.6 or DAS28 < 2.6, vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics.
    - Radiographic progression: Radiographic progression was statistically significantly reduced in those on biologic plus MTX/DMARD vs comparator. The absolute reduction was small and clinical relevance is uncertain.
    - Safety: Biologic plus MTX/DMARD was associated with a clinically significantly increased risk of serious AEs; statistical significance was borderline. TNF inhibitors did not differ significantly from non-TNF biologics.
- A similar Cochrane review focused on the use of biologic or Xeljanz (tofacitinib) monotherapy for RA in patients with traditional DMARD failure (*Singh et al 2016b*). A total of 41 randomized trials (n = 14,049) provided data for this review. Key results are as follows:
    - Biologic monotherapy was associated with a statistically significant and clinically meaningful improvement in ACR 50 and HAQ vs placebo and vs MTX or other DMARDs.
    - Biologic monotherapy was associated with a statistically significant and clinically meaningful greater proportion of patients with disease remission vs placebo.
    - Based on a single study, the reduction in radiographic progression was statistically significant for biologic monotherapy compared to active comparators, but the absolute reduction was small and of unclear clinical relevance.
- Another Cochrane review evaluated the use of biologics or Xeljanz (tofacitinib) in patients with RA who had been unsuccessfully treated with a previous biologic (*Singh et al 2017[a]*). The review included 12 randomized trials (n = 3,364). Key results are as follows:
    - Biologics, compared to placebo, were associated with statistically significant and clinically meaningful improvement in RA as assessed by ACR 50 and remission rates. Information was not available for HAQ or radiographic progression.
    - Biologics plus MTX, compared to MTX or other traditional DMARDs, were associated with statistically significant and clinically meaningful improvement in ACR 50, HAQ, and RA remission rates. Information was not available for radiographic progression.

  - There were no published data for tofacitinib monotherapy vs placebo.
  - Based on a single study, tofacitinib plus MTX, compared to MTX, was associated with a statistically significant and clinically meaningful improvement in ACR 50 and HAQ. RA remission rates were not statistically significantly different, and information was not available for radiographic progression.
- In another meta-analysis, ACR 20 and ACR 70 response rates for Xeljanz (tofacitinib) 5 mg and 10 mg were comparable to the other monotherapies (Orencia [abatacept], Humira [adalimumab], Kineret [anakinra], Cimzia [certolizumab], Enbrel [etanercept], Simponi [golimumab], Remicade [infliximab], Actemra [tocilizumab]) at 24 weeks (*Bergrath et al 2017*). ACR 50 response rates were also comparable for tofacitinib 10 mg and other monotherapies. At 24 weeks, ACR 20/50/70 response rates for the combination of tofacitinib 5 mg or 10 mg plus conventional DMARD were comparable to other biologic plus conventional DMARD therapies except tofacitinib 5 mg plus conventional DMARD and tofacitinib 10 mg plus conventional DMARD were both superior to certolizumab 400 mg every 4 weeks plus conventional DMARD for achieving ACR 70 response (OR, 59.16; [95% CI, 2.70 to infinity]; and OR, 77.40; [95% CI, 3.53 to infinity], respectively).
- Another recent Cochrane review (*Hazlewood et al 2016*) compared MTX and MTX-based DMARD combinations for RA in patients naïve to or with an inadequate response to MTX; DMARD combinations included both biologic and non-biologic agents. A total of 158 studies and over 37,000 patients were included. Evidence suggested that efficacy was similar for triple DMARD therapy (MTX plus sulfasalazine plus hydroxychloroquine) and MTX plus most biologic DMARDs or Xeljanz (tofacitinib). MTX plus some biologics were superior to MTX in preventing joint damage in MTX-naïve patients, but the magnitude of effect was small.
- An additional Cochrane review evaluated biologics for RA in patients naïve to MTX in 19 studies (*Singh et al 2017[b]*). Agents included in the review were Humira (adalimumab), Enbrel (etanercept), Simponi (golimumab), Remicade (infliximab), Orencia (abatacept), and Rituxan (rituximab). When combined with MTX, use of biologics showed a benefit in ACR 50 vs comparator (MTX/MTX plus methylprednisolone) (RR, 1.40; 95% CI, 1.30 to 1.49) and in RA remission rates (RR, 1.62; 95% CI, 1.33 to 1.98), but no difference was found for radiographic progression. When used without MTX, there was no significant difference in efficacy between biologics and MTX.
- A meta-analysis evaluated the efficacy of Remicade (infliximab) in combination with MTX compared to placebo plus MTX. There was a higher proportion of patients in the infliximab group that achieved an ACR 20 at 30 weeks compared to patients in the placebo group (RR, 1.87; 95% CI, 1.43 to 2.45). These effects were similar in the proportion of patients achieving ACR 50 and ACR 70 (RR, 2.68; 95% CI, 1.79 to 3.99 and RR, 2.68; 95% CI, 1.78 to 4.03) (*Wiens et al 2009*).
- Another meta-analysis of randomized controlled trials included Humira (adalimumab), Kineret (anakinra), Enbrel (etanercept), and Remicade (infliximab) with or without MTX. The odds ratio (OR) for an ACR 20 was 3.19 (95% CI, 1.97 to 5.48) with adalimumab, 1.7 (95% CI, 0.9 to 3.29) with anakinra, 3.58 (95% CI, 2.09 to 6.91) with etanercept and 3.47 (95% CI, 1.66 to 7.14) with infliximab compared to placebo. The OR to achieve an ACR 50 with adalimumab was 3.97 (95% CI, 2.73 to 6.07), 2.13 (95% CI, 1.27 to 4.22) with anakinra, 4.21 (95% CI, 2.74 to 7.43) and with etanercept 4.14 (95% CI, 2.42 to 7.46) compared to placebo. Further analysis of each agent against another was performed, and no significant difference was determined between individual agents in obtaining an ACR 20 and ACR 50. However, the TNF-blockers as a class showed a greater ACR 20 and ACR 50 response compared to anakinra (OR, 1.96; 95% CI, 1.03 to 4.01 and OR, 1.93; 95% CI,1.05 to 3.5; $p < 0.05$) (*Nixon et al 2007*).
- The Agency for Healthcare Research and Quality published a review of drug therapy to treat adults with RA (*Donahue et al 2012*). They concluded that there is limited head-to-head data comparing the biologics. Studies that are available are generally observational in nature or mixed treatment comparison meta-analysis. At this time, there appears to be no significant differences amongst the agents. Clinical trials have shown better efficacy with combination biologics and MTX and no additional increased risk of AEs. However, combinations of 2 biologic agents showed increased rate of serious AEs with limited or no increase in efficacy.
- A meta-analysis of 6 trials (n = 1,927) evaluated the efficacy of withdrawing biologics from patients with RA who were in sustained remission or had low disease activity (*Galvao et al 2016*). The biologics in the identified trials were TNF inhibitors, most commonly Enbrel (etanercept) or Humira (adalimumab). Compared to withdrawing the medication, continuing the biologic increased the probability of having low disease activity (RR, 0.66; 95% CI, 0.51 to 0.84) and remission (RR, 0.57; 95% CI, 0.44 to 0.74). Although outcomes were worse in patients withdrawing the biologic, the investigators noted that almost half of the patients maintained a low disease activity after withdrawal. The authors suggested that further research is necessary to identify subgroups for which withdrawal may be more appropriate.

Ankylosing spondylitis (AS)

- The FDA-approval of Humira (adalimumab) for the treatment of AS was based on 1 randomized, double-blind, placebo-controlled study (n = 315) in which a significantly greater proportion of patients achieved a 20% improvement in the Assessment of SpondyloArthritis International Society criteria (ASAS 20) (primary endpoint) with adalimumab

(58% vs 21% with placebo; p < 0.001). A greater than 50% improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score, a measure of fatigue severity, spinal and peripheral joint pain, localized tenderness, and morning stiffness which is considered clinically meaningful, was detected in 45% of adalimumab-treated patients compared to 16% of placebo-treated patients (p < 0.001) at week 12. This response was sustained through week 24, with 42% in the adalimumab group achieving a greater than or equal to 50% improvement in BASDAI score compared to 15% in the placebo group (p < 0.001) (*van der Heijde et al 2006*).

- In 2 double-blind, randomized, placebo-controlled trials, the efficacy of Enbrel (etanercept) was evaluated in patients with AS (*Calin et al 2004, Gorman et al 2002*). Etanercept had a significantly greater response to treatment compared to placebo (p < 0.001) (*Gorman et al 2002*). More patients achieved an ASAS 20 response compared to placebo (p < 0.001) (*Calin et al 2004*). An open-label extension study, evaluating the long-term safety and efficacy of etanercept in patients with AS, was conducted. Safety endpoints included AEs, serious AEs, serious infection, and death while efficacy endpoints included ASAS 20 response, ASAS 5/6 response and partial remission rates. After up to 192 weeks of treatment, the most common AEs were injection site reactions, headache and diarrhea. A total of 71% of patients were ASAS 20 responders at week 96 and 81% of patients were responders at week 192. The ASAS 5/6 response rates were 61% at week 96 and 60% at week 144, and partial remission response rates were 41% at week 96 and 44% at week 192. Placebo patients who switched to etanercept in the open-label extension trial showed similar patterns of efficacy maintenance (*Davis et al 2008*). A multicenter, randomized, double-blind trial compared etanercept and sulfasalazine in adult patients with active AS that failed treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). A significantly greater proportion of patients treated with etanercept compared to patients treated with sulfasalazine achieved the primary outcome of ASAS 20 at week 16 (p < 0.0001). There were also significantly more patients that achieved ASAS 40 and ASAS 5/6 in the etanercept group compared to the sulfasalazine group (p < 0.0001 for both) (*Braun et al 2011*).
- The FDA-approval of Simponi (golimumab) for AS was based on a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with active disease for at least 3 months (n = 356). Golimumab with or without a DMARD was compared to placebo with or without a DMARD and was found to significantly improve the signs and symptoms of AS as demonstrated by the percentage of patients achieving an ASAS 20 response at week 14 (*Inman et al 2008*). Sustained improvements in ASAS 20 and ASAS 40 response rates were observed for up to 5 years in an open-label extension trial (*Deodhar et al 2015*). Safety profile through 5 years was consistent with other TNF inhibitors.
- The efficacy of Remicade (infliximab) in the treatment of AS was demonstrated in 12- and 24-week double-blind, placebo-controlled trials. There was significantly more patients that achieved a 50% BASDAI score in the infliximab group compared to the placebo group at 12 weeks (p < 0.0001)(*Braun et al 2002*), At 24 weeks, significantly more patients in the infliximab group achieved ASAS 20 compared to the placebo group (p < 0.001)(*van der Heijde et al 2005*).
- Inflectra (infliximab-dyyb) was evaluated alongside Remicade (infliximab; European Union formulation) for the treatment of AS in PLANETAS (n = 250), a double-blind, multicenter, randomized trial (*Park et al 2013, Park et al 2016, Park et al 2017*). The primary endpoints related to pharmacokinetic equivalence. Secondary efficacy endpoints supported similar clinical activity between Inflectra and Remicade. An ASAS 20 response was achieved by 72.4% and 70.5% of patients in the Remicade and Inflectra groups, respectively, at 30 weeks, and by 69.4% and 67.0% of patients at 54 weeks. Other disease activity endpoints and a quality-of-life scale were also similar between groups.
    - In the extension study (n = 174) through 102 weeks, all patients received Inflectra. From weeks 54 to 102, the proportion of patients achieving a clinical response was maintained at a similar level to that of the main study in both the maintenance and switch groups and was comparable between groups.
- The efficacy of Cimzia (certolizumab) for the treatment of AS was established in 1 randomized, double-blind, placebo-controlled study (n = 325) in which a significantly greater proportion of patients achieved ASAS 20 response with certolizumab 200 mg every 2 weeks and certolizumab 400 mg every 4 weeks compared to placebo at 12 weeks (*Landewe et at 2014*). Patient-reported outcomes measured by the SF-36, health-related quality of life (HRQoL), and reports of pain, fatigue and sleep were significantly improved with certolizumab in both dose groups (*Sieper et al 2015a*). A Phase 3, randomized, placebo-controlled trial found that 62.5% of patients on certolizumab maintained ASAS 20 response to week 96 in a population of patients with axial spondyloarthritis which includes AS (*Sieper et al 2015b*).
- The efficacy and safety of Cosentyx (secukinumab) were evaluated in the double-blind, placebo-controlled, randomized MEASURE 1 and 2 studies (*Baeten et al 2015*). MEASURE 1 enrolled 371 patients and MEASURE 2 enrolled 219 patients with active AS with radiologic evidence treated with NSAIDs. Patients were treated with secukinumab 75 or 150 mg SQ every 4 weeks (following IV loading doses) or placebo. The primary outcome, ASAS 20 response at week 16, was significantly higher in the secukinumab 75 mg (60%) and 150 mg (61%) groups compared to placebo (29%, p < 0.001 for each dose) for MEASURE 1. For MEASURE 2 at week 16, ASAS 20

responses were seen in 61% of the secukinumab 150 mg group, 41% of the 75 mg group, and 28% of the placebo group ($p < 0.001$ for secukinumab 150 mg vs placebo; $p = 0.10$ for secukinumab 75 mg vs placebo). Common AEs reported included nasopharyngitis, headache, diarrhea, and upper respiratory tract infections. Improvements were observed from week 1 and sustained through week 52. In a long-term extension of MEASURE 1, ASAS 20 response rates were 73.7% with secukinumab 150 mg and 68.0% with 75 mg at week 104 and in MEASURE 2, ASAS 20 response rates were 71.5% with both doses at week 104 (*Braun et al 2017, Marzo-Ortega et al 2017*). In a 3-year extension of MEASURE-1, ASAS 20/40 response rates were 80.2%/61.6% for secukinumab 150 mg and 75.5%/50.0% for secukinumab 75 mg at week 156 (*Baraliakos et al 2017*). Four-year results from MEASURE-1 demonstrated sustained efficacy with ASAS 20/40 response rates of 79.7%/60.8% and 71%/43.5% with secukinumab 150 mg and 75 mg, respectively, at week 208 (*Braun et al 2018*).

- In 2 systematic reviews of TNF blockers for the treatment of AS, patients taking Simponi (golimumab), Enbrel (etanercept), Remicade (infliximab), and Humira (adalimumab) were more likely to achieve ASAS 20 or ASAS 40 responses compared with patients from control groups. The RR of reaching ASAS 20 after 12 or 14 weeks was 2.21 (95% CI, 1.91 to 2.56) (*Machado et al 2013*). After 24 weeks, golimumab, etanercept, infliximab, and adalimumab were more likely to achieve ASAS 40 compared to placebo (*Maxwell et al 2015*). A systematic review and network meta-analysis evaluated biologic agents for the treatment of AS, including adalimumab, etanercept, golimumab, infliximab, Cosentyx (secukinumab), and Actemra (tocilizumab; not FDA-approved for AS) (*Chen et al 2016*). A total of 14 studies were included. Infliximab was ranked best and secukinumab second best for achievement of ASAS 20 response; however, differences among agents were not statistically significant with the exception of infliximab 5 mg compared to tocilizumab (OR, 4.81; 95% credible interval [CrI], 1.43 to 17.04). Safety endpoints were not included in this analysis.

Crohn's disease (CD)

- In a trial evaluating Remicade (infliximab) for induction of remission, significantly more patients achieved remission at 4 weeks with infliximab compared to placebo ($p < 0.005$)(*Targan et al 1997*). In a placebo-controlled trial, significantly more patients treated with infliximab 5 and 10 mg/kg had a reduction greater than or equal to 50% in the number of fistulas compared to patients treated with placebo ($p = 0.002$ and $p = 0.02$, respectively)(*Present et al 1999*). In an open-label trial evaluating the use of infliximab in pediatric CD patients, 88.4% responded to the initial induction regimen, and 58.6% were in clinical remission at week 10 (*Hyams et al 2007*).
- The safety and efficacy of Entyvio (vedolizumab) was demonstrated in 2 trials for CD in patients who responded inadequately to immunomodulator therapy, TNF blockers, and/or corticosteroids. In 1 trial, a higher percentage of Entyvio-treated patients achieved clinical response and remission at week 52 compared to placebo. However, in the second trial, Entyvio did not achieve a statistically significant clinical response or clinical remission over placebo at week 6 (*Sandborn et al 2013, Sands et al 2014*).
- A meta-analysis evaluating Cimzia (certolizumab) use over 12 to 26 weeks for the treatment of CD demonstrated that the agent was associated with an increased rate of induction of clinical response (RR, 1.36; $p = 0.004$) and remission (RR, 1.95; $p < 0.0001$) over placebo. However, risk of infection was higher with certolizumab use (*Shao et al 2009*).
- Additionally, Humira (adalimumab), Cimzia (certolizumab) and Remicade (infliximab) demonstrated the ability to achieve clinical response (RR, 2.69; $p < 0.00001$; RR, 1.74; $p < 0.0001$ and RR, 1.66; $p = 0.0046$, respectively) and maintain clinical remission (RR, 1.68; $p = 0.000072$ with certolizumab and RR, 2.5; $p = 0.000019$ with infliximab; adalimumab, data not reported) over placebo in patients with CD. Adalimumab and infliximab also had a steroid-sparing effect (*Behm et al 2008*). Other systematic reviews have further demonstrated the efficacy of these agents in CD (*Singh et al 2014, Fu et al 2017*).
- In a systematic review of patients with CD who had failed a trial with Remicade (infliximab), the administration of Humira (adalimumab) was associated with remission rates of 19 to 68% at 1 year. Serious cases of sepsis, cellulitis, and fungal pneumonia occurred in 0 to 19% of patients in up to 4 years of treatment (*Ma et al 2009*).
- A systematic review of 8 randomized clinical trials with TYSABRI (natalizumab) or Entyvio (vedolizumab) for the management of CD evaluated the rates of failure of remission induction (*Chandar et al 2015*). Fewer failures of remission induction were reported with natalizumab and vedolizumab compared to placebo (RR 0.87; 95% CI, 0.84 to 0.91; I^2=0%). The summary effect sizes were similar for both natalizumab (RR 0.86; 95% CI, 0.80 to 0.93) and vedolizumab (RR 0.87; 95% CI, 0.79 to 0.95). No significant difference was detected between the 2 active treatments ($p = 0.95$). No significant differences between natalizumab and vedolizumab were observed for rates of serious AEs, infections (including serious infections), and treatment discontinuation. Rates of infusion reactions in induction trials were more common with natalizumab over vedolizumab ($p = 0.007$). Progressive multifocal leukoencephalopathy (PML) has been reported with natalizumab but has not been reported with vedolizumab.
- The use of Stelara (ustekinumab) for the treatment of CD was evaluated in the UNITI-1, UNITI-2, and IM-UNITI studies (*Feagan et al 2016*). All were Phase 3, double-blind, placebo-controlled trials.

- UNITI-1 (n = 741) was an 8-week induction trial that compared single IV doses of ustekinumab 130 mg IV, weight-based ustekinumab (~6 mg/kg), and placebo in patients with nonresponse or intolerance to ≥ 1 TNF inhibitors. The primary endpoint was clinical response at week 6, which was defined as a decrease from baseline in the CDAI of ≥100 points or a CDAI score of < 150. A clinical response was achieved by 34.4%, 33.7%, and 21.5% of patients in the ustekinumab 130 mg, weight-based ustekinumab, and placebo groups, respectively (p = 0.002 for 130 mg dose vs placebo; p = 0.003 for weight-based dose vs placebo). Benefits were also demonstrated on all major secondary endpoints, which included clinical response at week 8, clinical remission (CDAI < 150) at week 8, and CDAI decrease of ≥70 points at weeks 3 and 6.
- UNITI-2 (n = 628) had a similar design to UNITI-1, but was conducted in patients with treatment failure or intolerance to immunosuppressants or glucocorticoids (with no requirement for prior TNF inhibitor use). In this trial, a clinical response was achieved by 51.7%, 55.5%, and 28.7% of patients in the ustekinumab 130 mg, weight-based ustekinumab, and placebo groups, respectively (p < 0.001 for both doses vs placebo). Benefits were also demonstrated on all major secondary endpoints.
- IM-UNITI was a 44-week maintenance trial that enrolled patients completing UNITI-1 and UNITI-2. Of 1,281 enrolled patients, there were 397 randomized patients (primary population); these were patients who had had a clinical response to ustekinumab induction therapy and were subsequently randomized to ustekinumab 90 mg SQ every 8 or 12 weeks or placebo. The primary endpoint, clinical remission at week 44, was achieved by 53.1%, 48.8%, and 35.9% of patients in the ustekinumab every 8 week, ustekinumab every 12 week, and placebo groups, respectively (p = 0.005 for every 8 week regimen vs placebo; p = 0.04 for every 12 week regimen vs placebo). Numerical and/or statistically significant differences for ustekinumab vs placebo were observed on key secondary endpoints including clinical response, maintenance of remission, and glucocorticoid-free remission.

Hidradenitis suppurativa (HS)

- Two 36-week, Phase 3, double-blind, multicenter, placebo-controlled, randomized trials, PIONEER I and II, evaluated Humira (adalimumab) for the treatment of HS (*Kimball et al 2016*). A total of 633 adults (307 in PIONEER I and 326 in PIONEER II) with moderate to severe HS were enrolled. The study consisted of 2 treatment periods; in the first period, patients were randomized to placebo or weekly adalimumab for 12 weeks; in the second period, patients initially assigned to placebo received weekly adalimumab (PIONEER I) or placebo (PIONEER II) for 24 weeks and patients initially assigned to adalimumab were re-randomized to placebo, weekly adalimumab, or every-other-week adalimumab. The adalimumab dosage regimen was 160 mg at week 0, followed by 80 mg at week 2, followed by 40 mg doses starting at week 4.
  - The primary endpoint was HS clinical response (HiSCR) at week 12, defined as at least 50% reduction in total abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula count compared to baseline. HiSCR rates at week 12 were significantly higher for the groups receiving adalimumab than for the placebo groups: 41.8% vs 26.0% in PIONEER I (p = 0.003) and 58.9% vs 27.6% in PIONEER II (p < 0.001).
  - Among patients with a clinical response at week 12, response rates in all treatment groups subsequently declined over time. During period 2, there were no significant differences in clinical response rates in either trial between patients randomly assigned to adalimumab at either a weekly dose or an every-other-week dose and those assigned to placebo, regardless of whether the patients had a response at week 12. For patients who received placebo in period 1, 41.4% of those assigned to adalimumab weekly in period 2 (PIONEER I) and 15.9% of those reassigned to placebo in period 2 (PIONEER II) had a clinical response at week 36.
  - The authors noted that the magnitude of improvement with adalimumab treatment was modest compared with adalimumab treatment in other disease states, and patients were unlikely to achieve complete symptom resolution.

Juvenile idiopathic arthritis (JIA)

- In a trial of pediatric patients (6 to 17 years of age) with JIA (extended oligoarticular, polyarticular, or systemic without systemic manifestations), the patients treated with placebo had significantly more flares than the patients treated with Orencia (abatacept) (p = 0.0003). The time to flare was significantly different favoring abatacept (p = 0.0002) (*Ruperto et al 2008*).
- Humira (adalimumab) was studied in a group of patients (4 to 17 years of age) with active polyarticular JIA who had previously received treatment with NSAIDs. Patients were stratified according to MTX use and received 24 mg/m^2 (maximum of 40 mg) of adalimumab every other week for 16 weeks. The patients with an American College of Rheumatology Pediatric 30 (ACR Pedi 30) response at week 16 were randomly assigned to receive adalimumab or placebo in a double-blind method every other week for up to 32 weeks. The authors found that 74% of patients not receiving MTX and 94% of those receiving MTX had an ACR Pedi 30 at week 16. Among those not receiving MTX,

flares occurred in 43% receiving adalimumab and 71% receiving placebo (p = 0.03). In the patients receiving MTX, flares occurred in 37 and 65% in the adalimumab and placebo groups, respectively (p = 0.02). ACR Pedi scores were significantly greater with adalimumab than placebo and were sustained after 104 weeks of treatment (*Lovell et al 2008*).

- A double-blind, multicenter, randomized controlled trial compared Humira (adalimumab) and placebo in 46 children ages 6 to 18 years with enthesitis-related arthritis (*Burgos-Vargas et al 2015*). Patients were TNF inhibitor naïve. At week 12, the percentage change from baseline in the number of active joints with arthritis was significantly reduced with adalimumab compared to placebo (-62.6% vs -11.6%, p = 0.039). A total of 7 patients (3 placebo; 4 adalimumab) escaped the study early during the double-blind phase and moved to open-label adalimumab therapy. Analysis excluding these patients produced similar results (adalimumab, -83.3 vs placebo -32.1; p = 0.018). At week 52, adalimumab-treated patients had a mean reduction in active joint count from baseline of 88.7%. A total of 93.5% of patients achieved complete resolution of their swollen joints with a mean of 41 days of adalimumab therapy.
- In a trial involving 69 pediatric patients with active polyarticular JIA despite treatment with NSAIDs and MTX, Enbrel (etanercept) was associated with a significant reduction in flares compared to placebo (28% vs 81%; p = 0.003) (*Lovell et al 2000*). Ninety-four percent of patients who remained in an open-label 4 year extension trial met ACR Pedi 30; C-reactive protein (CRP) levels, articular severity scores, and patient pain assessment scores all decreased. There were 5 cases of serious AEs related to etanercept therapy after 4 years (*Lovell et al 2006*).
- The approval of Actemra (tocilizumab) for the indication of SJIA was based on a randomized, placebo-controlled trial (n = 112). Children age 2 to 17 years of age with active SJIA and inadequate response to NSAIDs and corticosteroids were included in the study. The primary endpoint was ACR 30 and absence of fever at week 12. At week 12, the proportion of patients achieving ACR 30 and absence of fever was significantly greater in the tocilizumab-treated patients compared to the placebo treated patients (85% vs 24%; p < 0.0001)(*De Benedetti et al 2012*). The double-blind, randomized CHERISH study evaluated tocilizumab for JIA flares in patients ages 2 to 17 years with JIA with an inadequate response or intolerance to MTX (*Brunner et al 2015*). Tocilizumab-treated patients experienced significantly fewer JIA flares at week 40 compared to patients treated with placebo (25.6% vs 48.1%; p < 0.0024).
- In 2 trials in patients with SJIA, Ilaris (canakinumab) was more effective at reducing flares than placebo. It also allowed for glucocorticoid dose tapering or discontinuation. More patients treated with canakinumab experienced infections than patients treated with placebo (*Ruperto et al 2012*). Patients enrolled in these trials were eligible for an open-label extension and were followed for 5 years. At 3 years, aJIA-ACR 50/70/90 response rates were 54.8%, 53.7%, and 49.7%, respectively (*Ruperto et al 2018*).
- A meta-analysis of trials evaluating biologics for the treatment of SJIA included 5 trials; 1 each for Kineret (anakinra), Ilaris (canakinumab), and Actemra (tocilizumab), and 2 for rilonacept (not FDA-approved for JIA and not included in this review) (*Tarp et al 2016*). The primary endpoint, the proportion of patients achieving a modified ACR Pedi 30 response, was superior to placebo for all agents, but did not differ significantly among anakinra, canakinumab, and tocilizumab. However, comparisons were based on low-quality, indirect evidence and no firm conclusions can be drawn on their relative efficacy. No differences among drugs for serious AEs were demonstrated.

Plaque psoriasis (PsO)

- In a randomized, double-blind, double-dummy trial, Humira (adalimumab) was compared to MTX and placebo in patients with moderate to severe PsO despite treatment with topical agents. The primary outcome was the proportion of patients that achieved Psoriasis Area and Severity Index (PASI) 75 at 16 weeks. Significantly more patients in the adalimumab group achieved the primary endpoint compared to patients in the MTX (p < 0.001) and placebo (p < 0.001) groups, respectively (*Saurat et al 2008*).
- More than 2,200 patients were enrolled in 2 published, pivotal, phase III trials that served as the primary basis for the FDA approval of Stelara (ustekinumab) in PsO. PHOENIX 1 and PHOENIX 2 enrolled patients with moderate to severe PsO to randomly receive ustekinumab 45 mg, 90 mg or placebo at weeks 0, 4, and every 12 weeks thereafter (*Leonardi et al 2008, Papp et al 2008, Langley et al 2015*). In PHOENIX 1, patients who were initially randomized to ustekinumab at week 0 and achieved long-term response (at least PASI 75 at weeks 28 and 40) were re-randomized at week 40 to maintenance ustekinumab or withdrawal from treatment. Patients in the 45 mg ustekinumab and 90 mg ustekinumab groups had higher proportion of patients achieving PASI 75 compared to patients in the placebo group at week 12 (p < 0.0001 for both). PASI 75 response was better maintained to at least 1 year in those receiving maintenance ustekinumab than in those withdrawn from treatment at week 40 (p < 0.0001) (*Leonardi et al 2008*). In PHOENIX 2, the primary endpoint (the proportion of patients achieving a PASI 75 response at week 12) was achieved in significantly more patients receiving ustekinumab 45 and 90 mg compared to patients receiving placebo (p < 0.0001). Partial responders were re-randomized at week 28 to continue dosing every 12 weeks or escalate to dosing every 8 weeks. More partial responders at week 28 who received 90 mg every 8 weeks achieved PASI 75 at week 52 than did those who continued to receive the same dose every 12 weeks. There was no such response to changes in

dosing intensity in partial responders treated with 45 mg. AEs were similar between groups (*Papp et al 2008*). A total of 70% (849 of 1212) of ustekinumab-treated patients completed therapy through week 244. At week 244, the proportions of patients initially randomized to ustekinumab 45 mg and 90 mg who achieved PASI 75 were 76.5% and 78.6%, respectively. A total of 50.0% and 55.5% of patients, respectively, achieved PASI 90 (*Langley et al 2015*).

- In a study comparing Enbrel (etanercept) and Stelara (ustekinumab), a greater proportion of PsO patients achieved the primary outcome (PASI 75 at week 12) with ustekinumab 45 (67.5%) and 90 mg (73.8%) compared to etanercept 50 mg (56.8%; p = 0.01 vs ustekinumab 45 mg; p < 0.001 vs ustekinumab 90 mg). In this trial, etanercept therapy was associated with a greater risk of injection site erythema (14.7% vs 0.7% of all ustekinumab patients) (*Griffiths et al 2010).*
- Approval of Otezla (apremilast) for moderate to severe PsO was based on results from the ESTEEM trials. In the trials, 1,257 patients with moderate to severe PsO were randomized 2:1 to apremilast 30 mg twice daily (with a titration period) or placebo. The primary endpoint was the number of patients with a 75% improvement on the PASI 75. In ESTEEM 1, significantly more patients receiving apremilast achieved PASI 75 compared to placebo (33.1% vs 5.3%; p < 0.0001) at 16 weeks. In ESTEEM 2, significantly more patients receiving apremilast also achieved PASI 75 compared to placebo (28.8% vs 5.8%; p < 0.0001) at 16 weeks (*Papp et al 2015, Paul et al 2015a*).
    - Additional analyses of the ESTEEM trials have been published. In 1 analysis (*Thaçi et al 2016*), the impact of apremilast on health-related quality of life, general function, and mental health was evaluated using patient-reported outcome assessments. The study demonstrated improvement with apremilast vs placebo, including improvements on the dermatology life quality index (DLQI) and SF-36 mental component summary (MCS) that exceeded minimal clinically important differences. In another analysis (*Rich et al 2016*), effects of apremilast on difficult-to-treat nail and scalp psoriasis were evaluated. At baseline in ESTEEM 1 and ESTEEM 2, respectively, 66.1% and 64.7% of patients had nail psoriasis and 66.7% and 65.5% had moderate to very severe scalp psoriasis. At week 16, apremilast produced greater improvements in Nail Psoriasis Severity Index (NAPSI) score vs placebo; greater NAPSI-50 response (50% reduction from baseline in target nail NAPSI score) vs placebo; and greater response on the Scalp Physician Global Assessment (ScPGA) vs placebo. Improvements were generally maintained over 52 weeks in patients with a PASI response at week 32.
- Cosentyx (secukinumab) was evaluated in 2 large, phase 3, double-blind trials in patients with moderate to severe PsO. The co-primary endpoints were the proportions of patients achieving PASI 75 and the proportions of patients with clear or almost clear skin (score 0 or 1) on the modified investigator's global assessment (IGA) at 12 weeks.
    - In ERASURE (n = 738), 81.6%, 71.6%, and 4.5% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 65.3%, 51.2%, and 2.4% achieved a score of 0 or 1 on the IGA (*Langley et al 2014*).
    - In FIXTURE (n = 1306), 77.1%, 67%, 44%, and 4.9% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, Enbrel (etanercept) at FDA-recommended dosing, and placebo, respectively, and 62.5%, 51.1%, 27.2%, and 2.8% achieved a score of 0 or 1 on the IGA (*Langley et al 2014*).
- Two smaller, phase 3, double-blind, placebo-controlled trials evaluated Cosentyx (secukinumab) given by prefilled syringe (FEATURE) or auto-injector/pen (JUNCTURE). Again, co-primary endpoints were the proportions of patients achieving PASI 75 and obtaining a score of 0 or 1 on the modified IGA at 12 weeks.
    - In FEATURE (n = 177), 75.9%, 69.5%, and 0% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 69%, 52.5%, and 0% achieved a score of 0 or 1 on the IGA (*Blauvelt et al 2015*).
    - In JUNCTURE (n = 182), 86.7%, 71.7%, and 3.3% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 73.3%, 53.3%, and 0% achieved a score of 0 or 1 on the IGA (*Paul et al 2015b*).
- Secondary endpoints, including the proportions of patients demonstrating a reduction of 90% or more on the PASI (PASI 90), a reduction of 100% (PASI 100), and change in the DLQI further support the efficacy of Cosentyx (secukinumab) (*Blauvelt et al 2015, Langley et al 2014, Paul et al 2015b*).
- In the CLEAR study, Cosentyx (secukinumab) 300 mg SQ every 4 weeks and Stelara (ustekinumab) 45 mg or 90 mg SQ (based on body weight) every 12 weeks were compared for safety and efficacy in a double-blind, randomized controlled trial in 676 patients with moderate to severe PsO (*Thaçi et al 2015*). The primary endpoint, proportion of patients achieving PASI 90 at week 16, was significantly higher with secukinumab compared to ustekinumab (79% vs 57.6%; p < 0.0001). Achievement of PASI 100 response at week 16 was also significantly higher with secukinumab over ustekinumab (44.3% vs 28.4%; p < 0.0001). Infections and infestations were reported in 29.3% of secukinumab- and 25.3% of ustekinumab-treated patients. Most infections were not serious and were managed without discontinuation. The most commonly reported AEs included headache and nasopharyngitis. Serious AEs were reported in 3% of each group.

- Cosentyx (secukinumab) and Stelara (ustekinumab) were also compared in the 16-week randomized, double-blind CLARITY trial, which included 1102 patients with moderate to severe PsO. The co-primary endpoints were proportion of patients achieving PASI 90 response at week 12 and modified IGA score of 0/1 at week 12. Secukinumab was found be to superior to ustekinumab for both PASI 90 response (66.5% vs 47.9%; p < 0.0001) and modified IGA score of 0/1 (72.3% vs 55.3%; p < 0.0001) (*Bagel et al 2018*).
- A meta-analysis of 7 Phase 3 clinical trials demonstrated the efficacy of Cosentyx (secukinumab) vs placebo and vs Enbrel (etanercept) in patients with PsO (*Ryoo et al 2016*). The ORs for achieving PASI 75 and for achieving IGA 0 or 1 were both 3.7 for secukinumab vs etanercept. Secukinumab 300 mg was significantly more effective than 150 mg. Secukinumab was well-tolerated throughout the 1-year trials.
- The use of Taltz (ixekizumab) for the treatment of PsO was evaluated in the UNCOVER-1, UNCOVER-2, and UNCOVER-3 trials. All were Phase 3, double-blind, randomized trials.
    - UNCOVER-1 (n = 1296) compared ixekizumab 160 mg loading dose then 80 mg every 2 weeks, ixekizumab 160 mg loading dose then 80 mg every 4 weeks, and placebo (*Gordon et al 2016, Taltz product dossier 2016*). Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving a physician's global assessment (PGA) score of 0 or 1 (clear or almost clear) at week 12. In the ixekizumab every 2 week, ixekizumab every 4 week, and placebo groups, PASI 75 was achieved by 89.1%, 82.6%, and 3.9% of patients, respectively (p < 0.001 for both doses vs placebo), and PGA 0 or 1 was achieved by 81.8%, 76.4%, and 3.2% of patients, respectively (p < 0.001 for both doses vs placebo). Improvements for ixekizumab vs placebo were also seen in secondary endpoints including PASI 90, PASI 100, PGA 0, and change in DLQI.
    - UNCOVER-2 (n = 1224) compared ixekizumab 160 mg loading dose then 80 mg every 2 weeks, ixekizumab 160 mg then 80 mg every 4 weeks, etanercept 50 mg twice weekly, and placebo (*Griffiths et al 2015*). Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving a PGA 0 or 1 at week 12. The proportions of patients achieving PASI 75 were 89.7%, 77.5%, 41.6%, and 2.4% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively (p < 0.0001 for all active treatments vs placebo and for both ixekizumab arms vs etanercept). The proportions of patients achieving PGA 0 or 1 were 83.2%, 72.9%, 36%, and 2.4% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively (p < 0.0001 for all active treatments vs placebo and for both ixekizumab arms vs etanercept). Improvements were also greater for ixekizumab vs placebo, etanercept vs placebo, and ixekizumab vs etanercept for all secondary endpoints including PGA 0, PASI 90, PASI 100, and DLQI.
    - UNCOVER-3 (n = 1346) had the same treatment groups and primary and secondary endpoints as UNCOVER-2 (*Griffiths et al 2015*). The proportions of patients achieving PASI 75 were 87.3%, 84.2%, 53.4%, and 7.3% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively (p < 0.0001 for all active treatments vs placebo and for both ixekizumab arms vs etanercept). The proportions of patients achieving PGA 0 or 1 were 80.5%, 75.4%, 41.6%, and 6.7% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively (p < 0.0001 for all active treatments vs placebo and for both ixekizumab arms vs etanercept). Improvements were also greater for ixekizumab vs placebo, etanercept vs placebo, and ixekizumab vs etanercept for all secondary endpoints including PGA 0, PASI 90, PASI 100, and DLQI.
    - Results through week 60 for UNCOVER-1, UNCOVER-2, and UNCOVER-3 have been reported (*Gordon et al 2016*). At week 12 in UNCOVER-1 and UNCOVER-2, patients responding to ixekizumab (PGA 0 or 1) were re-randomized to receive ixekizumab 80 mg every 4 weeks, ixekizumab 80 mg every 12 weeks, or placebo through week 60. Among the patients who were randomly reassigned at week 12 to receive 80 mg of ixekizumab every 4 weeks (the approved maintenance dosing), 80 mg of ixekizumab every 12 weeks, or placebo, a PGA score of 0 or 1 was maintained by 73.8%, 39.0%, and 7.0% of the patients, respectively, and high rates were maintained or attained for additional measures such as PASI 75, PASI 90, and PASI 100 (pooled data for UNCOVER-1 and UNCOVER-2). At week 12 in UNCOVER-3, patients entered a long-term extension period in which they received ixekizumab 80 mg every 4 weeks through week 60. At week 60, at least 73% had a PGA score of 0 or 1 and at least 80% had a PASI 75 response. In addition, most patients had maintained or attained PASI 90 or PASI 100 at week 60.
- The IXORA-Q study (n = 149) evaluated the efficacy of Taltz (ixekizumab) to placebo in patients with moderate-to-severe genital psoriasis. At week 12, ixekizumab was superior to placebo for the primary endpoint of the proportion of patients achieving a score of 0 or 1 on the static PGA of genitalia (73% vs 8%, p < 0.001) (*Ryan et al 2018*).
- The IXORA-S study (n = 676) was a head-to-head study that compared Taltz (ixekizumab) (160 mg LD, then 80 mg every 2 weeks for 12 weeks, then 80 mg every 4 weeks) to Stelara (ustekinumab) (45 mg or 90 mg weight-based dosing per label) (*Reich et al 2017[b]).* The primary endpoint, PASI 90 response at week 12, was achieved by 72.8%

and 42.2% of patients in the ixekizumab and ustekinumab groups, respectively (p < 0.001); superior efficacy of ixekizumab was maintained through week 24. Response rates for PASI 75, PASI 100, and PGA 0 or 1 also favored ixekizumab over ustekinumab (adjusted p < 0.05).

- The use of Siliq (brodalumab) for the treatment of PsO was evaluated in the AMAGINE-1, AMAGINE-2, and AMAGINE-3 trials. All were Phase 3, double-blind, randomized trials.
    - AMAGINE-1 (n = 661) compared brodalumab 210 mg, brodalumab 140 mg, and placebo; each treatment was given at weeks 0, 1, and 2, followed by every 2 weeks to week 12 (*Papp et al 2016*). This 12-week induction phase was followed by a withdrawal/retreatment phase through week 52: patients receiving brodalumab who achieved PGA 0 or 1 (PGA success) were re-randomized to the placebo or induction dose, and patients randomized to brodalumab with PGA ≥ 2 and those initially receiving placebo received brodalumab 210 mg every 2 weeks. Patients in the withdrawal phase who had disease recurrence (PGA ≥ 3) between weeks 16 and 52 were retreated with their induction doses of brodalumab. Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving PGA success at week 12. PASI 75 was achieved by 83% (95% CI, 78 to 88), 60% (95% CI, 54 to 67), and 3% (95% CI, 1 to 6) of patients in the brodalumab 210 mg, brodalumab 140 mg, and placebo groups, respectively; PGA success was achieved by 76% (95% CI, 70 to 81), 54% (95% CI, 47 to 61), and 1% (95% CI, 0 to 4), respectively (p < 0.001 for all comparisons of brodalumab vs placebo). Differences in key secondary endpoints at week 12 also favored brodalumab vs placebo, including PASI 90, PASI 100, and PGA 0. In the randomized withdrawal phase, high response rates were maintained in those who continued brodalumab, while most patients re-randomized to placebo experienced return of disease (but were able to recapture disease control with retreatment).
    - AMAGINE-2 (n = 1831) and AMAGINE-3 (n = 1881) were identical in design and compared brodalumab 210 mg, brodalumab 140 mg, Stelara (ustekinumab), and placebo (*Lebwohl et al 2015*). Brodalumab was given at weeks 0, 1, and 2, followed by every 2 weeks to week 12. Ustekinumab was given in weight-based doses per its FDA-approved labeling. At week 12, patients receiving brodalumab were re-randomized to receive brodalumab at a dose of 210 mg every 2 weeks or 140 mg every 2, 4, or 8 weeks; patients receiving ustekinumab continued ustekinumab; and patients receiving placebo were switched to brodalumab 210 mg every 2 weeks; maintenance continued though week 52. The primary endpoints included a comparison of both brodalumab doses vs placebo with regard to the proportion of patients achieving PASI 75 and the proportion of patients achieving PGA success (PGA 0 or 1) at week 12, as well as a comparison of brodalumab 210 mg vs ustekinumab with regard to the proportion of patients achieving PASI 100 at week 12.
        - In AMAGINE-2, the proportion of patients achieving PASI 75 was 86% (95% CI, 83 to 89), 67% (95% CI, 63 to 70), 70% (95% CI, 65 to 75), and 8% (95% CI, 5 to 12) in the brodalumab 210 mg, brodalumab 140 mg, ustekinumab, and placebo groups, respectively, and the proportion of patients achieving PGA success was 79% (95% CI, 75 to 82), 58% (95% CI, 54 to 62), 61% (95% CI, 55 to 67), and 4% (95% CI, 2 to 7), respectively (p < 0.001 for all comparisons of brodalumab vs placebo). The proportion of patients achieving PASI 100 was 44% (95% CI, 41 to 49), 26% (95% CI, 22 to 29), 22% (95% CI, 17 to 27), and 1% (95% CI, 0 to 2), respectively (p < 0.001 for both brodalumab doses vs placebo and for brodalumab 210 mg vs ustekinumab; p = 0.08 for brodalumab 140 mg vs ustekinumab).
        - In AMAGINE-3, the proportion of patients achieving PASI 75 was 85% (95% CI, 82 to 88), 69% (95% CI, 65 to 73), 69% (95% CI, 64 to 74), and 6% (95% CI, 4 to 9) in the brodalumab 210 mg, brodalumab 140 mg, ustekinumab, and placebo groups, respectively, and the proportion of patients achieving PGA success was 80% (95% CI, 76 to 83), 60% (95% CI, 56 to 64), 57% (95% CI, 52 to 63), and 4% (95% CI, 2 to 7), respectively (p < 0.001 for all comparisons of brodalumab vs placebo). The proportion of patients achieving PASI 100 was 37% (95% CI, 33 to 41), 27% (95% CI, 24 to 31), 19% (95% CI, 14 to 23), and 0.3% (95% CI, 0 to 2), respectively (p < 0.001 for both brodalumab doses vs placebo and for brodalumab 210 mg vs ustekinumab; p = 0.007 for brodalumab 140 mg vs ustekinumab).
        - In both studies, the 2 brodalumab doses were superior to placebo with regard to all key secondary endpoints. Patients receiving brodalumab 210 mg throughout the induction and maintenance phases demonstrated an increase in PASI response rates through week 12 and a stabilization during weeks 16 to 52. Based on PGA success rates, maintenance with brodalumab 210 mg or 140 mg every 2 weeks was superior to the use of the less frequent maintenance regimens, and the 210 mg regimen was superior to the 140 mg regimen.
- The use of Tremfya (guselkumab) for the treatment of moderate to severe PsO was evaluated in the VOYAGE 1, VOYAGE 2, and NAVIGATE trials. All were phase 3, double-blind, randomized trials.

- Patients in both VOYAGE 1 and VOYAGE 2 were initially assigned to receive guselkumab (100 mg at weeks 0 and 4, then every 8 weeks), placebo, or Humira (adalimumab) (80 mg at week 0, 40 mg at week 1, then every 2 weeks). Patients in the placebo group were switched to guselkumab at week 16. The coprimary endpoints included the proportion of patients achieving an IGA score of 0 or 1 at week 16 as well as the proportion of patients achieving a PASI 90 response at week 16 in the guselkumab group compared with placebo. Comparisons between guselkumab and adalimumab were assessed as secondary endpoints at weeks 16, 24, and 48. To evaluate maintenance and durability of response in VOYAGE 2, subjects randomized to guselkumab at week 0 and who were PASI 90 responders at week 28 were re-randomized to either continue treatment with guselkumab every 8 weeks or be withdrawn from therapy (ie, receive placebo).
  - In VOYAGE 1 (n = 837), IGA 0 or 1 was achieved in more patients treated with guselkumab (85.1%) compared to placebo (6.9%) at week 16 ($p < 0.001$), and a higher percentage of patients achieved PASI 90 with guselkumab (73.3%) compared to placebo (2.9%; $p<0.001$) (*Blauvelt et al 2017*). Additionally, IGA 0 or 1 was achieved in more patients with guselkumab vs adalimumab at week 16 (85.1% vs 65.9%), week 24 (84.2% vs. 61.7%), and week 48 (80.5% vs 55.4%; $p < 0.001$). PASI 90 score was also achieved in a higher percentage of patients with guselkumab vs adalimumab at week 16 (73.3% vs 49.7%), week 24 (80.2% vs 53%), and week 48 (76.3% vs 47.9%; $p < 0.001$).
  - In VOYAGE 2 (n = 992), IGA 0 or 1 and PASI 90 were achieved by a higher proportion of patients who received guselkumab (84.1% and 70%) vs placebo (8.5% and 2.4%) ($p < 0.001$ for both comparisons). At week 16, IGA score of 0 or 1 and PASI 90 were achieved in more patients with guselkumab (84.1% and 70%) vs adalimumab (67.7% and 46.8%) ($p < 0.001$). PASI 90 was achieved in 88.6% of patients who continued on guselkumab vs 36.8% of patients who were rerandomized to placebo at week 48. In patients who were nonresponders to adalimumab and switched to guselkumab, PASI 90 was achieved by 66.1% of patients.
- In NAVIGATE (n = 871), patients were assigned to open-label ustekinumab 45 or 90 mg at weeks 0 and 4 (*Langley et al 2017*). Patients with IGA 0 or 1 at week 16 were continued on ustekinumab, while patients with an inadequate response to ustekinumab at week 16 (IGA ≥ 2) were randomized to guselkumab 100 mg or ustekinumab. Patients treated with guselkumab had a higher mean number of visits with IGA of 0 or 1 and ≥ 2-grade improvement (relative to week 16) compared to randomized ustekinumab from week 28 to 40 (1.5 vs 0.7; $p < 0.001$). A higher proportion of patients achieved IGA of 0 or 1 with ≥ 2 grade improvement at week 28 with guselkumab (31.1%) vs randomized ustekinumab (14.3%; $p = 0.001$); at week 52, 36.2% of guselkumab-treated patients achieved this response vs 17.3% of the ustekinumab-treated patients. The proportion of patients with PASI 90 response at week 28 was 48.1% for the guselkumab group vs 22.6% for the ustekinumab group ($p \leq 0.001$).

- The approval of Ilumya (tildrakizumab-asmn) was based on 2 randomized, double-blind, multicenter, phase 3 trials: reSURFACE1 (772 patients) and reSURFACE2 (1,090 patients). Enrolled adult patients with moderate-to-severe chronic plaque psoriasis received tildrakizumab-asmn 200 mg, tildrakizumab-asmn 100 mg, or placebo in both studies; reSURFACE 2 also included an Enbrel (etanercept) arm. Only the tildrakizumab-asmn 100 mg dose was approved by the FDA. The coprimary endpoints included the proportion of patients achieving PASI 75 and PGA response (score of 0 or 1 with ≥ 2 reduction from baseline) at week 12 (*Reich et al 2017*).
  - In reSURFACE 1, PASI 75 response was achieved by 64% and 6% of the tildrakizumab-asmn 100 mg and placebo arms at week 12, respectively; a PGA response was achieved by 58% vs 7% of the tildrakizumab-asmn 100 mg and placebo groups, respectively ($p < 0.0001$ for both comparisons).
  - In reSURFACE 2, PASI 75 response was achieved by 61% and 6% of the tildrakizumab-asmn 100 mg and placebo arms, respectively; a PGA response was achieved by 55% vs 4% of the tildrakizumab-asmn 100 mg and placebo groups, respectively ($p < 0.0001$ for both comparisons). A higher proportion of patients in the tildrakizumaz 100 mg group achieved PASI 75 vs etanercept (61% vs 48%, respectively; $p = 0.001$), but the rates of PGA responses did not differ significantly between groups (55% vs 48%, respectively; $p = 0.0663$).
- For most immunomodulators that are FDA-approved for the treatment of PsO, the indication is limited to adults. In 2016, Enbrel (etanercept) received FDA approval for treatment of PsO in pediatric patients age ≥ 4 years. Limited information from published trials is also available on the use of Stelara (ustekinumab) in adolescent patients (age 12 to 17 years).
  - A 48-week, double-blind, placebo-controlled trial (n = 211) evaluated the use of etanercept in patients 4 to 17 years of age with moderate-to-severe PsO (*Paller et al 2008*). Patients received etanercept 0.8 mg SQ once weekly or placebo for 12 weeks, followed by 24 weeks of open-label etanercept; 138 patients underwent a second randomization to placebo or etanercept at week 36 to investigate effects of withdrawal and retreatment. The primary endpoint, PASI 75 at week 12, was achieved by 57% and 11% of patients receiving etanercept and placebo, respectively. A significantly higher proportion of patients in the etanercept group than

in the placebo group achieved PASI 90 (27% vs 7%) and a PGA of 0 or 1 (53% vs 13%) at week 12 ($p < 0.001$). During the withdrawal period from week 36 to week 48, response was lost by 29 of 69 patients (42%) assigned to placebo at the second randomization. Four serious AEs (including 3 infections) occurred in 3 patients during treatment with open-label etanercept; all resolved without sequelae. The authors concluded that etanercept significantly reduced disease severity in this population. Results of a 5-year, open-label extension study (n = 182) demonstrated that etanercept was generally well tolerated and efficacy was maintained in those who remained in the study for up to 264 weeks (69 of 181 patients) (*Paller et al 2016*).

  - A 52-week, double-blind, placebo-controlled trial (n = 110) evaluated the use of ustekinumab in patients 12 to 17 years of age with moderate-to-severe PsO (*Landells et al 2015*). Patients received a weight-based standard dose (SD), a half-strength dose (HSD), or placebo. The primary endpoint, the proportion of patients achieving a PGA 0 or 1 at week 12, was significantly greater in the SD (69.4%) and HSD (67.6%) groups vs placebo (5.4%) ($p < 0.001$ for both doses vs placebo). The proportions of patients achieving PASI 75 at this time point were 80.6%, 78.4%, and 10.8% in the SD, HSD, and placebo groups, respectively ($p < 0.001$ for both doses vs placebo), and the proportions of patients achieving PASI 90 were 61.1%, 54.1%, and 5.4% in the SD, HSD, and placebo groups, respectively ($p < 0.001$ for both doses vs placebo). In both groups, the proportions of patients achieving these endpoints were maintained from week 12 through week 52. The authors concluded that ustekinumab appears to be a viable treatment option for moderate-to-severe PsO in the adolescent population. The standard dose provided a response comparable to that in adults with no unexpected AEs through 1 year of treatment.

- Combination therapy is commonly utilized, such as with different topical therapies, systemic plus topical therapies, and combinations of certain systemic therapies with phototherapy (*Feldman 2015*). Combinations of different systemic therapies have not been adequately studied; however, there are some data to show that combined therapy with Enbrel (etanercept) plus MTX may be beneficial for therapy-resistant patients (*Busard et al 2014; Gottlieb et al 2012*).
- In a meta-analysis evaluating the efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate to severe PsO, Humira (adalimumab) use was associated with a risk difference of 64% compared to placebo in achieving a PASI 75 response ($p < 0.00001$) while Enbrel (etanercept) 25 and 50 mg twice weekly were associated with a risk difference of 30 and 44% compared to placebo ($p < 0.00001$ for both strengths vs placebo). The Remicade (infliximab) group had the greatest response with a risk difference of 77% compared to the placebo group ($p < 0.0001$). The withdrawal rate was 0.5% with adalimumab, 0.4 to 0.5% with etanercept and 1.3% with infliximab (*Schmitt et al 2008*).
- Another meta-analysis evaluated the efficacy and safety of long-term treatments (≥24 weeks) for moderate-to-severe PsO (*Nast et al 2015a*). A total of 25 randomized trials (n = 11,279) were included. Compared to placebo, RRs for achievement of PASI 75 were 13.07 (95% CI, 8.60 to 19.87) for Remicade (infliximab), 11.97 (95% CI, 8.83 to 16.23) for Cosentyx (secukinumab), 11.39 (95% CI, 8.94 to 14.51) for Stelara (ustekinumab), 8.92 (95% CI, 6.33 to 12.57) for Humira (adalimumab), 8.39 (95% CI, 6.74 to 10.45) for Enbrel (etanercept), and 5.83 (95% CI, 2.58 to 13.17) for Otezla (apremilast). Head-to-head studies demonstrated better efficacy for secukinumab and infliximab vs etanercept, and for infliximab vs MTX. The biologics and apremilast also had superior efficacy vs placebo for endpoints of PASI 90 and PGA 0 or 1. The investigators stated that based on available evidence, infliximab, secukinumab, and ustekinumab are the most efficacious long-term treatments, but noted that additional head-to-head comparisons and studies on safety and patient-related outcomes are desirable.
- In a meta-analysis of 41 RCTs that used hierarchical clustering to rate efficacy and tolerability, Humira (adalimumab), Cosentyx (secukinumab), and Stelara (ustekinumab) were characterized by high efficacy and tolerability, Remicade (infliximab) and Taltz (ixekizumab) were characterized by high efficacy and poorer tolerability, and Enbrel (etanercept), MTX, and placebo were characterized by poorer efficacy and moderate tolerability in patients with PsO (*Jabbar-Lopez et al 2017*).
- A Cochrane review evaluated biologics in patients with moderate to severe PsO in 109 studies (*Sbidian E et al 2017*) between 12 and 16 weeks after randomization. Agents included in the review were Humira (adalimumab), Enbrel (etanercept), Cimzia (certolizumab), Stelara (ustekinumab), Cosentyx (secukinumab), Taltz (ixekizumab), Siliq (brodalumab), Remicade (infliximab), and Tremfya (guselkumab). The network meta-analysis showed that all of the biologics were significantly more effective in achieving PASI 90 compared to placebo. Cosentyx (secukinumab), Taltz (ixekizumab), and Siliq (brodalumab) were significantly more effective than Remicade (infliximab), Humira (adalimumab), and Enbrel (etanercept), but not Cimzia (certolizumab). Stelara (ustekinumab) was superior to Enbrel (etanercept). There was no significant difference amongst the agents in the risk of serious adverse effects.

Psoriatic arthritis (PsA)

- In 2 trials, PsA patients receiving Humira (adalimumab) 40 mg every other week achieved an ACR 20 at a higher rate than with placebo. Thirty-nine percent in the active treatment group vs 16% in the placebo group achieved this

endpoint by week 12 (p = 0.012) in a trial (n = 100); while 58 and 14% of patients, respectively, achieved this endpoint in a second trial (p < 0.001) (*Genovese et al 2007, Mease et al 2005*). Adalimumab use was also associated with an improvement in structural damage, as measured by the mTSS, compared to those receiving placebo (-0.2 vs 1; p < 0.001) (*Mease et al 2005*).

- In a 12-week trial in adult patients with PsA despite NSAID therapy, 87% of Enbrel (etanercept) treated patients met PsA response criteria, compared to 23% of those on placebo (p < 0.0001). A PASI 75 improvement and ACR 20 response were detected in 26 and 73% of etanercept-treated patients vs 0 (p = 0.0154) and 13% (p < 0.0001) of placebo-treated patients (*Mease et al 2000*). In a second trial, the mean annualized rate of change in the mTSS with Enbrel (etanercept) was -0.03 unit, compared to 1 unit with placebo (p < 0.0001). At 24 weeks, 23% of etanercept patients eligible for PsO evaluation achieved at least a PASI 75, compared to 3% of placebo patients (p = 0.001). Additionally, HAQ scores were significantly improved with etanercept (54%) over placebo (6%; p < 0.0001). Injection site reaction occurred at a greater rate with etanercept than placebo (36% vs 9%; p < 0.001) (*Mease et al 2004*).
- A 24-week trial of adult patients with PsA randomized 851 patients to oral methotrexate monotherapy, etanercept monotherapy, or combination therapy. At week 24, ACR 20 response rates were significantly greater with etanercept monotherapy (60.9%) compared to methotrexate monotherapy (50.7%), but combination therapy (65%) did not provide any significant improvement over etanercept monotherapy (*Mease et al 2019*).
- The FDA approval of Simponi (golimumab) for PsA was based on the GO-REVEAL study, a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with moderate to severely active PsA despite NSAID or DMARD therapy (n = 405). Golimumab with or without MTX compared to placebo with or without MTX, resulted in significant improvement in signs and symptoms as demonstrated by the percentage of patients achieving a ACR 20 response at week 14. The ACR responses observed in the golimumab-treated groups were similar in patients receiving and not receiving concomitant MTX therapy (*Kavanaugh et al 2009*).
    - Subcutaneous golimumab for patients with active PsA demonstrated safety and efficacy over 5 years in the long-term extension of the GO-REVEAL study. Approximately one-half of patients took MTX concurrently. ACR 20 response rates at year 5 were 62.8 to 69.9% for golimumab SQ 50 or 100 mg every 4 weeks (*Kavanaugh et al 2014b*).
    - Post-hoc analyses of the 5-year GO-REVEAL results evaluated the relationship between achieving minimal disease activity (MDA; defined as the presence of ≥5 of 7 PsA outcomes measures [≤1 swollen joint, ≤1 tender joint, PASI ≤1, patient pain score ≤15, patient global disease activity score ≤20, HAQ disability index [HAQ DI] ≤0.5, and ≤1 tender enthesis point]) and long-term radiographic outcomes including radiographic progression. Among golimumab-treated patients, achieving long-term MDA was associated with better long-term functional improvement, patient global assessment, and radiographic outcomes. Radiographic benefit was more pronounced in patients using MTX at baseline. The authors conclude that in patients with active PsA, aiming for MDA as part of a treat-to-target strategy may provide long-term functional and radiographic benefits (*Kavanaugh et al 2016*).
- In another trial, more Remicade (infliximab) treated patients achieved ACR 20 at weeks 12 and 24 compared to placebo treated patients (p < 0.001) (*Antoni et al 2005*).
- The efficacy of Cimzia (certolizumab) in the treatment of PsA was established in 1 multicenter, double-blind, placebo controlled trial (n = 409). Patients were randomized to receive placebo, Cimzia 200 mg every 2 weeks, or Cimzia 400 mg every 4 weeks. At week 12, ACR 20 response was significantly greater in both active treatment groups compared to placebo (*Mease et al 2014*).
- The FDA-approval of Stelara (ustekinumab) for PsA was based on the results of 2 randomized, double-blind, placebo-controlled trials in adult patients with active PsA despite NSAID or DMARD therapy (PSUMMIT 1 and PSUMMIT 2). In PSUMMIT 1 (n = 615), a greater proportion of patients treated with ustekinumab 45 mg or 90 mg alone or in combination with MTX achieved ACR 20 response at week 24 compared to placebo (42.4% and 49.5% vs 22.8%; p < 0.0001 for both comparisons); responses were maintained at week 52 (*McInnes et al 2013*). Similar results were observed in the PSUMMIT 2 trial (n = 312) with 43.8% of ustekinumab-treated patients and 20.2% of placebo-treated patients achieving an ACR 20 response (p < 0.001) (*Ritchlin et al 2014*).
    - In PSUMMIT-1, patients taking placebo or ustekinumab 45 mg could adjust therapy at week 16 if they had an inadequate response, and all remaining patients in the placebo group at week 24 were crossed over to receive treatment with ustekinumab 45 mg (*McInnes et al 2013*). At week 100 (*Kavanaugh et al 2015a*), the ACR 20 responses were 63.6%, 56.7%, and 62.7% in the 90 mg, 45 mg, and placebo crossover groups, respectively. ACR 50 and ACR 70 responses followed a similar pattern and ranged from 37.3% to 46% and 18.6% to 24.7%, respectively. At week 100, the proportions of patients achieving PASI 75 were 71.3%, 72.5%, and 63.9% in the 90 mg, 45 mg, and placebo crossover groups, respectively. Improvements in physical function and health-related quality of life (HRQoL) were sustained over time, with median decreases

in HAQ-DI scores from baseline to week 100 of 0.38, 0.25, and 0.38 in the 90 mg, 45 mg, and placebo crossover groups, respectively.

- Cosentyx (secukinumab) gained FDA approval for the treatment of PsA based on 2 multicenter, double-blind, placebo-controlled randomized controlled trials – FUTURE 1 and FUTURE 2 *(Mease et al 2015, McInnes et al 2015*). The FUTURE 1 study randomized patients to secukinumab 75 mg or 150 mg every 4 weeks (following IV loading doses) or placebo and evaluated ACR 20 at week 24. In the FUTURE 2 study, patients were randomized to secukinumab 75 mg, 150 mg, or 300 mg SQ every 4 weeks (following SQ loading doses given at weeks 0, 1, 2, 3, and 4) or placebo and evaluated at week 24 for ACR 20 response.
    - In FUTURE 1 at week 24, both the secukinumab 75 mg and 150 mg doses demonstrated significantly higher ACR 20 responses vs placebo (50.5% and 50.0% vs 17.3%, respectively; $p < 0.0001$ vs placebo).
    - All pre-specified endpoints including dactylitis, enthesitis, SF-36 PCS, HAQ-DI, DAS28-CRP, ACR 50, PASI 75, PASI 90, and mTSS score were achieved by week 24 and reached statistical significance.
    - At week 104 in a long-term extension study of FUTURE 1, ACR 20 was achieved in 66.8% of patients with secukinumab 150 mg and 58.6% of patients with secukinumab 75 mg (*Kavanaugh et al 2017*).
    - In FUTURE 2 at week 24, ACR 20 response rates were significantly greater with secukinumab than with placebo: 54.0%, 51.0%, and 29.3% vs 15.3% with secukinumab 300 mg, 150 mg, and 75 mg vs placebo, respectively ($p < 0.0001$ for secukinumab 300 mg and 150 mg; $p < 0.05$ for 75 mg vs placebo).
    - Improvements were seen with secukinumab 300 mg and 150 mg with regard to PASI 75/90 scores, DAS28-CRP, SF-36 PCS, HAQ-DI, dactylitis, and enthesitis. Efficacy was observed in both TNF-naïve patients and in patients with prior TNF inadequate response or intolerance.
- The efficacy of Otezla (apremilast) was demonstrated in 3 placebo-controlled trials in patients with PsA. At week 16, significantly more patients in the Otezla groups had ≥ 20% improvement in symptoms, as defined by ACR response criteria (*Cutolo et al 2013, Edwards et al 2016, Kavanaugh et al 2014a*). Clinical improvements observed at 16 weeks were sustained at 52 weeks (*Edwards et al 2016, Kavanaugh et al 2015b*).
- Orencia (abatacept) gained FDA approval for the treatment of PsA based on 2 double-blind, placebo-controlled clinical trials in patients with an inadequate response or intolerance to DMARD therapy (*Mease et al 2011, Mease et al 2017[a]*). In a phase 2 dose-finding trial (n = 170), patients received abatacept 3 mg/kg, 10 mg/kg, or 30/10 mg/kg (2 doses of 30 mg/kg then 10 mg/kg) on days 1, 15, 29 and then every 28 days (*Mease et al 2011*). Compared to placebo (19%), the proportion of patients achieving ACR 20 was significantly higher with abatacept 10 mg/kg (48%; $p = 0.006$) and 30/10 mg/kg (42%; $p = 0.022$) but not 3 mg/kg (33%). A phase 3 trial (n = 424) randomized patients to abatacept 125 mg weekly or placebo (*Mease et al 2017[a]*). At week 24, the proportion of patients with ACR 20 response was significantly higher with abatacept (39.4%) vs placebo (22.3%; $p < 0.001$).
- Taltz (ixekizumab) received FDA approval for the treatment of PsA based on 2 double-blind clinical trials, SPIRIT-P1 and SPIRIT-P2 (*Mease et al 2017[b], Nash et al 2017*). SPIRIT-P1 randomized 417 biologic naïve patients to placebo, adalimumab 40 mg every 2 weeks, ixekizumab 80 mg every 2 weeks, or ixekizumab 80 mg every 4 weeks. At week 24, ACR 20 response rates for ixekizumab every 2 weeks and every 4 weeks were 62.1% and 57.9%, respectively, which was significantly greater than the ACR 20 reponse rate with placebo (30.2%; $p \leq 0.001$). The active reference treatment, adalimumab, had an ACR 20 at week 24 of 57.4% (*Mease et al 2017[b]*). SPIRIT-P2 randomized 363 patients who had a previous inadequate response to a TNF inhibitor to placebo, ixekizumab 80 mg every 2 weeks, or ixekizumab 80 mg every 4 weeks. At week 24, ACR 20 response rates for ixekizumab every 2 weeks and every 4 weeks were 48% and 53%, respectively, which was significantly greater than the ACR 20 reponse rate with placebo (20%; $p < 0.0001$) (*Nash et al 2017*).
    - An open-label extension of the SPIRIT-P1 trial followed patients through week 52, demonstrating sustained efficacy with ixekizumab. The ACR 20, ACR 50, and ACR 70 reponse rates for the every 4 week and every 2 weeks groups were 69.1% and 68.8%, 54.6% and 53.1%, and 39.2% and 39.6% at week 52, respectively (*van der Heijde et al 2018*).
- Xeljanz (tofacitinib) received FDA approval for the treatment of PsA based on 2 double-blind, placebo-controlled clinical trials in patients with an inadequate response or intolerance to DMARD therapy (*Mease et al 2017[c], Gladman et al 2017*). The OPAL Broaden trial randomized 422 patients to tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, adalimumab 40 mg every 2 weeks, placebo with a blinded switch to tofacitinib 5 mg after 3 months, or placebo with a blinded switch to tofacitinib 10 mg after 3 months. The primary endpoint of the proportion of patients achieving ACR 20 at month 3 occurred in 50% in the tofacitinib 5 mg group, 61% in the tofacitinib 10 mg group, 33% in the placebo group ($p = 0.01$ vs 5 mg; $p < 0.001$ vs 10 mg), and 52% in the adalimumab group (*Mease et al 2017[c]*). The OPAL Beyond trial randomized 395 patients to tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, placebo with a blinded switch to tofacitinib 5 mg after 3 months, or placebo with a blinded switch to tofacitinib 10 mg after 3 months. The primary endpoint of the proportion of patients achieving ACR 20 at month 3 occurred in 50% in

the tofacitinib 5 mg group, 47% in the tofacitinib 10 mg group, and 24% in the placebo group (p < 0.001 for both comparisons) (*Gladman et al 2017*).

- A small, single-center randomized trial (N = 100) compared Remicade (infliximab), Enbrel (etanercept), and Humira (adalimumab) in patients with PsA who had had an inadequate response to DMARDs (*Atteno et al 2010*). The investigators found that each of the agents effectively controlled the signs and symptoms of PsA, and ACR response rates were similar among agents. Patients receiving infliximab and adalimumab showed the greatest improvement in PASI scores, whereas patients receiving etanercept showed the greatest improvement on the tender joint count and HAQ. Limitations of this trial were lack of blinding and lack of a placebo group.
- A meta-analysis based on both direct and indirect comparisons evaluated the efficacy and safety of Humira (adalimumab), Enbrel (etanercept), Remicade (infliximab), and Simponi (golimumab) over 24 weeks for the treatment of PsA (*Fénix et al 2013*). The investigators found no differences among products for the primary endpoint of ACR 50 or secondary endpoints of ACR 20 and ACR 70, except that etanercept was associated with a lower ACR 70 response. However, low sample sizes limited the power of the analysis.
- A meta-analysis of 9 randomized controlled trials and 6 observational studies evaluated Humira (adalimumab), Enbrel (etanercept), Simponi (golimumab), or placebo in the achievement of ACR 20, ACR 50, and ACR 70 endpoints in patients with moderate to severe PsA (*Lemos et al 2014*). Patients who used adalimumab, etanercept and golimumab were more likely to achieve ACR 20 and ACR 50 after 12 or 24 weeks of treatment. In long-term analysis (after all participants used anti-TNF for at least 24 weeks), there was no difference in ACR 20 and ACR 50 between the anti-TNF and control groups, but patients originally randomized to anti-TNF were more likely to achieve ACR 70.
- A meta-analysis of 8 studies evaluated Cosentyx (secukinumab), Taltz (ixekizumab), Siliq (brodalumab), and Stelara (ustekinumab) in the achievement of ACR 20, ACR 50, and ACR 70 endpoints in patients with PsA (*Bilal et al 2018*). Patients who used these agents were more likely to achieve ACR 20, ACR 50, and ACR70 after 24 weeks of treatment. Another network meta-analysis of 6 studies evaluated Cosentyx (secukinumab), Taltz (ixekizumab), and Stelara (ustekinumab) over 24 weeks in patients with active PsA (*Wu et al 2018*). The investigators found that all agents improved ACR20 and ACR50 at week 24 compared to placebo. A different network meta-analysis of 8 studies evaluated Orencia (abatacept), Otezla (apremilast), Stelara (ustekinumab), and Cosentyx (secukinumab) in the achievement of ACR 20 and ACR 50 in adults with moderate to severe PsA (*Kawalec et al 2018*). The investigators found a significant difference in ACR20 response rate between Cosentyx (secukinumab) 150 mg and Otezla (apremilast) 20 mg (RR, 2.55; 95% CI, 1.24 to 5.23) and Cosentyx (secukinumab) 300 mg and Otezla (apremilast) 20 mg (RR, 3.57; 95% CI, 1.48 to 8.64) or Otezla (apremilast) 30 mg (RR, 2.84; 95% CI, 1.18 to 6.86).
- Two indirect comparison meta-analyses sought to compare the efficacy of biologics for the treatment of PsA in patients with an inadequate response to prior therapies.
    - An analysis of 12 randomized trials compared various biologics in patients having an inadequate response to NSAIDs or traditional DMARDs (*Ungprasert et al 2016a*). The investigators determined that patients receiving older TNF inhibitors (evaluated as a group: Enbrel [etanercept], Remicade [infliximab], Humira [adalimumab], and Simponi [golimumab]) had a statistically significantly higher chance of achieving ACR 20 compared to patients receiving Cimzia (certolizumab), Otezla (apremilast), or Stelara (ustekinumab). Patients receiving Cosentyx (secukinumab) also had a higher chance of achieving ACR 20 compared to certolizumab, ustekinumab, and apremilast, but the relative risk did not always reach statistical significance. There was no statistically significant difference in this endpoint between secukinumab and the older TNF inhibitors, or between apremilast, ustekinumab, and certolizumab.
    - An analysis of 5 randomized trials compared various non-TNF inhibitor biologics (Orencia [abatacept], secukinumab, ustekinumab, and apremilast) in patients having an inadequate response or intolerance to TNF inhibitors (*Ungprasert et al 2016b*). The investigators found no difference for any between-agent comparison in the likelihood of achieving an ACR 20 response.
    - These meta-analyses had limitations, notably being based on a small number of trials, and should be interpreted with caution.

Ulcerative colitis (UC)

- Two trials (ACT 1 and ACT 2) evaluated Remicade (infliximab) compared to placebo for the treatment of UC. In both trials, clinical response at week 8 was significantly higher in infliximab 5 and 10 mg/kg treated patients compared to placebo treated patients (all p < 0.001). A significantly higher clinical response rate in both infliximab groups was maintained throughout the duration of the studies (*Rutgeerts et al 2005*). A randomized open-label trial evaluated infliximab at different dosing intervals for the treatment of pediatric UC. At week 8, 73.3% of patients met the primary endpoint of clinical response (95% CI, 62.1 to 84.5%) (*Hyams et al 2012*).
- In the ULTRA 2 study, significantly more patients taking Humira (adalimumab) 160 mg at week 0, 80 mg at week 2, and then 40 mg every other week for 52 weeks achieved clinical remission and clinical response vs patients taking

placebo (*Sandborn et al 2012*). These long term results confirm the findings of ULTRA 1. This 8-week induction trial demonstrated that adalimumab in same dosage as ULTRA 2 was effective for inducing clinical remission (*Reinisch et al 2011*). In ULTRA 1, significant differences between the adalimumab and placebo groups were only achieved for 2 of the secondary end points at week 8, i.e., rectal bleeding and PGA subscores. Conversely, in ULTRA 2, significantly greater proportions of adalimumab-treated patients achieved almost all secondary end points at week 8. This may have been because of the high placebo response rates in ULTRA 1. A meta-analysis of 3 randomized trials comparing adalimumab to placebo demonstrated that adalimumab increased the proportion of patients with clinical responses, clinical remission, mucosal healing, and inflammatory bowel disease questionnaire responses in the induction and maintenance phases. It also increased the proportion of patients with steroid-free remission in the maintenance phase (*Zhang et al 2016*).

- Simponi (golimumab) was studied in 1,064 patients with moderate to severe UC. Patients receiving golimumab 200 mg then 100 mg or golimumab 400 mg then 200 mg at weeks 0 and 2 were compared to patients receiving placebo. At week 6, significantly greater proportions of patients in the golimumab 200/100 mg and golimumab 400/200 mg groups (51.8%, and 55%, respectively) were in clinical response than patients assigned to placebo (29.7%; $p < 0.0001$ for both comparisons) (*Sandborn et al 2014b*). In a study enrolling patients who responded in a prior study with golimumab, the proportion of patients who maintained a clinical response through week 54 was greater for patients treated with golimumab 100 mg and 50 mg compared to placebo (49.7 and 47 vs 31.2%; $p < 0.001$ and $p = 0.01$, respectively) (*Sandborn et al 2014a*).
- The safety and efficacy of Entyvio (vedolizumab) was evaluated in a trial for UC in patients who responded inadequately to previous therapy. A higher percentage of Entyvio-treated patients achieved or maintained clinical response and remission over placebo at weeks 6 and 52, as measured by stool frequency, rectal bleeding, endoscopic findings, and PGA (*Feagan et al 2013*). A systematic review and meta-analysis (n = 606; 4 trials) demonstrated that vedolizumab was superior to placebo for clinical response (RR, 0.82; 95% CI, 0.75 to 0.91), induction of remission (RR, 0.86; 95% CI, 0.80 to 0.91), and endoscopic remission (RR, 0.82; 95% CI, 0.75 to 0.91) (*Bickston et al 2014, Mosli et al 2015*).
- The efficacy of Xeljanz (tofacitinib) for ulcerative colitis was evaluated in two 8-week induction trials followed by a 52-week maintance trial. In the induction trials, patients were assigned to tofacitinib 10 mg twice daily or placebo. At week 8, remission occurred in 18.5% vs 8.2% of patients in the tofacitinib and placebo groups, respectively, in the OCTAVE 1 trial and 16.6% vs 3.6% of patients of patients in the tofacitinib and placebo groups, respectively, in the OCTAVE 2 trial. In the OCTAVE Sustain maintenance trial, patients who achieved a clinical response were continued on either tofacitinib 5 mg, tofacitinib 10 mg, or placebo. At week 52, remission occurred in 34.3%, 40.6%, and 11.1% of patients in the tofacitinib 5 mg, tofacitinib 10 mg, and placebo groups, respectively (*Sandborn et al 2017*).
- A network meta-analysis of 12 trials of biologic-naïve patients with moderate-severe UC ranked infliximab and vedolizumab highest for induction of clinical remission and mucosal healing among tofacitinib, vedolizumab, golimumab, adalimumab, and infliximab (*Singh et al 2018*). Among patients with prior exposure to anti-TNF agents (4 trials), the results ranked tofacitinib the highest for induction of clinical remission and mucosal healing.

Uveitis (UV)

- The safety and efficacy of Humira (adalimumab) were assessed in adult patients with non-infectious intermediate, posterior, and panuveitis in 2 randomized, double-masked, placebo-controlled studies, VISUAL I and VISUAL II.
    - VISUAL I (n = 217) enrolled adults with active noninfectious intermediate UV, posterior UV, or panuveitis despite having received prednisone treatment for ≥2 weeks (*Jaffe et al 2016*). Patients were randomized to adalimumab (80 mg loading dose then 40 mg every 2 weeks) or placebo; all patients also received a prednisone burst followed by tapering of prednisone over 15 weeks. The primary endpoint was the time to treatment failure (TTF) at or after week 6. TTF was a multicomponent outcome that was based on assessment of new inflammatory lesions, visual acuity, anterior chamber cell grade, and vitreous haze grade. The median TTF was 24 weeks in the adalimumab group and 13 weeks in the placebo group. Patients receiving adalimumab were less likely than those in the placebo group to have treatment failure (hazard ratio, 0.50; 95% CI, 0.36 to 0.70; $p < 0.001$).
    - VISUAL II (n = 226) had a similar design to VISUAL I; however, VISUAL II enrolled patients with inactive UV on corticosteroids rather than active disease (*Nguyen et al 2016a*). Patients were randomized to adalimumab (80 mg loading dose then 40 mg every 2 weeks) or placebo; all patients tapered prednisone by week 19. TTF was significantly improved in the adalimumab group compared with the placebo group (median not estimable [>18 months] vs 8.3 months; hazard ratio, 0.57, 95% CI, 0.39 to 0.84; $p = 0.004$). Treatment failure occurred in 61 (55%) of 111 patients in the placebo group compared with 45 (39%) of 115 patients in the adalimumab group.

- The SYCAMORE study established the efficacy and safety of Humira (adalimumab) in pediatric patients with JIA-associated uveitis. The double-blind trial evaluated 90 children and adolescents ≥ 2 years of age and randomized them to adalimumab or placebo until treatment failure or 18 months had elapsed. The primary endpoint was the time to treatment failure. Sixteen treatment failures (27% of patients) occurred with adalimumab compared to 18 failures (60% of patients) with placebo (HR, 0.25; 95% CI, 0.12 to 0.90). Adverse events occurred more frequently with adalimumab (10.07 events per patient year [PY] vs 6.51 events per PY with placebo) (*Ramanan et al 2017*).

Multiple indications

- The efficacy of infliximab-dyyb (European Union formulation) in patients (n = 481) with CD, UC, RA, PsA, spondyloarthritis, and PsO who were treated with the originator infliximab (European Union formulation) for ≥ 6 months was assessed in the NOR-SWITCH trial (*Jørgensen et al 2017*). Twenty-five percent of patients in the infliximab originator group experienced disease worsening compared to 30% of patients in the infliximab-dyyb group (TD, -4.4%; 95% CI, -12.7% to 3.9%; noninferiority margin, 15%). The authors concluded that infliximab-dyyb was noninferior to originator infliximab.

CAPS, CRS, FMF, GCA, HIDS/MKD, and TRAPs

- The efficacy of Kineret (anakinra) for NOMID was evaluated in a prospective, open-label, uncontrolled study in 43 patients treated for up to 60 months. The study demonstrated improvements in all disease symptoms comprising the disease-specific Diary Symptom Sum Score (DSSS), as well as in serum markers of inflammation. A subset of patients (n = 11) who went through a withdrawal phase experienced worsening of disease symptoms and inflammatory markers, which promptly responded to reinstitution of treatment (*Kineret prescribing information 2016*). A cohort study of 26 patients followed for 3 to 5 years demonstrated sustained improvement in disease activity and inflammatory markers (*Sibley et al 2012*).
- The efficacy and safety of Ilaris (canakinumab) has been evaluated for the treatment of CAPS, TRAPS, HIDS/MKD, and FMF.
    - Efficacy and safety in CAPS were evaluated in a trial in patients aged 9 to 74 years with the MWS phenotype and in a trial in patients aged 4 to 74 years with both MWS and FCAS phenotypes. Most of the trial periods were open-label. Trials demonstrated improvements based on physician's assessments of disease activity and assessments of skin disease, CRP, and serum amyloid A (*Ilaris prescribing information 2016*). Published data supports the use of canakinumab for these various CAPS phenotypes (*Koné-Paut et al 2011, Kuemmerle-Deschner et al 2011, Lachmann et al 2009*).
    - Efficacy and safety in TRAPS, HIDS/MKD, and FMF were evaluated in a study in which patients having a disease flare during a screening period were randomized into a 16-week double-blind, placebo-controlled period. For the primary efficacy endpoint, canakinumab was superior to placebo in the proportion of TRAPS, HIDS/MKD, and FMF patients who resolved their index disease flare at day 15 and had no new flare for the duration of the double-blind period (45% vs 8%, 35% vs 6%, and 61% vs. 6%, respectively). Resolution of the flare was defined as a PGA score <2 (minimal or no disease) and CRP within normal range (or reduction ≥70% from baseline) (*De Benedetti et al 2018*).
- The efficacy and safety of Actemra (tocilizumab) has been evaluated for treatment of GCA and CRS.
    - Efficacy and safety of tocilizumab in GCA were evaluated in a double-blind, placebo-controlled phase 3 trial (GiACTA) in patients ≥ 50 years old with active GCA and a history of elevated ESR (*Stone et al 2017*). Patients received tocilizumab every week or every other week with a 26-week prednisone taper, or received placebo with a 26-week or 52-week prednisone taper. Patients who received tocilizumab every week and every other week experienced higher sustained remission rates at week 52 compared to placebo ($p < 0.01$).
    - The efficacy of tocilizumab in CRS was based on the result of a retrospective analysis of pooled outcome data from clinical trials of chimeric antigen receptor (CAR) T-cell therapies for hematological cancers (*Actemra prescribing information 2017*). Patients aged 3 to 23 years received tocilizumab with or without high-dose corticosteroids for severe or life-threatening CRS. Sixty-nine percent of patients treated with tocilizumab achieved a response. In a second study using a separate study population, CRS resolution within 14 days was confirmed.

Treatment Guidelines

- RA:
    - In patients with moderate or high disease activity despite DMARD monotherapy, the ACR recommends the use of combination DMARDs, a TNF inhibitor, or a non-TNF inhibitor biologic (tocilizumab, abatacept, or rituximab); tofacitinib is another option in patients with established RA, mainly in patients failing or intolerant to biologic DMARDs. If disease activity remains moderate or high despite use of a TNF inhibitor, a non-TNF

biologic is recommended over another TNF inhibitor or tofacitinib. Anakinra was excluded from the ACR guideline because of its low use and lack of new data (*Singh et al 2016c*).
    - EULAR guidelines are similar to ACR guidelines. These guidelines state that if the treatment target is not reached with a conventional DMARD strategy in a patient with poor prognostic factors, addition of a biologic DMARD or a targeted synthetic DMARD (eg, tofacitinib) should be considered, with current practice being a biologic DMARD. Biologic and targeted synthetic DMARDs should be combined with a conventional DMARD, but in patients who cannot use a conventional DMARD concomitantly, a targeted synthetic DMARD or an IL-6 inhibitor (eg, tocilizumab) may have some advantages compared with other biologic DMARDs. The guideline notes that if a TNF inhibitor has failed, patients may receive another TNF inhibitor or an agent with another mode of action. An effective biologic should not be switched to another biologic for non-medical reasons (*Smolen et al 2017*).
    - The ACR released a position statement on biosimilars, which stated that the decision to substitute a biosimilar product for a reference drug should only be made by the prescriber. The ACR does not endorse switching stable patients to a different medication (including a biosimilar) of the same class for cost saving reasons without advance consent from the prescriber and knowledge of the patient (*ACR 2018*). Similarly, the Task Force on the Use of Biosimilars to Treat Rheumatological Disorders recommends that both healthcare providers and patients should take part in the decision-making process for switching amongst biosimilars (*Kay et al 2018*).
    - EULAR has released guidelines for use of antirheumatic drugs in pregnancy, which state that etanercept and certolizumab are among possible treatment options for patients requiring therapy (*Götestam Skorpen et al 2016*).
- JIA:
    - The American College of Rheumatology (ACR) published recommendations for the treatment of JIA in 2011, followed by an update in 2013 focusing on the management of SJIA (and tuberculosis screening) (*Beukelman et al 2011, Ringold et al 2013*).
        - According to the 2011 guideline, recommendations for JIA treatment vary based on factors such as disease characteristics and activity, current medication, and prognostic features. For patients with a history of arthritis in ≥ 5 joints (which includes extended oligoarthritis, polyarthritis, and some related subtypes), a TNF inhibitor is generally recommended in patients with continued disease activity after receiving an adequate trial of a conventional DMARD. In patients with a history of ≥ 5 affected joints failing a TNF inhibitor, treatment approaches may include switching to a different TNF inhibitor or abatacept (*Beukelman et al 2011*).
        - According to the 2013 update, the inflammatory process in SJIA is likely different from that of other JIA categories, with IL-1 and IL-6 playing a central role. In patients with SJIA and active systemic features, recommendations vary based on the active joint count and the physician global assessment. Anakinra is 1 of the recommended first-line therapies; canakinumab, tocilizumab, and TNF-inhibitors are among the second-line therapies. In patients with SJIA and no active systemic features, treatments vary based on the active joint count. Abatacept, anakinra, tocilizumab, and TNF inhibitors are among the second-line treatments for these patients (*Ringold et al 2013*).
- UC:
    - For the treatment of UC, sulfasalazine is recommended by the American College of Gastroenterology (ACG) as first-line treatment of active disease. Balsalazide, mesalamine, olsalazine and sulfasalazine are recommended for maintenance of remission and reduction of relapses. If these therapies fail, infliximab should be considered (*Kornbluth et al 2010*). Note that other immunomodulators were not indicated for UC when these guidelines were written; an update is currently in process.
    - The American Gastroenterological Association (AGA) recommends standard-dose mesalamine or diazo-bonded 5-aminosalicylates (balsalazide, olsalazine) as first-line options for most patients with mild to moderate disease (*Ko et al 2019*). For patients at high-risk for colectomy, anti-TNF drugs and vedolizumab can be considered for induction and maintenance therapy (*Dassopoulos et al 2014*).
    - The European Crohn's and Colitis Organisation (ECCO) recommends thiopurine, anti-TNF drugs, vedolizumab, or methotrexate for patients with UC who have active steroid-dependent disease. In the case of further treatment failure, an alternative anti-TNF agent, vedolizumab, or colectomy can be considered. Anti-TNF agents and vedolizumab are also treatment options for patients who have steroid- or immunomodulator-refractory disease (*Harbord et al 2017*).
- CD:
    - The ACG states that the anti-TNF monoclonal antibodies adalimumab, certolizumab, and infliximab are effective in the treatment of moderate to severely active CD in patients who are resistant to corticosteroids or

are refractory to thiopurines or methotrexate. These agents can be considered for treating perianal fistulas, and infliximab can also treat enterocutaneous and rectovaginal fistulas in CD. Adalimumab, certolizumab, and infliximab are effective for the maintenance of anti-TNF induced remission; due to the potential for immunogenicity and loss of response, combination with azathioprine/6-mercaptopurine or methotrexate should be considered. The combination of infliximab with an immunomodulator (thiopurine) is more effective than monotherapy with individual agents in patients with moderate to severe CD and who are naïve to both agents. Infliximab can also treat fuliminant CD. Vedolizumab with or without an immunomodulator can be used for induction and maintenance of remission in patients with moderate to severe CD. Patients are candidates for ustekinumab therapy, including for the maintenance of remission, if they have moderate to severe CD and have failed corticosteroids, thiopurines, methotrexate, or anti-TNF inhibitors. The guideline acknowledges the effectiveness of biosimilar infliximab and biosimilar adalimumab for the management of moderate to severe CD (*Lichtenstein et al 2018*).

- The AGA recommends using anti-TNF drugs to induce remission in patients with moderately severe CD (*Terdiman et al 2013*). The AGA supports the use of TNF inhibitors and/or thiopurines as pharmacologic prophylaxis in patients with surgically-induced CD remission (*Nguyen et al 2017*).
- An AGA Institute clinical decision tool for CD notes the importance of controlling both symptoms and the underlying inflammation, and makes recommendations for treatments (budesonide, azathioprine, 6-mercaptopurine, prednisone, MTX, a TNF inhibitor, or certain combinations) based on the patient's risk level (*Sandborn 2014*).
- The ECCO recommends TNF inhibitors for patients with CD who have relapsed or are refractory to corticosteroids, depending on disease location and severity, and states that early TNF inhibitor therapy should be initiated in patients with high disease activity and features indicating a poor prognosis. Furthermore, the ECCO guideline states that all currently available TNF inhibitors seem to have similar efficacy in luminal CD and similar AE profiles; therefore the choice depends on availability, route of administration, patient preference, and cost. Vedolizumab is noted to be an appropriate alternative to TNF inhibitors for some patients (*Gomollón et al 2017*).

- Pregnancy in inflammatory bowel disease:
  - Consensus statements for the management of inflammatory bowel disease in pregnancy, coordinated by the Canadian Association of Gastroenterology, state that TNF inhibitor treatment does not appear to be associated with unfavorable pregnancy outcomes and should generally be continued during pregnancy. Because of the low risk of transfer across the placenta, certolizumab may be preferred in women who initiate TNF inhibitor therapy during pregnancy (*Nguyen et al 2016b*).
  - The AGA pregnancy care pathway for inflammatory bowel disease also recommends that biologics can be continued during pregnancy and delivery as the benefits of maintaining disease remission outweigh any risks associated with biologic maintenance therapy. The pathway does note that infliximab and adalimumab have the greatest amount of safety data (*Mahadevan et al 2019*).
- PsO and PsA:
  - Consensus guidelines from the National Psoriasis Foundation Medical Board state that treatment of PsO includes topical agents; oral therapies such as acitretin, cyclosporine, and MTX; and biologic therapies (*Hsu et al 2012*).
  - Guidelines from the American Academy of Dermatology state that for the management of PsO, topical agents including corticosteroids are used adjunctively to either ultraviolet light or systemic medications for resistant lesions in patients with more severe disease (*Menter et al 2008, Menter et al 2009a, Menter et al 2009b, Menter et al 2010, Menter et al 2011*). Biologic agents are routinely used when ≥ 1 traditional systemic agents are not tolerated, fail to produce an adequate response, or are unable to be used due to patient comorbidities. First-line agents for PsO (> 5% BSA) with concurrent PsA include adalimumab, etanercept, golimumab, infliximab, MTX, or a combination of a TNF blocker and MTX.
  - Joint guidelines from the American Academy of Dermatology/National Psoriasis Foundation on the treatment of psoriasis with biologics addresse the effectiveness of these drugs as monotherapy or in combination to treat moderate-to-severe disease in adults. The guideline does not provide relevant ranking for preferences of individual biologics, but does recommend that etanercept, infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, and tildrakizumab can all be recommended as a monotherapy option for patients. Further recommendations on specific presentations of the disease, combination therapy, and dosing recommendations are included in the guidance (*Menter et al 2019*).
  - Guidelines for PsO from the European Dermatology Forum, European Association for Dermatology and Venereology, and International Psoriasis Council (European S3 guidelines) state that adalimumab, etanercept, infliximab, and ustekinumab are recommended as second-line medications for induction and long-

term treatment if phototherapy and conventional systemic agents were inadequate, contraindicated, or not tolerated (*Nast et al 2015b*). In patients with PsA and active joint involvement despite use of NSAIDs and a potential poor prognosis due to polyarthritis, increased inflammatory markers and erosive changes, it is recommended to start synthetic DMARDs early to prevent progression of disease and erosive joint destruction. For inadequately responding patients with PsA after at least 1 synthetic DMARD, biologic DMARDS are recommended in combination with synthetic DMARDs or as monotherapy.
    - The American Academy of Dermatology recommends that moderate to severe PsA that is more extensive or aggressive in nature or that significantly impacts quality of life should be treated with MTX, TNF-blockers, or both (*Gottleib et al 2008, Menter et al 2009b, Menter et al 2011*).
    - EULAR 2015 PsA guidelines recommend TNF inhibitors in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, such as MTX. For patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, in whom a TNF inhibitor is not appropriate, biologics targeting IL-12/23 or IL-17 pathways may be considered. Apremilast is considered a treatment option in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, in whom biologics are not appropriate (*Gossec et al 2016, Ramiro et al 2016*).
    - The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommendations for PsA vary based on whether the arthritis is peripheral or axial and based on prior therapies, and may include DMARDS, NSAIDs, simple analgesics, a TNF inhibitor, an IL-12/23 inhibitor, or a PDE-4 inhibitor (*Coates et al 2016).*
    - The American College of Rheumatology/National Psoriasis Foundation guideline on PsA recommends that a TNF inhibitor is preferred in treatment-naïve patients with active PsA, although an oral therapy (MTX, sulfasalazine, leflunomide, cyclosporine, or apremilast) can be a first-line option in patients without severe PsA and without severe psoriasis, or if a patient has another compelling reason to avoid a TNF inhibitor. In patients who fail oral therapy, a switch to a TNF inhibitor is preferred and placed ahead of IL-17 biologics (secukinumab, ixekizumab, brodalumab), IL-12/23 biologics (ustekinumab), abatacept, and tofacitinib (*Singh et al 2019*).
- AS:
    - Joint recommendations for the management of axial spondyloarthritis are available from ASAS and EULAR. (Ankylosing spondylitis [AS] is synonymous with radiographic axial spondyloarthritis; these guidelines also include non-radiographic axial spondyloarthritis). The guidelines state that NSAIDs should be used first-line in patients with pain and stiffness; other analgesics might be considered if NSAIDs have failed or are contraindicated or poorly tolerated. Glucocorticoid injections may be considered but patients with axial disease should not receive long-term systemic glucocorticoids. Sulfasalazine may be considered in patients with peripheral arthritis, but patients with purely axial disease should normally not be treated with conventional DMARDs. Biologic DMARDs should be considered in patients with persistently high disease activity despite conventional treatments, and current practice is to start with a TNF inhibitor. If a TNF inhibitor fails, switching to another TNF inhibitor or to an IL-17 inhibitor should be considered (*van der Heijde et al 2017*).
    - The 2015 ACR, Spondylitis Association of America, and Spondyloarthritis Research and Treatment Network guidelines strongly recommend TNF inhibitors for patients who have active disease despite NSAIDs. No particular TNF inhibitor is preferred over another, except in patients with concomitant inflammatory bowel disease or recurrent iritis, in whom infliximab or adalimumab would be preferred over etanercept (*Ward et al 2016).*
- Ocular inflammatory disorders:
    - Expert panel recommendations for the use of TNF inhibitors in patients with ocular inflammatory disorders are available from the American Uveitis Society (*Levy-Clarke et al 2014*). Infliximab and adalimumab can be considered as first-line immunomodulatory agents for the treatment of ocular manifestations of Behçet's disease and as second-line immunomodulatory agents for the treatment of UV associated with juvenile arthritis. They also can be considered as potential second-line immunomodulatory agents for the treatment of severe ocular inflammatory conditions including posterior UV, panuveitis, severe UV associated with seronegative spondyloarthropathy, and selected patients with scleritis. Etanercept seems to be associated with lower rates of treatment success in these conditions.
- Additional indications:
    - Based upon guidelines from the European Dermatology Forum, adalimumab is recommended among first-line therapies for HS, and infliximab may be considered a second-line option (*Gulliver et al 2016, Zouboulis et al 2015*).
    - For the treatment of FMF, EULAR recommendations state that treatment with colchicine should begin as soon as FMF is diagnosed. Biologic treatment, such as anti-IL-1 therapy, is indicated in patients not responding to

the maximum tolerated dose of colchicine. TNF inhibitors have also been used in colchicine-resistant patients, with good responses seen in observational studies (*Ozen et al 2016*).
    - No recent guidelines were identified for CAPS, CRS, GCA, HIDS/MKD, or TRAPS.

SAFETY SUMMARY

- Contraindications:
    - Actemra (tocilizumab), Cimzia (certolizumab), Cosentyx (secukinumab), Entyvio (vedolizumab), Ilaris (canakinumab), Ilumya (tildrakizumab-asmn), Inflectra (infliximab-dyyb), Kevzara (sarilumab), Kineret (anakinra), Otezla (apremilast), Remicade (infliximab), Renflexis (infliximab-abda), Stelara (ustekinumab), and Taltz (ixekizumab) use in patients with hypersensitivity to any component of the product.
    - Siliq in patients with Crohn's disease because Siliq may cause worsening of disease.
    - Enbrel (etanercept) in patients with sepsis.
    - Kineret (anakinra) in patients with hypersensitivity to *E coli*-derived proteins.
    - Remicade (infliximab), Inflectra (infliximab-dyyb), and Renflexis (infliximab-abda) in patients with hypersensitivity to murine proteins; and doses >5 mg/kg in patients with moderate to severe heart failure.
- Boxed Warnings:
    - Actemra (tocilizumab), Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Inflectra (infliximab-dyyb), Kevzara (sarilumab), Olumiant (baricitinib), Remicade (infliximab), Renflexis (infliximab-abda), Simponi / Simponi Aria (golimumab), and Xeljanz / Xeljanz XR (tofacitinib) all have warnings for serious infections such as active tuberculosis, which may present with pulmonary or extrapulmonary disease; invasive fungal infections; and bacterial, viral, and other infections due to opportunistic pathogens.
    - In addition, Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Inflectra (infliximab-dyyb), Olumiant (baricitinib), Remicade (infliximab), Renflexis (infliximab-abda), Simponi / Simponi Aria (golimumab), and Xeljanz (tofacitinib) all have warnings for increased risk of malignancies.
    - Rituxan (rituximab) can cause fatal infusion reactions, hepatitis B activation, severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy (PML).
    - Siliq has a boxed warning that suicidal ideation and behavior, including completed suicides, have occurred in patients treated with Siliq. The prescriber should weigh potential risks and benefits in patients with a history of depression and/or suicidal ideation or behavior, and patients should seek medical attention if these conditions arise or worsen during treatment.
    - Olumiant (baricitinib) has a boxed warning for thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis.
- Warnings/Precautions (applying to some or all of the agents in the class):
    - Reactivation of HBV or other viral infections
    - Serious infections including tuberculosis
    - New onset or exacerbation of central nervous system demyelinating disease and peripheral demyelinating disease
    - Pancytopenia
    - Worsening and new onset congestive heart failure
    - Hypersensitivity reactions
    - Lupus-like syndrome
    - Malignancy and lymphoproliferative disorders
    - Avoiding live vaccinations
    - Noninfectious pneumonia with Stelara (ustekinumab)
    - Increased lipid parameters and liver function tests with Actemra (tocilizumab), Xeljanz / Xeljanz XR (tofacitinib) and Kevzara (sarilumab)
    - Increased incidence of CD and UC with Cosentyx (secukinumab) and Taltz (ixekizumab); risk of new-onset CD or exacerbation of CD with Siliq (brodalumab)
    - Diarrhea, nausea, and vomiting with Otezla (apremilast)
    - Depression with Otezla (apremilast)
    - Gastrointestinal perforations with Xeljanz / Xeljanz XR (tofacitinib), Olumiant (baricitinib), Actemra (tocilizumab), Kevzara (sarilumab), and Rituxan (rituximab)
    - PML with Entyvio (vedolizumab)
    - Thrombosis with Olumiant (baricitinib)
    - Consult prescribing information for other drug-specific warnings/precautions
- Adverse Reactions:
    - Infusion site reactions, diarrhea, nausea/vomiting, abdominal pain, infections, hypertension and headache.

- Consult prescribing information for other drug-specific AEs

- Risks of Long-Term Treatment: As it becomes accepted practice to treat patients with these conditions for long-term, it is imperative to assess the long-term safety of these products. Because these agents suppress the immune system, serious infections and malignancies are a concern. Several long-term efficacy and safety studies support several agents in this class. The extension studies were performed in an open-label manner and were subject to attrition bias.
  - Rheumatoid Arthritis
    - Safety of adalimumab for RA has been supported in a 5-year study in RA and a 10-year study in patients with early RA (*Keystone et al 2014a, Burmester et al 2014b*). In the 5-year extension study, overall rates of serious AEs and serious infections were 13.8 events per 100 PY and 2.8 events per 100 PY, respectively. The rate of serious events was highest in the first 6 months and then declined. No new safety signals were reported in the 10-year study.
    - Certolizumab plus MTX had a consistent safety profile over 5 years in patients with RA (*Keystone et al 2014b*). The most frequently reported AEs included urinary tract infections (rate of 7.9 per 100 patient-years), nasopharyngitis (rate of 7.3 per 100 PY), and upper respiratory infections (rate of 7.3 per 100 PY). Serious AE rates were 5.9 events per 100 patient-years for serious infections and 1.2 events per 100 PY for malignancies.
    - Abatacept has been evaluated in 2 long-term extension studies. Abatacept IV plus MTX demonstrated a similar safety profile between the 7 year follow-up and a 52-week double-blind study (*Westhovens et al 2014*). Serious AEs reported in both the double-blind and long-term follow-up studies were the following: serious infections (17.6 events per 100 PY), malignancies (3.2 events per 100 PY), and autoimmune events (1.2 events per 100 PY). In a 5-year extension trial, rates of serious infections, malignancies, and autoimmune events were 2.8, 1.5, and 0.99 events per 100 patient-years exposure, respectively. Efficacy was demonstrated by ACR 20 with response rates of 82.3% and 83.6% of patients at year 1 and year 5, respectively.
    - Data from 5 RCTs of Actemra (tocilizumab), their open-label extension trials, and a drug interaction study were analyzed for measures of safety. A total of 4,009 patients with moderate to severe RA received at least 1 dose of tocilizumab. Mean duration of tocilizumab treatment was 3.07 years (up to 4.6 years); total duration of observation was 12,293 PY. The most common AEs and serious AEs were infections. A longer-term safety profile from this analysis matches previous observations. No new safety signals were identified (*Genovese et al 2013*).
    - A Cochrane review showed no evidence of a statistically significant difference in the rate of withdrawal because of AEs in the Enbrel (etanercept) plus DMARD group and the DMARD alone group at 6 months, 12 months, and 2 years. At 3 years, withdrawals were significantly reduced in the etanercept 25 mg plus DMARD group compared with the DMARD alone group (RR, 0.7; 95% CI, 0.5 to 1). There was no evidence of statistically significant differences in the rates of breast cancer at 12 months, fever at 6 months, flu-like syndrome at 6 months and 2 years, infection at 6 months and 2 years, malignancy at 12 months and 2 years, pneumonia at 12 months, and serious infection at 12 months and 2 years between the etanercept plus DMARD group and the DMARD group (*Lethaby et al 2013*).
    - A systematic review analyzed 66 randomized controlled trials and 22 long-term extension studies evaluating biologics and tofacitinib for the rate of serious infections in patients with moderate to severe active RA (*Strand et al 2015b*). The estimated incidence rates (unique patients with events/100 patient-years) of serious infections were 3.04 (95% CI, 2.49 to 3.72) for abatacept, 3.72 (95% CI, 2.99 to 4.62) for rituximab, 5.45 (95% CI, 4.26 to 6.96) for tocilizumab, 4.90 (95% CI, 4.41 to 5.44) for TNF inhibitors, and 3.02 (95% CI, 2.25 to 4.05) for tofacitinib 5 mg and 3.00 (95% CI, 2.24 to 4.02) for tofacitinib 10 mg. Authors concluded that the rates of serious infections with tofacitinib in RA patients are within the range of those reported for biologic DMARDs.
    - A meta-analysis analyzed 50 randomized controlled trials and long-term extension studies evaluating biologic DMARDs and tofacitinib to compare the risks of malignancies in patients with RA (*Maneiro et al 2017*). The overall risk of malignancies was 1.01 (95% CI, 0.72 to 1.42) for all TNF antagonists, 1.12 (95% CI, 0.33 to 3.81) for abatacept, 0.54 (95% CI, 0.20 to 1.50) for rituximab, 0.70 (95% CI, 0.20 to 2.41) for tocilizumab, and 2.39 (95% CI, 0.50 to 11.5) for tofacitinib. The authors concluded that treatment with biologic DMARDs or tofacitinib does not increase the risk of malignancies.
    - A pooled analysis of 9 RA trials evaluating baricitinib included 3492 patients (7860 PY exposure). The incidence rate for major adverse cardiovascular events was comparable between placebo (0.5 per 100 PY) and baricitinib 4 mg (0.8 per 100 PY). Incidence rates for arterial thrombotic events and congestive heart failure were also similar between baricitinib and placebo. The occurrence of a deep

vein thrombosis or pulmonary embolism occurred more frequently in the baricinitib 4 mg group (6 events in 997 patients) versus placebo (0 events in 1070 patients) (*Taylor et al 2019*).

- PsO
  - A total of 3,117 patients treated with at least 1 dose of Stelara (ustekinumab) for moderate to severe PsO were evaluated for long-term safety. At least 4 years of ustekinumab exposure was seen in 1,482 patients (including 838 patients with ≥ 5 years of exposure). The most commonly reported AEs were nasopharyngitis, upper respiratory tract infection, headache and arthralgia. Infections, malignancies and cardiac disorders were the most commonly reported serious AEs. Twenty deaths were reported through year 5. The causes of death were considered related to cardiovascular events (n = 5), malignancy (n = 5), infection (n = 3) and other causes (n = 7). The observed mortality rate among ustekinumab-treated patients was consistent with that expected in the general U.S. population (SMR = 0.36; 95% CI, 0.22 to 0.55). From year 1 to year 5, rates of overall AEs, and AEs leading to discontinuation generally decreased. Serious AE rates demonstrated year-to-year variability with no increasing trend. The results of this long-term study of AEs are similar to reports of shorter-term studies (*Papp et al 2013*).
  - In a 5-year extension study, a total of 2510 patients on etanercept for the treatment of PsO were evaluated for long-term safety and efficacy (*Kimball et al 2015*). Serious AEs were reported as a cumulative incidence of the entire 5-year observation period. The following incidences were reported: serious infections (6.5%, 95% CI, 5.4 to 7.7%); malignancies excluding nonmelanoma skin cancer (3.2%, 95% CI, 2.3 to 4.1%); nonmelanoma skin cancer (3.6%, 95% CI, 2.7 to 4.1%); coronary artery disease (2.8%, 95% CI, 2 to 3.6%); PsO worsening (0.7%, 95% CI, 0.3 to 1.2%); CNS demyelinating disorder (0.2%, 95%CI, 0 to 0.4%); lymphoma and tuberculosis each (0.1%, 95% CI, 0 to 0.3%); and opportunistic infection and lupus each (0.1%, 95%CI, 0 to 0.2%). A total of 51% of patients reported clear/almost clear rating at month 6 and remained stable through 5 years.
  - In a ≥ 156-week extension study, a total of 1,184 patients treated with apremilast in ESTEEM 1 and 2 were evaluated for long-term safety and tolerability (*Crowley et al 2017*). Serious AEs (≥ 2 patients) were coronary artery disease (n = 6), acute myocardial infarction (n = 4), osteoarthritis (n = 4), and nephrolithiasis (n = 4). The exposure-adjusted incidence rate for major cardiac events was 0.5/100 patients years, for malignancies was 1.2/100 patient years, for serious infections was 0.9/100 patient-years, and for suicide attempts was 0.1/100 patient-years.
  - A multicenter registry called Psoriasis Longitudinal Assessment and Registry (PSOLAR) evaluated the risk of serious infections in patients with PsO (*Kalb et al 2015*). Patients were followed for up to 8 years with a total of 11,466 patients with PsO enrolled, 74.3% of whom were from the U.S. A total of 22,311 patient-years of data were collected. Ustekinumab, infliximab, adalimumab, and etanercept as well as traditional DMARDs were included in the data analysis. During the follow-up period, 323 serious infections were reported. The rates of serious infections per 100 patient-years were 0.83 (secukinumab), 1.47 (etanercept), 1.97 (adalimumab), and 2.49 (infliximab). The most commonly reported serious infection was cellulitis. Risk factors for serious infections were increasing age, diabetes mellitus, smoking, and history of significant infections prior to registry entry. Exposure to infliximab (hazard ratio, 2.51; 95% CI, 1.45 to 4.33; $p < 0.001$) and adalimumab (hazard ratio, 2.13; 95% CI, 1.33 to 3.41; $p = 0.002$) during the registry were independently associated with the risk of serious infections whereas use of ustekinumab or etanercept were not.
- PsA
  - Subcutaneous golimumab for patients with active PsA demonstrated safety and efficacy over 5 years in the long-term extension of the randomized, placebo-controlled GO-REVEAL study (*Kavanaugh et al 2014b*). Approximately one-half of patients also took MTX concurrently. No new safety signals were observed.
- AS
  - A meta-analysis of 25 randomized controlled studies with 2,403 patients with AS or non-radiographic axial spondyloarthritis treated with agents such as adalimumab, certolizumab, etanercept, golimumab, infliximab, sarilumab, tocilizumab, and secukinumab showed no significant increase in the risk of serious infections with biologic agents compared to controls (OR, 1.42; 95% CI, 0.58 to 3.47) (*Wang et al 2018*).
  - Another meta-analysis of 14 randomized controlled trials with 2,032 patients with AS that were treated with adalimumab, certolizumab, etanercept, golimumab, or infliximab revealed no significant difference between TNF inhibitors and placebo for overall serious adverse events (OR, 1.34; 95% CI, 0.87 to

2.05), risk of serious infections (OR, 1.59; 95% CI, 0.63 to 4.01), risk of malignancy (OR, 0.98; 95% CI, 0.25 to 3.85), and discontinuation due to adverse events (OR, 1.55; 95% CI, 0.95 to 2.54) (*Hou et al 2018*).

- Multiple indications
  - One study looked at 23,458 patients who were treated with Humira (adalimumab) for RA, JIA, AS, PsA, PsO and CD. Patients received adalimumab for up to 12 years. No new safety signals were observed from this analysis. Rates of malignancies and infections were similar to the general population and also similar to rates reported in other shorter-term trials for anti-TNF therapies (*Burmester et al 2013b*).
  - Pooled data from 5 Phase 3 trials of SQ golimumab over at least 3 years demonstrated a safety profile consistent with other TNF inhibitors (*Kay et al 2015*). A total of 1,179 patients with RA, PsA or AS were treated for at least 156 weeks. Rates of AEs up to week 160 for placebo, golimumab 50 mg and golimumab 100 mg, respectively, were as follows: 0.28, 0.30, 0.41 for death; 5.31, 3.03, 5.09 for serious infection; 0, 0.17, 0.35 for tuberculosis; 0, 0.13, 0.24 for opportunistic infection; 0, 0, 0.12 for demyelination; and 0, 0.04, 0.18 for lymphoma.
  - A total of 18 multicenter, placebo-controlled, randomized controlled trials evaluated the safety profile of certolizumab pegol monotherapy or in combination with DMARDs in RA, CD, AS, PsA and PsO (*Capogrosso Sansone et al 2015).* All but 1 trial was conducted in a double-blind manner. The overall pooled risk ratios for all doses of certolizumab pegol were reported as follows: AEs (defined as AE reported but not evaluated for causality) 1.09 (95% CI, 1.04 to 1.14), serious AEs 1.50 (95% CI, 1.21 to 1.86), ADRs (defined as an AE possibly related to drug treatment by investigators) 1.20 (95% CI, 1.13 to 1.45), infectious AEs 1.28 (95% CI, 1.13 to 1.45), infectious serious AEs 2.17 (95% CI, 1.36 to 3.47), upper respiratory tract infections 1.34 (95% CI, 1.15 to 1.57), neoplasms 1.04 (95% CI, 0.49 to 2.22), and tuberculosis 2.47 (95% CI, 0.64 to 9.56). Rare AEs may not have been captured by the studies due to limiting the reporting of most AEs to those occurring in > 3 to 5%.
  - The safety of ustekinumab was examined in a pooled analysis of 12 trials in patients with PsO, PsA, and CD. A total of 5584 patients were evaluated, equating to 4521 PYs. Respective incidences per 100 PY of infections (125.4 vs 129.4), major cardiovascular adverse events (0.5 vs 0.3), malignancies (0.4 vs 0.2), and death (0.1 vs 0.0) were similar between ustekinumab and placebo, respectively (*Ghosh et al 2019*).
  - Several recent meta-analyses evaluated the safety of TNF inhibitors.
    - An analysis of TNF inhibitors in RA, PsA, and AS included data from 71 randomized trials (follow-up 1 to 36 months) and 7 open-label extension studies (follow-up 6 to 48 months) (*Minozzi et al 2016*). The data demonstrated that use of TNF inhibitors increases the risk of infectious AEs. Overall, there was a 20% increase of any infections, a 40% increase of serious infections, and a 250% increase of tuberculosis. The tuberculosis incidence rate was higher with infliximab and adalimumab compared to etanercept. There was little data on the incidence of opportunistic infections.
    - An analysis of TNF inhibitors in RA, PsA, and AS included data from 32 randomized trials (follow-up 2 to 36 months) and 6 open-label extension trials (follow-up 6 to 48 months) (*Bonovas et al 2016*). Synthesis of the data did not demonstrate that the use of TNF inhibitors significantly affects cancer risk during this length of treatment. However, few malignancy events were observed and evidence may be insufficient to make definitive conclusions, particularly regarding longer-term risks.

- Drug interactions
  - Do not give with live (including attenuated) vaccines; additionally, non-live vaccines may not elicit a sufficient immune response.
  - Do not give 2 immunomodulators together.
  - For Xeljanz / Xeljanz XR (tofacitinib), adjust dose with potent inhibitors of cytochrome P450 (CYP) 3A4 and medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19. Coadministration with potent CYP3A4 inducers and potent immunosuppressive drugs is not recommended.
- Risk Evaluation and Mitigation Strategy (REMS)
  - Siliq (brodalumab) is available only through the Siliq REMS program. The goal of the program is to mitigate the risk of suicidal ideation and behavior, including completed suicides, which occurred in clinical trials. Key requirements of the REMS program include:
    - Prescribers must be certified with the program.
    - Patients must sign a patient-prescriber agreement form.

- Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive the product.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Actemra (tocilizumab)	Vials: 80 mg/4 mL; 200 mg/10 mL; 400 mg/20 mL Prefilled syringe or autoinjector: 162 mg/0.9 mL	**RA:** IV: 4 mg/kg IV every 4 weeks. May increase to 8 mg/kg IV every 4 weeks. Maximum dose = 800 mg. SQ: <100 kg, administer 162 mg SQ every other week, followed by an increase to every week based on clinical response; >100 kg, 162 mg administered SQ every week. **PJIA:** <30 kg, 10 mg/kg IV every 4 weeks; ≥30 kg, 8 mg/kg IV every 4 weeks. <30 kg, 162 mg SQ every 3 weeks; ≥30 kg, 162 mg SQ every 2 weeks. **SJIA:** <30 kg, 12 mg/kg IV every 2 weeks; ≥30 kg, 8 mg/kg IV every 2 weeks; <30 kg, 162 mg SQ every 2 weeks; ≥30 kg, 162 mg SQ once weekly. **GCA:** 162 mg SQ every week with tapering glucocorticoids. May give every other week depending on clinical considerations. **CRS:** <30 kg, 12 mg/kg IV; ≥30 kg, 8 mg/kg IV; maximum, 800 mg per infusion.	**RA:** Can give with MTX or other DMARDs. **PJIA and SJIA:** Can give with MTX. **GCA:** Can use alone after discontinuation of glucocorticoids. **CRS:** Can give with corticosteroids. May repeat up to 3 additional doses if no clinical improvement, with at least 8 hours between doses. **RA, PJIA, and SJIA, and GCA**: Adjust dose for liver enzyme abnormalities, low platelet count and low ANC.	Give as a single 60-minute intravenous infusion. <30 kg, use a 50 mL infusion bag. ≥30 kg, use a 100 mL infusion bag. Before infusion, allow bag to come to room temperature. Do not administer with other drugs. Patients can self-inject with the prefilled syringe or autoinjector. Rotate injection sites.
Cimzia (certolizumab)	Powder for reconstitution: 200 mg Prefilled syringe: 200 mg/mL	**CD:** 400 mg SQ initially and at weeks 2 and 4. Maintenance dose is 400 mg every 4 weeks. **RA, PsA:** 400 mg SQ initially and at weeks 2 and 4. Then 200 mg every 2 weeks. Can consider a maintenance dose of 400 mg every 4 weeks.	Patients can self-inject with the prefilled syringe.	When a 400 mg dose is required, give as 2 200 mg SQ injections in separate sites in the thigh or abdomen.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		PsO: 400 mg SQ every other week or 400 mg SQ initially and at weeks 2 and 4, followed by 200 mg every other week **AS:** 400 mg SQ initially and at weeks 2 and 4. Maintenance dose is 200 mg every 2 weeks or 400 mg every 4 weeks.		
Cosentyx (secukinumab)	Sensoready pen: 150 mg/1 mL Prefilled syringe: 150 mg/1 mL Vial: 150 mg lyophilized powder	**PsO:** 300 mg by SQ injection at weeks 0, 1, 2, 3 and 4, followed by 300 mg every 4 weeks **PsA, AS:** With a loading dose (not required): 150 mg at weeks 0, 1, 2, 3, and 4, followed by 150 mg every 4 weeks; without loading dose: 150 mg every 4 weeks	**PsO:** For some patients, a dose of 150 mg may be acceptable. **PsA:** For PsA patients with coexistent moderate to severe PsO, dosing for PsO should be followed. If active PsA continues, consider 300 mg dose.	Each 300 mg dose is given as 2 subcutaneous injections of 150 mg. Patients may self-administer with the pen or prefilled syringe. The vial is for healthcare professional use only.
Enbrel (etanercept)	Prefilled syringe: 25 mg and 50 mg Prefilled SureClick autoinjector: 50 mg Multiple-use vial: 25 mg lyophilized powder Solution Cartridge: 50 mg	**RA, AS, PsA:** 50 mg SQ weekly **PsO (adults):** 50 mg SQ twice weekly for 3 months, then 50 mg weekly **PJIA and PsO (pediatrics):** ≥63 kg, 50 mg SQ weekly; <63 kg, 0.8 mg/kg SQ weekly	**RA, AS, PsA:** MTX, NSAIDs, glucocorticoids, salicylates, or analgesics may be continued **JIA:** NSAIDs glucocorticoids, or analgesics may be continued	Patients may be taught to self-inject. May bring to room temperature prior to injecting.
Entyvio (vedolizumab)	Lyophilized cake for injection in 300 mg single-dose vial	**CD and UC:** 300 mg administered by intravenous infusion at time 0, 2, and 6 weeks, and then every 8weeks thereafter. Discontinue therapy if there is no evidence of therapeutic benefit by week 14.	All immunizations should be to date according to current guidelines prior to initial dose.	Entyvio should be reconstituted at room temperature and prepared by a trained medical professional. It should be used as soon as possible after reconstitution and dilution.
Humira (adalimumab)	Prefilled syringe: 10 mg/0.1 mL	**RA, AS, PsA**: 40 mg SQ every other week.	**RA, AS, PsA:** MTX, other non-	Patients may be taught to self-inject.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	10 mg/0.2 mL 20 mg/0.2 mL 20 mg/0.4 mL 40 mg/0.4 mL 40 mg/0.8 mL 80 mg/0.8 mL Single-use pen: 80 mg/0.8 mL 40 mg/0.8 mL 40 mg/0.4 mL Single-use vial: 40 mg/0.8 mL	For RA, may increase to 40 mg every week if not on MTX. **PJIA or pediatric uveitis:** 10 kg to <15 kg: 10 mg SQ every other week; 15 kg to <30 kg: 20 mg SQ every other week; ≥30 kg, 40 mg SQ every other week **CD, HS and UC:** 160 mg SQ on Day 1 (given in 1 day or split over 2 consecutive days), followed by 80 mg SQ 2 weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40 mg SQ every other week. **PsO and UV:** initial dose of 80 mg SQ, followed by 40 mg SQ every other week starting 1 week after the initial dose. **CD in pediatric patients ≥ 6 years and older:** 17 kg to < 40 kg: 80 mg on day 1 (given as two 40 mg injections) and 40 mg 2 weeks later (on day 15); maintenance dose is 20 mg every other week starting at week 4. ≥40 kg: 160 mg on day (given in 1 day or split over 2 consecutive days) and 80 mg 2 weeks later (on day 15); maintenance dose is 40 mg every other week starting at week 4. **HS in adolescent patients ≥12 years and older:** 30 kg to <60 kg: 80 mg on day 1, 40 mg on day 8; maintenance dose is 40 mg every other week. ≥60 kg: 160 mg on day	biologic DMARDS, glucocorticoids, NSAIDs, and/or analgesics may be continued. **JIA:** NSAIDs, MTX, analgesics, and/or glucocorticoids, may be continued. **CD and UC:** aminosalicylates and/or corticosteroids may be continued. Azathioprine, 6-MP or MTX may be continued if necessary. Needle cover of the syringe contains dry rubber (latex).	Injections should occur at separate sites in the thigh or abdomen. Rotate injection sites. May bring to room temperature prior to injecting.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		1, 80 mg on day 15, 40 mg on day 29; maintenance dose is 40 mg every week.		
Ilaris (canakinumab)	Vial: 150 mg (lyophilized powder and injection solution formulations)	**SJIA:** ≥7.5 kg, 4 mg/kg SQ every 4 weeks (maximum dose of 300 mg). **CAPS**: ≥15 to ≤40 kg, 2 mg/kg SQ; >40 kg, 150 mg SQ; frequency every 8 weeks **TRAPS, HIDS/MKD, and FMF**: ≤40 kg, 2 mg/kg SQ; >40 kg, 150 mg SQ; frequency every 4 weeks	For CAPS: children 15 to 40 kg with an inadequate response can be increased to 3 mg/kg For TRAPS, HIDS/MKD, and FMF: If the clinical response is inadequate, the dose may be increased to 4 mg/kg (weight ≤40 kg) or 300 mg (weight >40 kg)	Do not inject into scar tissue.
Ilumya (tildrakizumab-asmn)	Prefilled syringe: 100 mg/mL	**PsO:** 100 mg SQ at weeks 0 and 4, and then every 12 weeks		Should be administered only by a healthcare provider. Bring to room temperature (30 minutes) prior to injecting.
Inflectra (infliximab-dyyb)	Vial: 100 mg	**CD (≥6 years old), PsA, PsO and UC**: 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. In adults with CD who lose response, can increase dose to 10 mg/kg. **RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg or give every 4 weeks. **AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.	**RA:** give with MTX **CD:** If no response by week 14, consider discontinuation.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion. Infuse over 2 hours. Do not administer with other drugs.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Kevzara (sarilumab)	Prefilled syringe: 150 mg/1.14 mL 200 mg/1.14 mL Prefilled pen: 150 mg/1.14 mL 200 mg/1.14 mL	**RA:** 200 mg SQ every 2 weeks.	**RA:** give with or without MTX or other conventional DMARDs Reduce dose for neutropenia, thrombocytopenia, and elevated liver enzymes.	Patients may be taught to self-inject. Bring to room temperature (30 minutes [pre-filled syringe] or 60 minutes [pre-filled pen]) prior to injecting. Rotate injection sites.
Kineret (anakinra)	Prefilled syringe: 100 mg/0.67 mL	**RA:** 100 mg SQ once daily. **CAPS (NOMID):** 1 to 2 mg/kg SQ once daily. Maximum dose is 8 mg/kg/day.	**NOMID**: dose can be given once or twice daily.	Patients may be taught to self-inject. A new syringe must be used for each dose.
Olumiant (baricitinib)	Tablet: 2 mg	**RA:** 2 mg once daily	Avoid use in combination with other JAK inhibitiors, biologic DMARDs, or potent immunosuppressants such as azathioprine and cyclosporine	May be taken with or without food.
Orencia (abatacept)	Vial: 250 mg Prefilled syringe: 50 mg/0.4 mL 87.5 mg/0.7 mL 125 mg/1 mL ClickJect autoinjector: 125 mg/mL	**RA:** IV: <60kg, 500 mg IV; 60 to 100 kg, 750 mg IV; >100 kg, 1,000 mg IV initially, then 2 and 4 weeks after the first infusion and every 4 weeks thereafter SQ: 125 mg SQ once weekly initiated with or without an IV loading dose. With IV loading dose, use single IV infusion as per body weight listed above, followed by the first 125 mg SQ injection within a day of the IV infusion and then once weekly. **PJIA:** IV: 6 to 17 years and <75 kg: 10 mg/kg IV initially, then 2 and 4 weeks after the first infusion and every 4 weeks thereafter. >75 kg, follow adult RA IV		IV infusion should be over 30 minutes. Use 100 mL bag for IV infusion. Do not administer with other drugs. Patients may be taught to self-inject the SQ dose. For SQ, injection sites should be rotated.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		schedule; maximum dose = 1,000 kg. SQ: 2 to 17 years, 10 to <25 kg, 50 mg once weekly; 25 to < 50 kg, 87.5 mg once weekly, ≥ 50 kg, 125 mg once weekly. **PsA:** IV: follow adult RA IV schedule. SQ: 125 mg once weekly without IV dose.		
Otezla (apremilast)	Tablet: 10 mg, 20 mg, and 30 mg	**PsA, PsO:** Day 1: 10 mg in the morning Day 2: 10 mg in the morning and in the evening Day 3: 10 mg in the morning and 20 mg in evening Day 4: 20 mg in the morning and evening Day 5: 20 mg in the morning and 30 mg in the evening Day 6 and thereafter: 30 mg twice daily	Titrate according to the labeling when initiating therapy to reduce gastrointestinal symptoms. Dosage should be reduced to 30 mg once daily in patients with severe renal impairment (CrCl <30 mL/min as estimated by the Cockcroft-Gault equation). For initial dosing in these patients, use only the morning titration schedule listed above (evening doses should be excluded).	May be taken with or without food. Do not crush, split, or chew the tablets.
Remicade (infliximab)	Vial: 100 mg	**CD (≥6 years old), PsA, PsO and UC (≥6 years old)**: 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. In adults with CD who lose response, can increase dose to 10 mg/kg. **RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8	**RA:** give with MTX **CD:** If no response by week 14, consider discontinuation.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion. Infuse over 2 hours. Do not administer with other drugs.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		weeks. Can increase to 10 mg/kg or give every 4 weeks. **AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.		
Renflexis	Vial: 100 mg	**CD (≥6 years old), PsA, PsO and UC**: 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. In adults with CD who lose response, can increase dose to 10 mg/kg. **RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg or give every 4 weeks. **AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.	**RA:** give with MTX **CD:** If no response by week 14, consider discontinuation.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion. Infuse over 2 hours. Do not administer with other drugs.
Rituxan (rituximab)	Vial: 100 mg 500 mg	**RA:** 1,000 mg IV every 2 weeks times 2 doses. Additional doses should be given every 24 weeks or based on clinical evaluation but no sooner than 16 weeks.	Give with MTX.	Give methyl-prednisolone 100 mg IV 30 minutes prior to each infusion to reduce the incidence and severity of infusion reactions.
Siliq (brodalumab)	Prefilled syringe: 210 mg/1.5 mL	**PsO:** 210 mg SQ at weeks 0, 1, and 2 followed by every 2 weeks	**PsO**: If an adequate response has not been achieved after 12 to 16 weeks, consider discontinuation	Patients may self-inject when appropriate and after proper training. The syringe should be allowed to reach room temperature before injecting.
Simponi/ Simponi Aria (golimumab)	SmartJect® autoinjector: 50 mg and 100 mg Prefilled syringe: 50 mg and 100 mg	**RA, PsA, and AS**: 50 mg SQ once monthly **UC:** 200 mg SQ at week 0; then 100 mg at week 2; then 100 mg every 4 weeks.	**RA:** give with MTX **PsA and AS**: may give with or without MTX or other DMARDs.	Patients may be taught to self-inject the SQ dose. For SQ, injection sites should be rotated.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	Aria, Vial: 50 mg/4 mL	**Aria (RA, PsA, and AS)**: 2 mg/kg IV at weeks 0 and 4, then every 8 weeks.	Needle cover of the syringe contains dry rubber (latex). **Aria (RA)**: give with MTX (**PsA, AS)**: give with or without MTX or other non-biologic DMARDs. Corticosteroids, NSAIDs, and/or analgesics may be continued. Efficacy and safety of switching between IV and SQ formulations have not been established.	For SQ, bring to room temperature for 30 minutes prior to injecting. **Aria**: IV infusion should be over 30 minutes. Dilute with 0.9% sodium chloride or 0.45% sodium chloride for a final volume of 100 mL. Do not administer with other drugs.
Stelara (ustekinumab)	Prefilled syringe: 45 mg and 90 mg Vial: 130 mg	**PsO, PsA**: ≤100 kg, 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. >100 kg, 90 mg SQ initially and 4 weeks later, followed by 90 mg every 12 weeks. **PsO (adolescents):** <60 kg, 0.75 mg/kg (injection volume based on weight) 60 to 100 kg, 45 mg >100 kg, 90 mg **CD**: Initial single IV dose: ≤55 kg, 260 mg; >55 kg to ≤85 kg, 390 mg; >85 kg, 520 mg; followed by 90 mg SQ every 8 weeks (irrespective of body weight)	Needle cover of the syringe contains dry rubber (latex).	Patients may be taught to self-inject using the prefilled syringes. Stelara for IV infusion must be diluted, prepared and infused by a healthcare professional; it is diluted in 0.9% sodium chloride and infused over at least 1 hour. Rotate injection sites.
Taltz (ixekizumab)	Prefilled syringe: 80 mg Autoinjector: 80 mg	**PsO:** 160 mg by SQ injection at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks		Patients may be taught to self-inject with either the prefilled syringe or the autoinjector. Bring to room temperature prior to injecting. Rotate injection sites.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		PsA: 160 mg by SQ injection at week 0, followed by 80 mg every 4 weeks NOTE: For patients with PsA with coexistent moderate-to-severe PsO, use dosing regimen for PsO.		
Tremfya (guselkumab)	Prefilled syringe or single-dose patient-controlled injector: 100 mg	**PsO:** 100 mg by SQ injection at week 0, week 4, and then every 8 weeks		Patients may be taught to self-inject. Bring to room temperature (30 minutes) prior to injecting.
Xeljanz / Xeljanz XR (tofacitinib)	Tablet: 5 mg, 10 mg Extended release Tablet: 11 mg	**RA:** 5 mg PO twice daily or 11 mg PO once daily **PsA:** 5 mg PO twice daily, used in combination with non-biologic DMARDs; 11 mg once daily used in combination with nonbiologic DMARDs **UC (Xeljanz):** 10 mg PO twice daily for at least 8 weeks, then 5 or 10 mg twice daily. Discontinue 10 mg twice daily dose after 16 weeks if no response	Patients may switch from Xeljanz 5 mg twice daily to Xeljanz XR 11 mg once daily the day following the last dose of Xeljanz 5 mg. Use as monotherapy or in combination with MTX or other nonbiologic DMARDs. Use of Xeljanz in combination DMARDs or with potent immunosuppres-sants such as azathioprine and cyclosporine is not recommended. Dose interruption is recommended for management of lymphopenia (< 500 cells/mm^3), neutropenia (ANC < 500 cells/mm^3) and anemia. Dose adjustment needed for hepatic and renal impairment and	May take with or without food. Swallow Xeljanz XR tablets whole; do not crush, split, or chew.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			patients taking CYP450 inhibitors.	

ANC=absolute neutrophil count; AS=ankylosing spondylitis; CRS=cytokine release syndrome; DMARD=disease-modifying anti-rheumatic drug; GCA=giant cell arteritis; HS=hidradenitis suppurative; IV=intravenous infusion; JAK=Janus kinase; JIA=juvenile idiopathic arthritis; MTX=methotrexate; NOMID=neonatal-onset multisystem inflammatory disease; NSAID=non-steroidal anti-inflammatory drug; PJIA=polyarticular juvenile idiopathic arthritis; PO=orally; PsA=psoriatic arthritis; PsO=plaque psoriasis; RA=rheumatoid arthritis; SJIA=systemic juvenile idiopathic arthritis; SQ=subcutaneously; UC=ulcerative colitis.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Actemra (tocilizumab)	Frequency of serious infection greater in ≥65 years. Use caution.	Not studied in children <2 years. Safety and efficacy only established in SJIA, PJIA, and CRS.	No dose adjustment in mild or moderate impairment. Not studied in severe impair-ment.	Not studied in patients with impairment.	Unclassified† Limited data in pregnant women not sufficient to determine risks. Unknown whether excreted in breast milk; risks and benefits should be considered.
Cimzia (certolizumab)	The number of subjects ≥65 years in clinical trials was not sufficient to determine whether they responded differently from younger subjects. Use caution.	Safety and effectiveness have not been established.	No data	No data	Unclassified† Limited data from ongoing pregnancy registry not sufficient to inform risks. Minimal exrection in breast milk; risks and benefits should be considered.
Cosentyx (secukinumab)	The number of subjects ≥65 years in clinical trials was not sufficient to determine whether they responded differently from younger subjects.	Safety and efficacy have not been established.	No data	No data	Unclassified† Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk; use with caution.
Entyvio (vedolizumab)	The number of patients ≥65 years in clinical trials was insufficient to determine differences.	Safety and efficacy have not been established.	Safety and efficacy have not been established.	Safety and efficacy have not been established.	Pregnancy category B* Unknown whether excreted in breast milk; use with caution.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Enbrel (etanercept)	Use caution.	Not studied in children <2 years with PJIA or <4 years with PsO.	No data	No data	Unclassified† Available studies do not reliably support association with major birth defects. Present in low levels in breast milk; consider risks and benefits.
Humira (adalimumab)	Frequency of serious infection and malignancies is greater in ≥65 years. Use caution.	Only studied in PJIA, pediatric uveitis (ages 2 years and older), CD (6 years and older), and hidradenitis suppurativa (12 years and older).	No data	No data	Unclassified† Present in low levels in breast milk; consider risks and benefits.
Ilaris (canakinumab)	The number of patients ≥65 years in clinical trials was insufficient to determine differences.	Not studied in children <2 years (SJIA, TRAPS, HIDS/ MKD, and FMF) or <4 years (CAPS).	No data	No data	Unclassified† Limited data from postmarketing reports not sufficient to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.
Ilumya (tildrakizumab-asmn)	The number of patients ≥65 years in clinical trials was insufficient to determine differences.	Safety and efficacy have not been established.	No data	No data	Unclassified† Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.
Inflectra (infliximab-dyyb)	Frequency of serious infection is greater in ≥65 years. Use caution.	Not recom-mended in <6 years in children with CD.	No data	No data	Pregnancy category B* Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Kevzara (sarilumab)	Frequency of serious infection is greater in ≥ 65 years. Use caution.	Safety and efficacy not established.	Dosage adjustment not required in mild to moderate renal impairment. Kevzara has not been studied in severe renal impairment.	No data.	Unclassified† Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.
Kineret (anakinra)	Use caution.	For NOMID, has been used in all ages. Not possible to give a dose <20 mg.	CrCl<30 mL/min: give dose every other day	No data	Unclassified† Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk; use caution.
Olumiant (baricitinib)	No overall differences were observed in the safety and efficacy profiles of elderly patients.	Safety and efficacy have not been established.	Use not recommended in patients with estimated glomerular filtration rate < 60 mL/min/1.73 m^2	No dose adjustment for mild or moderate impairment; not recommended in patients with severe hepatic impairment	Unclassified† Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk; use caution.
Orencia (abatacept)	Frequency of serious infection and malignancies is greater in ≥65 years. Use caution.	Not recom-mended in <2 years. IV dosing has not been studied in patients < 6 years old. ClickJect autoinjector subcutaneous injection has not been studied in patients < 18 years.	No data	No data	Unclassified† Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk.
Otezla (apremilast)	No overall differences were observed in the safety profile of elderly patients.	Safety and efficacy have not been established.	The dose of Otezla should be reduced to 30 mg once daily in patients with severe renal	No dosage adjustment necessary.	Pregnancy category C* Unknown whether excreted in breast milk; use caution.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
			impairment (CrCl<30 mL/min).		
Remicade (infliximab)	Frequency of serious infection is greater in ≥65 years. Use caution.	Not recom-mended in <6 years in children with CD or UC.	No data	No data	Pregnancy category B* Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug.
Renflexis (infliximab-abda)	Frequency of serious infection is greater in ≥ 65 years. Use caution.	Not recom-mended in < 6 years in children with CD.	No data	No data	Unclassified† Available data do not report clear association with adverse outcomes. Unknown whether excreted in breast milk; consider risks and benefits.
Rituxan (rituximab)	Rates of serious infections, malignancies, and cardiovascular events were higher in older patients.	Safety and effectiveness have not been established.	No data	No data	Unclassified† May potentially cause B-cell lymphocytopenia due to in-utero exposure. Unknown whether excreted in breast milk; risks and benefits should be weighed before use.
Siliq (brodalumab)	No differences in safety or efficacy were observed between older and younger patients, but the number of patients ≥65 years was insufficient to determine any differences in response.	Safety and effectiveness in <18 years have not been established.	No data	No data	Unclassified† There are no human data in pregnant women to inform risks. Unknown whether excreted in breast milk; risks and benefits should be weighed before use.
Simponi/ Simponi Aria (golimumab)	SQ: No differences in AEs observed between older and younger patients. Use caution.	Effectiveness in <18 years has not been established (Simponi).	No data	No data	Pregnancy category B* (Aria) Unclassified† No adequate and well-controlled trials

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	IV Aria: Use caution.	Safety and effectiveness in < 18 years have not been established (Aria).			in pregnant women. (Simponi). Unknown whether excreted in breast milk. Discontinue nursing or discontinue the drug (Aria). Consider risks and benefits (Simponi).
Stelara (ustekinumab)	No differences observed between older and younger patients. Use caution.	Safety and effectiveness have not been established.	No data	No data	Unclassified† Limited data in pregnant women are insufficient to inform risks. Unknown whether excreted in breast milk; systemic exposure to breasted infant expected to be low; consider risks and benefits.
Taltz (ixekizumab)	No differences observed between older and younger patients; however, the number of patients ≥65 years was not sufficient to determine differences.	Safety and effectiveness have not been established.	No data	No data	Unclassified† There are no available data in pregnant women to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.
Tremfya (guselkumab)	No differences observed between older and younger patients; however, the number of patients ≥ 65 years was not sufficient to determine differences.	Safety and efficacy have not been established.	No data	No data	Unclassified† No available data in pregnant women to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Xeljanz / Xeljanz XR (tofacitinib)	Frequency of serious infection is greater in ≥65 years. Use caution.	Safety and effectiveness have not been established.	Moderate to severe impairment: Patients with RA or PsA receiving Xeljanz XR should switch to Xejanz and reduce dose to 5 mg daily. Patients with UC should switch to 5 mg twice daily (if on 10 mg twice daily) or 5 mg once daily (if on 5 mg twice daily).	Moderate impairment: Patients receiving Xeljanz XR should switch to Xejanz and reduce dose to 5 mg daily. Patients with UC should switch to 5 mg twice daily (if on 10 mg twice daily) or 5 mg once daily (if on 5 mg twice daily). Not recom-mended in severe hepatic impairment.	Unclassified† No adequate and well-controlled studies in pregnancy are available. Unknown whether excreted in breast milk; discontinue nursing or discontinue the drug.

CrCl=creatinine clearance; CRS=cytokine release syndrome; NOMID= Neonatal-Onset Multisystem Inflammatory Disease; PJIA=polyarticular juvenile idiopathic arthritis; PsA=psoriatic arthritis; RA=rheumatoid arthritis; SJIA=systemic juvenile idiopathic arthritis; UC=ulcerative colitis
*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

CONCLUSION

- Immunomodulators for a variety of conditions associated with inflammation are available. Mechanisms of action and indications vary among the products. Products in this class have clinical trial data supporting efficacy for their FDA-approved indications.
- Limited head-to-head clinical trials between the agents have been completed.
    - In patients with RA, abatacept and infliximab showed comparable efficacy at 6 months, but abatacept demonstrated greater efficacy after 1 year on some endpoints such as DAS28-ESR, EULAR response, LDAS, and ACR 20 responses (*Schiff et al 2008*).
    - In patients with RA, abatacept and adalimumab were comparable for ACR 20 and ACR 50 responses over 2 years in a single-blind study (*Schiff et al 2014*).
    - In patients with RA and an inadequate response or intolerance to MTX, sarilumab significantly improved change from baseline in DAS28-ESR over adalimumab (*Burmester et al 2017*). DAS28-ESR remission, ACR 20/50/70 response rates, and improvements in HAQ-DI scores were also more likely with sarilumab.
    - Patients with severe arthritis who could not take MTX were randomized to monotherapy with tocilizumab or adalimumab for 24 weeks in a randomized, double-blind study (*Gabay et al 2013*). The patients in the tocilizumab group had a significantly greater improvement in DAS28 at week 24 than patients in the adalimumab group.
    - In biologic-naïve patients with RA and an inadequate response to DMARDs, initial treatment with rituximab was demonstrated to have non-inferior efficacy to initial TNF inhibitor treatment (*Porter et al 2016*).
    - A randomized, open-label trial evaluated biologic treatments in patients with RA who had had an inadequate response to a TNF inhibitor. In this population, a non-TNF biologic (tocilizumab, rituximab, or abatacept) was more effective in achieving a good or moderate disease activity response at 24 weeks than use of a second

TNF inhibitor. However, a second TNF inhibitor was also often effective in producing clinical improvement (*Gottenberg et al 2016*). Another recent randomized trial did not demonstrate clinical efficacy differences between abatacept, rituximab, and use of a second TNF inhibitor in this patient population *(Manders et al 2015*).

- Secukinumab and ustekinumab were compared for safety and efficacy in the CLEAR and CLARITY studies, which were double-blind, randomized controlled trials in 676 in 1102 patients, respectively, with moderate to severe PsO (*Bagel et al 2018, Thaçi et al 2015*). In both studies, the proportion of patients achieving PASI 90 was significantly higher with secukinumab compared to ustekinumab (CLEAR: 79% vs 57.6%, p < 0.0001; CLARITY: 66.5% vs 47.9%, p < 0.0001) at week 16 in CLEAR and at week 12 in CLARITY.
- In the IXORA-S study, the proportion of patients achieving PASI 90 at week 12 was significantly higher with ixekizumab compared to ustekinumab (72.8% vs 42.2%, respectively; p < 0.001) (*Reich et al 2017 [b]).*
- A greater proportion of PsO patients achieved the primary outcome, PASI 75 at week 12, with ustekinumab 45 mg (67.5%) and 90 mg (73.8%) compared to etanercept 50 mg (56.8%; p = 0.01 vs ustekinumab 45 mg; p < 0.001 vs ustekinumab 90 mg). In this trial, etanercept therapy was associated with a greater risk of injection site erythema than ustekinumab (14.7% vs 0.7%) (*Griffiths et al 2010*).
- In the FIXTURE study in patient with moderate to severe PsO, 77.1%, 67%, 44%, and 4.9% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, etanercept at FDA-recommended dosing, and placebo, respectively (*Langley et al 2014*).
- In the UNCOVER-2 and UNCOVER-3 studies, the proportions of patients achieving PASI 75 and achieving PGA 0 or 1 were higher in patients treated with ixekizumab compared to those treated with etanercept.
- In the AMAGINE-2 and AMAGINE-3 studies, the proportions of patients achieving PASI 100 were higher in patients treated with brodalumab compared to those treated with ustekinumab (*Lebwohl et al 2015*).
- In the VOYAGE 1 and VOYAGE 2 studies, the proportions of patients with moderate to severe PsO achieving IGA 0 or 1 and PASI 90 were higher with guselkumab compared to those treated with adalimumab *(Blauvelt et al 2017, Reich et al 2017[a]*).
- No meaningful differences were shown in the treatment of RA and PsA in comparisons of infliximab and infliximab-dyyb conducted to establish biosimilarity between these agents (*Park et al 2013, Park et al 2016, Park et al 2017, Yoo et al 2013, Yoo et al 2016, Yoo et al 2017*). Similarly, no meaningful differences between infliximab and infliximab-abda were found in treatment of RA in clinical studies to establish biosimilarity (*Choe et al 2017, Shin et al 2015*).
- In patients with CD, UC, RA, PsA, spondyloarthritis, and PsO who were treated with the originator infliximab for ≥ 6 months, infliximab-dyyb was noninferior to infliximab originator group for disease worsening (*Jørgensen et al 2017*).
- More comparative studies are needed.

- For RA, patients not responding to initial DMARD treatment may be treated with combination DMARDs, TNF inhibitors, non-TNF inhibitor biologics, and/or tofacitinib (*Singh et al 2016c; Smolen et al 2017*). EULAR has released guidelines for use of antirheumatic drugs in pregnancy, which state that the TNF inhibitors etanercept and certolizumab are among possible treatment options for patients requiring therapy (*Götestam Skorpen et al 2016*).
- For the management of PsO, biologic agents are routinely used when ≥ 1 traditional systemic agents are not tolerated, fail to product an adequate response, or are unable to be used due to patient comorbidities (*Gottleib et al 2008, Menter et al 2008, Menter et al 2009a, Menter et al 2009b, Menter et al 2010, Menter et al 2011, Nast et al 2015b*). EULAR 2015 PsA guidelines recommend TNF inhibitors in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, such as MTX (*Gossec et al 2016, Ramiro et al 2016*). For patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, in whom a TNF inhibitor is not appropriate, biologics targeting IL-12/23 or IL-17 pathways may be considered. Apremilast is considered a treatment option in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, in whom biologics are not appropriate. Guidelines from GRAPPA recommend various biologics for the treatment of PsO and PsA based on patient-specific factors, including TNF inhibitors, IL-17 and IL-12/23 inhibitors, and PDE-4 inhibitors (*Coates et al 2016*). Joint guidelines from the American Academy of Dermatology/National Psoriasis Foundation on the treatment of psoriasis with biologics do not provide ranking for preferences of individual biologics, but do note that etanercept, infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, and tildrakizumab can be recommended as a monotherapy option for patients with moderate to severe PsO (*Menter et al 2019*).
- The American College of Rheumatology/National Psoriasis Foundation guideline on PsA recommends that a TNF inhibitor is preferred in treatment-naïve patients with active PsA, although an oral therapy can be a first-line option in patients without severe PsA and without severe psoriasis, or if a patient has another compelling reason to avoid a

TNF inhibitor. In patients who fail oral therapy, a switch to a TNF inhibitor is preferred and placed ahead of IL-17 biologics, IL-12/23 biologics, abatacept, and tofacitinib (*Singh et al 2019*).

- In patients with JIA and involvement of ≥ 5 joints, the ACR recommends the use of a TNF inhibitor after an adequate trial of a conventional DMARD (*Beukelman et al 2011*). The ACR updated guideline for SJIA notes that IL-1 and IL-6 play a central role in the inflammatory process for this condition, and recommend agents such as anakinra, canakinumab, tocilizumab, abatacept, and TNF inhibitors among either first- or second-line treatments (*Ringold et al 2013*).
- According to the ACG, for the treatment of UC, infliximab should be considered after failure of first-line non-biologic agents (*Kornbluth et al 2010*). Other immunomodulators were not indicated for UC when these guidelines were written. The AGA recommends that for patients at high-risk for colectomy, anti-TNF drugs and vedolizumab can be considered for induction and maintenance therapy (*Dassopoulos et al 2014*). ECCO guidelines recommend thiopurine, anti-TNF drugs, vedolizumab, or methotrexate for patients with UC who have active steroid-dependent disease and anti-TNF agents or vedolizumab for patients who have steroid- or immunomodulator-refractory disease (*Harbord et al 2017*).
- The ACG states that the anti-TNF monoclonal antibodies adalimumab, certolizumab, and infliximab are effective in the treatment of moderate to severely active CD in patients who are resistant to corticosteroids or are refractory to thiopurines or methotrexate. These agents can be considered for treating perianal fistulas, and infliximab can also treat enterocutaneous and rectovaginal fistulas in CD. Adalimumab, certolizumab, and infliximab are effective for the maintenance of anti-TNF induced remission as monotherapy or in combination with azathioprine/6-mercaptopurine or methotrexate. The combination of infliximab with an immunomodulator (thiopurine) is more effective than monotherapy with individual agents in patients with moderate to severe CD and who are naïve to both agents. Infliximab can also treat fuliminant CD. Vedolizumab with or without an immunomodulator can be used for induction and maintenance of remission in patients with moderate to severe CD. Patients are candidates for ustekinumab therapy, including for the maintenance of remission, if they have moderate to severe CD and have failed corticosteroids, thiopurines, methotrexate, or anti-TNF inhibitors. The guideline acknowledges the effectiveness of biosimilar infliximab and biosimilar adalimumab for the management of moderate to severe CD (*Lichtenstein et al 2018*). The AGA recommends using anti-TNF drugs to induce remission in patients with moderately severe CD (*Terdiman et al 2013*). ECCO recommends TNF inhibitors for patients with CD who have relapsed or are refractory to corticosteroids, depending on disease location and severity, and states that early TNF inhibitor therapy should be initiated in patients with high disease activity and features indicating a poor prognosis; vedolizumab is an alternative for some patients (*Gomollón et al 2017*).
- Consensus statements for the management of inflammatory bowel disease in pregnancy, from the Canadian Association of Gastroenterology and from the AGA, recommend that biologics can be continued during pregnancy and delivery as the benefits of maintaining disease remission outweigh any risks associated with biologic maintenance therapy (*Mahadevan et al 2019, Nguyen et al 2016b*).
- Based upon guidelines from the European Dermatology Forum, adalimumab is recommended among first-line therapies for HS, with infliximab a potential second-line option (*Gulliver et al 2016, Zouboulis et al 2015*).
- Joint guidelines from ASAS and EULAR state that biologic DMARDs should be considered in patients with AS and persistently high disease activity despite conventional treatments (*van der Heijde et al 2017*). The 2015 ACR, Spondylitis Association of America, and Spondyloarthritis Research and Treatment Network guidelines strongly recommend TNF inhibitors for patients who have active disease despite NSAIDs; no TNF inhibitor is preferred over another for AS for most patients (*Ward et al 2016*).
- Infliximab and adalimumab are recommended over etanercept for various ocular inflammatory disorders (*Levy-Clarke et al 2016*).
- Caution is warranted with these biologic agents due to severe infections and malignancies that can occur with their use. Tocilizumab, TNF inhibitors, and tofacitinib have boxed warnings regarding a risk of serious infections. TNF inhibitors and tofacitinib also have boxed warnings regarding an increased risk of malignancies. Brodalumab has a boxed warning regarding the risk of suicidal ideation and behavior.
- Warnings, precautions, and AE profiles vary in this class.
- All of the biologic agents with the exception of apremilast and tofacitinib are given by subcutaneous injection and/or intravenous infusion. Administration schedule varies among the injectable agents in the class. Apremilast and tofacitinib are given orally.
- Selection of an agent for a patient is determined by approved indications, response, administration method, tolerability, AE profile, and cost of the agent.

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Therapeutic Class Overview
Angiotensin II Receptor Blockers (ARBs)

INTRODUCTION

- Approximately 121.5 million American adults are living with some form of cardiovascular (CV) disease (congestive heart disease, heart failure, stroke, and hypertension) according to the American Heart Association (AHA) Heart Disease and Stroke Statistics 2019 update *(Benjamin et al 2019).* Cardiovascular disease accounts for an estimated 840,678 deaths in the US annually and is the leading cause of death globally.
- The estimated prevalence of heart failure (HF) is 6.2 million for Americans aged ≥ 20 years. Projections show that the prevalence of HF will increase 46% from 2012 to 2030, resulting in > 8 million people ≥ 18 years of age with HF (*Benjamin et al 2019*).
- Hypertension (HTN) is an independent risk factor for CV disease and increases the mortality risks of CV disease and other diseases *(Benjamin et al 2019).* The 2017 American College of Cardiology (ACC)/AHA clinical practice guideline defines HTN as blood pressure (BP) ≥ 130/80 mm Hg (*Whelton et al 2018).* Nearly half of American adults (46%) have HTN based on this definition.
- Lowering of BP has been shown to reduce the risk of fatal and nonfatal CV events including stroke and myocardial infarctions (MIs). Lipid control, diabetes mellitus (DM) management, smoking cessation, exercise, weight management, and limiting sodium intake may also reduce CV risk *(Benjamin et al 2019).*
- Numerous classes of antihypertensives are available to reduce BP. Some examples of antihypertensives include diuretics, angiotensin converting enzyme inhibitors (ACE-Is), angiotensin II receptor blockers (ARBs), beta blockers, and calcium channel blockers (CCBs). Selection of antihypertensive therapy for a specific patient is determined by patient characteristics such as ethnic group, and the presence of compelling indications such as HF, DM, chronic kidney disease (CKD), history of stroke or MI, and risk factors for coronary heart disease (CHD). Some patients require 2 or more antihypertensives from different pharmacological classes to achieve BP control *(Go et al 2014, Weber et al 2014, Whelton et al 2018).*
- In general, guideline-recommended BP goals in hypertensive adults range from < 130/80 mm Hg to < 140/90 mm Hg *(Arnett et al 2019, de Boer et al 2017, Whelton et al 2018).*
  - Blood pressure goals for older patients have long been a point of debate. The SPRINT trial followed patients ≥ 50 years with high BP and increased CV risks under intense hypertensive treatment (with a systolic blood pressure [SBP] goal of < 120 mm Hg) compared to standard HTN treatment (with an SBP goal of < 140 mm Hg) over a period of 3.2 years. The trial ended early; however, results demonstrated a reduced primary composite outcome of MI, acute coronary syndrome (ACS), stroke, HF, or CV death driven mainly by reduced HF events and CV death with intense treatment compared to standard treatment. The SPRINT trial pointed to potential clinical benefits associated with more intensive treatment in certain patients, although early termination of the trial and variations in the BP-measurement technique employed have called into question the generalizability of the results *(SPRINT Research Group 2015).*
  - A recent guideline from the American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP) on treatment of HTN in adults aged ≥ 60 years recommends standard and intense SBP treatment goals of < 150 mm Hg and < 140 mm Hg, respectively, with more intense BP reduction reserved for patients with a history of stroke or transient ischemic attack *(Qaseem et al 2017).*
- The cardinal symptoms of HF are dyspnea and fatigue. HF leads to exercise intolerance, fluid retention, pulmonary congestion, and peripheral edema, often resulting in hospitalization (*Yancy* et al, *2013*).
- There are 2 forms of HF:
  - Heart failure with reduced ejection fraction (HFrEF) or systolic HF: ejection fraction (EF) ≤ 40%
  - Heart failure with preserved ejection fraction (HFpEF) or diastolic HF: EF ≥ 50%
- Recent guideline updates from the ACC/AHA/Heart Failure Society of America (HFSA) state that in patients with chronic symptomatic HFrEF New York Heart Association (NYHA) Class II or III who tolerate an ACE-I or ARB, replacement by an angiotensin receptor and neprilysin inhibitor (ARNI), such as sacubitril/valsartan, is recommended to further reduce morbidity and mortality (*Yancy et al 2016, Yancy et al 2017*).

- Sacubitril/valsartan is usually administered in place of an ACE-I or other ARB; although, the role for the management of HF is not as well established as ACE-Is or other ARBs. Based on study data, there is minimal evidence of benefits and harms in the following populations: very elderly patients, African Americans, NYHA Class I or IV, patients with low BP or co-morbid HTN refractory to treatment, and patients with HFpEF. Further studies are warranted in these groups.
- This review includes the ARBs, the ARB combination products, and the only approved ARNI (sacubitril/valsartan). ARBs work primarily through reduction of systemic vascular resistance as a result of selective antagonism of angiotensin II at the angiotensin II AT1 receptor. Angiotensin II is the primary vasoactive hormone.
  - The ARBs are Food and Drug Administration (FDA)-approved to treat HTN. Some ARBs have additional indications for HF, diabetic nephropathy, or CV risk reduction in certain high-risk populations.
  - The ARB combinations are products that combine an ARB with a diuretic (ie, chlorthalidone, hydrochlorothiazide [HCTZ]), a beta blocker (ie, nebivolol), and/or a CCB (ie, amlodipine) in a fixed-dose formulation. By combining agents from different classes, these combination products are meant to increase the effectiveness of antihypertensive therapy through complementary mechanisms of action while minimizing the potential for dose-related adverse effects. All ARB combination products are FDA-approved for the treatment of HTN. Losartan/HCTZ is also indicated to reduce the risk of stroke in patients with HTN and left ventricular (LV) hypertrophy.
  - Sacubitril/valsartan is indicated to reduce the risk of CV death and hospitalization for HF in patients with chronic HFrEF.
- Medispan classes: Angiotensin II Receptor Antagonists; Antihypertensive Combinations - ARB/CCB combinations, beta blocker/ARB combination, ARB/thiazide and thiazide-like combinations, and ARB/CCB/thiazide combinations; Cardiovascular Agents, ARNI – Angiotensin II receptor antagonist/neprilysin inhibitor combination

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single-Entity ARBs	
Atacand (candesartan)	✔
Avapro (irbesartan)	✔
Benicar (olmesartan)	✔
Cozaar (losartan)	✔
Diovan (valsartan)	✔ *
Edarbi (azilsartan)	-
eprosartan	✔ †
Micardis (telmisartan)	✔
ARB/Diuretic Combinations	
Atacand HCT (candesartan/hydrochlorothiazide)	✔
Avalide (irbesartan/hydrochlorothiazide)	✔
Benicar HCT (olmesartan/hydrochlorothiazide)	✔
Diovan HCT (valsartan/hydrochlorothiazide)	✔
Edarbyclor (azilsartan/chlorthalidone)	-
Hyzaar (losartan/hydrochlorothiazide)	✔
Micardis HCT (telmisartan/hydrochlorothiazide)	✔
ARB/Beta Blocker Combinations	
Byvalson (valsartan/nebivolol) ‡	-
ARB/CCB Combinations	
Azor (olmesartan/amlodipine)	✔
Exforge (valsartan/amlodipine)	✔
Twynsta (telmisartan/amlodipine)	✔
ARB/CCB/Diuretic Combinations	
Exforge HCT (valsartan/amlodipine/hydrochlorothiazide)	✔
Tribenzor (olmesartan/amlodipine/hydrochlorothiazide)	✔
ARB/Neprilysin inhibitor Combination	

Drug	Generic Availability
Entresto (sacubitril/valsartan)	-

Abbreviations: ARB = angiotensin II receptor blocker; CCB = calcium channel blocker
*Prexxartan (valsartan) oral solution was FDA-approved in December 2017; however, it has been discontinued.
†Branded Teveten (eprosartan) is no longer marketed.
‡In December 2018, Allergan announced that it would be discontinuing Byvalson (*FDA Drug Shortages 2019*).

(Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019)

INDICATIONS

Table 2. FDA-approved indications for single-entity ARBs

Indication	Atacand (candesartan)	Avapro (irbesartan)	Benicar (olmesartan)	Cozaar (losartan)	Diovan (valsartan)	Edarbi (azilsartan)	eprosartan	Micardis (telmisartan)
Hypertension in adults	✔	✔	✔	✔	✔	✔	✔	✔
Hypertension in children ages 1 to < 17 years	✔							
Hypertension in children ages 6 to 16 years			✔	✔	✔			
Treatment of diabetic nephropathy in hypertensive patients with type 2 DM, an elevated serum creatinine, and proteinuria		✔		✔				
Heart failure (NYHA Class II to IV) in adults	✔				✔			
Reduction in the risk of stroke in patients with hypertension and LV hypertrophy				✔				
Post-MI: Reduction of cardiovascular mortality in clinically stable patients with LV failure or LV dysfunction					✔			
Cardiovascular risk reduction in patients 55 years of age or older at high risk of developing major cardiovascular events who are unable to take ACE-Is								✔

Abbreviations: ACE-I = angiotensin converting enzyme inhibitor; LV = left ventricular; MI = myocardial infarction; NYHA = New York Heart Association

(Prescribing information: Atacand 2018, Avapro 2018, Benicar 2017, Cozaar 2018, Diovan 2017, Edarbi 2016, eprosartan 2014, Micardis 2018)

Table 3. FDA-approved indications for combination products containing ARBs

Drug	Hypertension	Reduction in the Risk of CV Death and HF Hospitalization in Patients with Chronic HF and Reduced EF	Reduction in the Risk of Stroke in Patients with Hypertension and Left Ventricular Hypertrophy
ARB/Diuretic Combinations			
Atacand HCT (candesartan/hydrochlorothiazide)	✔ *	-	-
Avalide (irbesartan/hydrochlorothiazide)	✔ †	-	-
Benicar HCT (olmesartan/hydrochlorothiazide)	✔ *	-	-

Drug	Hypertension	Reduction in the Risk of CV Death and HF Hospitalization in Patients with Chronic HF and Reduced EF	Reduction in the Risk of Stroke in Patients with Hypertension and Left Ventricular Hypertrophy
Diovan HCT (valsartan/hydrochlorothiazide)	✔ †	-	-
Edarbyclor (azilsartan/chlorthalidone)	✔ †	-	-
Hyzaar (losartan/hydrochlorothiazide)	✔ ‡	-	✔ §
Micardis HCT (telmisartan/hydrochlorothiazide)	✔ *	-	-
ARB/Beta Blocker Combination			
Byvalson (valsartan/nebivolol)	✔ *	-	-
ARB/CCB Combinations			
Azor (olmesartan/amlodipine)	✔ †	-	-
Exforge (valsartan/amlodipine)	✔ †	-	-
Twynsta (telmisartan/amlodipine)	✔ †	-	-
ARB/CCB/Diuretic Combinations			
Exforge HCT (valsartan/amlodipine/hydrochlorothiazide)	✔ *	-	-
Tribenzor (olmesartan/amlodipine/hydrochlorothiazide)	✔ *	-	-
ARB/Neprilysin inhibitor Combination			
Entresto (sacubitril/valsartan)		✔ ‖	

Abbreviations: ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; CV = cardiovascular; EF = ejection fraction; HF = heart failure

*This fixed-dose combination is not indicated for initial therapy.

†Indicated to treat HTN in patients not adequately controlled on monotherapy or as initial therapy in patients who are likely to need multiple drugs to achieve their BP goals.

‡The fixed-dose combination is not indicated for initial therapy, except when the HTN is severe enough that the value of achieving prompt BP control exceeds the risks of initiating combination therapy in these patients.

§There is evidence that this benefit does not extend to African American patients.

‖NYHA Class II to IV

(Prescribing information: Atacand HCT 2018, Avalide 2018, Azor 2017, Benicar HCT 2017, Byvalson 2019, Diovan HCT 2015, Edarbyclor 2016, Entresto 2018, Exforge 2015, Exforge HCT 2015, Hyzaar 2018, Micardis HCT 2018, Tribenzor 2017, Twynsta 2018)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Single-Entity ARBs

- ARBs have demonstrated efficacy for the treatment of HTN in adults. A Cochrane systematic review of 46 randomized, placebo-controlled trials evaluated the BP lowering ability of 9 different ARBs (N = 13,451) in patients with a baseline BP of 156/101 mm Hg. On average, SBP was lowered by 8 mm Hg and diastolic blood pressure (DBP) by 5 mm Hg with maximum recommended doses of ARBs. No clinically meaningful differences within the ARB class were observed in the reduction of BP *(Heran et al 2008).* A systematic review and network meta-analysis of 36 RCTs evaluated the comparative effectiveness of ARBs (versus another ARB, HCTZ, or placebo) in lowering BP and CV event rates (including MI, stroke, cardiovascular mortality, and all-cause mortality) in patients with hypertension. BP reduction and CV event rates were found to be similar among all ARBs assessed, and the authors concluded that evidence is not sufficient to show differences in reduction of blood pressure or CV disease among members of the ARB drug class (*Tsoi et al 2018*).

  - Meta-analyses have shown that ACE-Is and ARBs have similar long-term effects on BP *(Sanders et al 2011, Savarese et al 2013).* Additionally, a Cochrane review involving 11,007 subjects with primary HTN found no evidence of a difference in total mortality or CV outcomes for ACE-Is in comparison to ARBs (*Li 2014*).
- Telmisartan is indicated to reduce CV risk in patients unable to take ACE-Is. The ONTARGET trial compared telmisartan and ramipril monotherapy and in combination with each other and demonstrated no significant difference between any groups in death from CV causes, MI, stroke, or hospitalization for HF *(ONTARGET Investigators 2008).* In the TRANSCEND trial, no significant difference was observed between telmisartan and placebo in death from CV causes, MI, stroke, or HF hospitalizations. The composite endpoint of death from CV causes, MI, and stroke occurred in significantly fewer patients in the telmisartan group, but this significance was lost after adjustment for multiplicity of comparisons and overlap with the primary outcome *(Foulquier et al 2014, TRANSCEND Investigators 2008)*.
- Losartan is indicated to reduce the risk of stroke in patients with HTN and LV hypertrophy. The efficacy of losartan was demonstrated in the LIFE trial and its corresponding sub-analyses. Losartan was compared to therapy with atenolol. Results demonstrated a 24.9% relative risk reduction for stroke in patients treated with losartan-based regimens compared to atenolol-based regimens *(Dahlöf et al 2002)*. However, a post-hoc analysis in African American patients showed an increase in the composite of CV death, MI, and stroke with losartan compared to atenolol *(Julius et al 2004)*.
- Candesartan and valsartan are indicated to treat HF. Trials demonstrated the efficacy of candesartan alone and in combination with ACE-I therapy compared to placebo in reducing the risk of all-cause mortality, CV death, and/or HF hospitalization *(McMurray et al 2003, Pfeffer et al 2003b, Yusuf et al 2003)*. When compared to enalapril in the RESOLVD trial, candesartan was not significantly better in improving 6-minute walking distance, NYHA functional class, or quality of life *(McKelvie et al 1999)*. Losartan was compared to captopril in patients with HF, and no significant difference was observed in renal function or all-cause mortality *(Pitt et al 1997, Pitt et al 2000)*. However, there was a significantly lower risk of sudden death and resuscitated cardiac arrest with losartan *(Pitt et al 2000)*. The Val-HeFT trial showed no significant difference in all-cause mortality between valsartan and placebo. However, the valsartan group demonstrated a significant improvement in NYHA functional class, HF hospitalizations, morbidity, and mortality *(Cohn et al 2001)*.
- Valsartan is indicated to reduce CV mortality in patients with post-MI LV failure or dysfunction. The VALIANT trial compared valsartan with captopril and combination therapy with valsartan plus captopril. No significant differences in all-cause mortality, CV death, reinfarction, or HF hospitalization were observed between monotherapy groups or combination therapy compared to captopril monotherapy *(Pfeffer et al 2003a)*. Losartan has also been evaluated in patients post-MI compared to and in combination with captopril. Results were similar to those of the VALIANT trial *(Dickstein et al 2002)*.
- Irbesartan and losartan are indicated for the treatment of diabetic nephropathy in patients with type 2 DM and HTN. However, clinical benefit in diabetic nephropathy has been shown with other ARBs, including candesartan, losartan, telmisartan, and valsartan *(Barnett et al 2004, Galle et al 2008, Hou et al 2007, Mogensen et al 2000, Viberti et al 2002)*.
- The ORIENT and ROADMAP studies followed patients with DM and compared the effects of olmesartan versus placebo. Outcomes demonstrated a higher rate of death from CV causes in both trials compared to placebo. This finding contradicts outcomes of other studies that include ARBs and/or olmesartan. A number of factors may have contributed to these outcomes including concomitant medications, patients with higher CV risks, and other potential confounders. Further studies in diabetic patients are needed to validate findings *(Haller et al 2011, Imai et al 2011)*.
- Studies have demonstrated that the combination of 2 inhibitors of the renin angiotensin-aldosterone system (RAAS), including an ACE-I with an ARB, provides no renal or CV benefits, with an increase in significant adverse events, particularly in patients with DM and/or renal insufficiency. Most notably, patients receiving combination therapy had increased rates of hyperkalemia, hypotension, and renal dysfunction. All agents in the class have safety warnings against combined use *(Fried et al 2013, ONTARGET Investigators 2008, Parving et al 2012, Pfeffer et al 2003a, Sakata et al 2015)*.

Combination Products Containing ARBs

- Clinical trials assessing the combination ARBs in the treatment of HTN have demonstrated that, in general, dual therapy combinations of ARBs plus a diuretic (either HCTZ or chlorthalidone) or amlodipine achieve greater reductions in BP and higher BP control rates compared to monotherapy regimens of ARBs, amlodipine, or diuretics *(Chrysant et al 2004, Chrysant et al 2008, Derosa et al 2014, Destro et al 2008, Flack et al 2009, Littlejohn et al 2009, Neutel et al 2006, Neutel et al 2008, Neutel et al 2012, Philipp et al 2007, Sachse et al 2002, Salerno et al 2004, Sharma et al 2007a, Sharma et al 2012, Waeber et al 2001, Zhu et al 2012)*. A meta-analysis by Conlin et al found that combination therapy

with ARBs and HCTZ resulted in substantially greater reductions in SBP and DBP compared to ARB monotherapy *(Conlin et al 2000)*.

- Trials assessing triple therapy regimens with an ARB, amlodipine, and HCTZ demonstrate significantly greater BP reductions with triple therapy compared to combination and monotherapy *(Calhoun et al 2009a, Calhoun et al 2009b, Destro et al 2010, Ohma et al 2000, Wright et al 2011)*.
- The safety and efficacy of nebivolol/valsartan 5/80 mg was based on a double-blind, placebo-controlled, parallel-group, dose-escalating, Phase 3, randomized controlled trial in 4,159 patients with Stage 1 or 2 HTN. Patients were randomized to 1 of 4 treatment arms (with a total of 7 dose groups plus placebo): (1) nebivolol/valsartan (5/80 mg, 5/160 mg, or 10/160 mg); (2) nebivolol monotherapy (5 mg or 20 mg); (3) valsartan monotherapy (160 mg or 320 mg); or (4) placebo. All treatment was administered in fixed doses once per day for 4 weeks; doses were then doubled for weeks 5 to 8 of treatment. Compared to placebo, nebivolol/valsartan 5/80 mg significantly lowered SBP by 8.3 mmHg and DBP by 7.2 mmHg, monotherapy with nebivolol 5 mg lowered SBP by 4.7 mmHg and DBP by 4.4 mmHg, and monotherapy with valsartan 80 mg lowered SBP by 5.4 mmHg and DBP by 3.9 mmHg after 4 weeks of treatment. Higher doses of the combination did not lead to further clinically meaningful reductions in BP. No adverse events were observed more frequently with nebivolol/valsartan compared to placebo. As anticipated with beta blocker and ARB therapy, serious adverse reactions such as hypotension or hyperkalemia may occur *(Giles et al 2014)*.
- Head-to-head trials have not consistently demonstrated superiority of one ARB combination product over another *(Ambrosioni et al 2010, Bobrie et al 2005, Cushman et al 2012, Derosa et al 2014, Fogari et al 2006, Lacourcière et al 2003, Ohma et al 2000, Sharma et al 2007b, Toh et al 2016, White et al 2008, Wright et al 2011)*.
- The efficacy and safety of sacubitril/valsartan were evaluated in the PARADIGM-HF trial. (*McMurray et al 2014*). A total of 8,442 patients were randomized head-to-head to enalapril 10 mg twice daily or sacubitril/valsartan 97/103 mg twice daily.
- In the PARADIGM-HF trial, the following results were demonstrated after 2.25 years of treatment:
  - CV mortality: The absolute risk was 3.1% less for sacubitril/valsartan-treated patients than those treated with enalapril (risk reduction [RR], 20%; hazard ratio [HR], 0.8; 95% confidence interval [CI], 0.71 to 0.89; P < 0.001; number needed to treat [NNT], 32; 95% CI, 22 to 62).
  - HF hospitalization: The absolute risk was 2.8% less for sacubitril/valsartan-treated patients than those treated with enalapril (RR, 21%; HR, 0.79; 95% CI, 0.71 to 0.89; P < 0.001; NNT, 36; 95% CI, 21 to 77).
  - Combined measure of CV mortality or HF hospitalization (primary endpoint): The absolute risk was 4.7% less for sacubitril/valsartan-treated patients than those treated with enalapril (RR, 20%; HR, 0.8; 95% CI, 0.73 to 0.87; P < 0.001; NNT, 22; 95% CI, 15 to 35).
  - Symptomatic relief: Kansas City Cardiomyopathy Questionnaire (KCCQ) scores were utilized to measure a patient's physical functioning, symptoms, and quality of life (range, 0 to 100 points) with higher scores indicating better health status. At 8 months, scores significantly improved by 1.64 points favoring sacubitril/valsartan over enalapril (P = 0.001). There are different approaches to determining clinical significant KCCQ scores. Based on the varied approaches, clinically significant changes in KCCQ scores have ranged from a difference of 5-point to 10-point declines. In trials, changes of 4 points have been noted in stable HF patients; therefore, the 1.6-point difference in KCCQ for sacubitril/valsartan may not have resulted in an enhanced quality of life when compared to those treated with enalapril regardless of statistical significance (*Green et al 2000, Cardiovascular Outcomes 2008*).
- *Packer et al* published a follow-up analysis of the PARADIGM-HF trial, which outlined the incremental effects of sacubitril/valsartan over enalapril for those with non-fatal progression of HF in surviving patients.
  - Data demonstrated that sacubitril/valsartan-treated patients had slower progression of clinical deterioration compared to enalapril-treated patients in many endpoints that are markers for HF progression (ie, intensified outpatient therapy, emergency department visits, number of hospitalizations, etc.). However, sacubitril/valsartan was not significantly different from enalapril in the number of hospitalized days per admission per patient or in patients requiring cardiac resynchronization therapy, ventricular assist device implants, or a heart transplant (*Packer et al 2015*).
- A separate analysis of the PARADIGM-HF trial reported results for additional composite endpoint rates:
  - CV mortality, HF hospitalization, MI, stroke, and resuscitated sudden death: 24.3% with sacubitril/valsartan vs 28.4% with enalapril (HR, 0.83; 95% CI, 0.76 to 0.90; P < 0.001).
  - CV mortality, non-fatal MI, unstable or other hospitalized angina, or percutaneous or surgical coronary revascularization: 17.1% with sacubitril/valsartan vs 20.3% with enalapril (HR, 0.83; 95% CI, 0.75 to 0.92; P < 0.001) (*Mogensen et al 2017*).

- The 5-year estimated NNT was analyzed for the overall PARADIGM-HF cohort. The 5-year NNT for sacubitril/valsartan compared to enalapril for the primary outcome (CV death or HF hospitalization) and all-cause mortality was 14 and 21, respectively, in the overall cohort (*Srivastava et al 2018*).
- *Lewis et al* published an analysis focused specifically on the health-related quality of life outcomes in PARADIGM-HF. Consistent with the main publication, small but statistically significant improvements in KCCQ scores were reported. At 8 months, the sacubitril/valsartan group noted improvements versus the enalapril group in both KCCQ clinical summary score (CSS) (+0.64 vs -0.29; P = 0.008) and KCCQ overall summary score (OSS) (+1.13 vs -0.14; P < 0.001). Additionally, at 8 months, the proportion of patients with a clinically significant improvement (≥ 5-point increase) in KCCQ score was slightly greater with sacubitril/valsartan vs enalapril (34.5% vs 33.4% for OSS and 32.8% vs 32.6% for CSS) and the proportion with deterioration (≥ 5-point decrease) was less with sacubitril/valsartan versus enalapril (27.2% vs 30.5% for OSS and 27.2% vs 31.2% for CSS). Trends were similar through the 36-month time period but were not statistically significant at some later time points; the ability to draw conclusions is limited by the low completion rate of 29% at 36 months (*Lewis et al 2017*).
- *Chandra et al* examined the effects of sacubitril/valsartan on physical and social activity limitations in patients with HF in a secondary analysis of the PARADIGM-HF trial. Patients receiving this therapy had significantly better adjusted change scores in most physical and social activities at 8 months and during 36 months as compared to patients given enalapril. The largest improvements were in household chores (adjusted change score difference, 2.35; 95% CI: 1.19 to 3.50; P < 0.001) and sexual relationships (adjusted change score difference, 2.71; 95% CI, 0.97 to 4.46; P = 0.002) (*Chandra et al 2018*).
- Based on a cohort analysis of data from the run-in period of PARADIGM-HF, a total of 2,079 patients (19.8%) discontinued treatment with sacubitril/valsartan and were identified as not tolerating treatment. A total of 55% of patients who withdrew from therapy discontinued due to adverse effects (53.7% during phase 1 of the run-in period with enalapril and 56.1% during phase 2 of the run-in period with sacubitril/valsartan).
  - According to the analysis, an increased risk of discontinuation of either drug during run-in was associated with patients with a low estimated glomerular filtration rate (adjusted odds ratio [OR], 1.49; 95% CI, 1.35 to 1.65), HF due to ischemic cause (adjusted OR, 1.25; 95% CI, 1.13 to 1.39), higher N-terminal pro-B-type natriuretic peptide (adjusted OR, 1.2 per log increment; 95% CI, 1.14 to 1.26), and lower systolic BP (adjusted OR, 1.11 per 10 mmHg decrease; 95% CI, 1.07 to 1.14).
  - In patients tolerant to enalapril, an increased risk of sacubitril/valsartan discontinuation was associated with lower DBP (adjusted OR, 1.19 per 10 mm Hg decrease; 95% CI, 1.11 to 1.27).
  - The most common adverse effects for enalapril and sacubitril/valsartan were hypotension (24.7% vs 29.8%, respectively), hyperkalemia (29.4% vs 22.5%, respectively), and worsening renal function (30.6% vs 31.6%, respectively). Of note, angioedema occurred in 0.2% of patients entering the run-in period; however, taking into account the baseline group, this may be lower than observed in a real world setting (*Desai et al 2016*).
- Sacubitril/valsartan was compared to enalapril in patients with HFrEF hospitalized for acute decompensated HF in the multicenter, randomized PIONEER-HF study. Change from baseline to weeks 4 and 8 in the primary endpoint, time-averaged proportional change in N-terminal pro-B-type natriuretic peptide (NT-proBNP), was greater with sacubitril/valsartan compared to enalapril (percent change, -46.7% vs -25.3%; ratio of change with sacubitril/valsartan vs enalapril, 0.71; 95% CI, 0.63 to 0.81). Rates of safety outcomes, including worsening renal function, hyperkalemia, and symptomatic hypotension, were not significantly different between groups. Sacubitril/valsartan also reduced the risk of composite of death, rehospitalization for HF, left ventricular device implantation, and inclusion on heart transplantation list (HR, 0.54; 95% CI, 0.37 to 0.79); however, this was an exploratory endpoint *(Velazquez et al 2018).*
- As part of the post-marketing requirements for sacubitril/valsartan, a clinical trial evaluating cognitive effects was required. This trial is not anticipated to be completed until October 2021 (*FDA approval letter 2015*). However, an analysis of cognitive-related events in HFrEF trials was conducted. Based on a search of adverse event reports, dementia-related adverse effects were similar for enalapril and sacubitril/valsartan for both the narrow (0.36% vs 0.29%, respectively; HR, 0.73; 95% CI, 0.33 to 1.59) and broad search terms (2.3% vs 2.48%, respectively; HR, 1.01; 95% CI, 0.75 to 1.37). PARADIGM-HF patients were followed for a median of 2.25 years (upper range to 4.3 years); however, longer term follow-up may be warranted in order to detect any potential impacts on cognition (*Cannon et al 2016*).

CLINICAL GUIDELINES

- The 2017 ACC/AHA guideline for the prevention, detection, evaluation, and management of high BP in adults *(Whelton et al 2018)* offers updated classifications of HTN and goals of treatment (see Table 4).

Table 4. Classification of BP measurements

BP Category	BP	Treatment or follow-up
Normal	SBP < 120 mm Hg *and* DBP < 80 mm Hg	▪ Evaluate yearly; lifestyle changes are recommended
Elevated	SBP 120 - 129 mm Hg *and* DBP < 80 mm Hg	▪ Evaluate in 3 to 6 months; lifestyle changes are recommended
HTN stage 1	SBP 130 - 139 mm Hg *or* DBP 80 - 89 mm Hg	▪ Assess the 10-year risk for heart disease and stroke using the ASCVD risk calculator. ▪ If ASCVD risk is < 10%, lifestyle changes are recommended. A BP target of < 130/80 mm Hg may be reasonable. ▪ If ASCVD risk is > 10%, or the patient has known CVD, DM, or CKD, lifestyle changes and 1 BP-lowering medication are recommended. A target BP of < 130/80 mm Hg is recommended.
HTN stage 2	SBP ≥ 140 mm Hg *or* DBP ≥ 90 mm Hg	▪ Lifestyle changes and BP-lowering medication from 2 different classes are recommended.

Abbreviations: ASCVD = atherosclerotic cardiovascular disease, BP = blood pressure, CKD = chronic kidney disease, CVD = cardiovascular disease, DBP = diastolic blood pressure, DM = diabetes mellitus, HTN = hypertension, SBP = systolic blood pressure

  - In patients with stage 1 HTN, it is reasonable to initiate therapy with a single antihypertensive agent. In patients with stage 2 HTN and BP more than 20/10 mm Hg higher than their target, 2 first-line agents of different classes should be initiated.
    - First-line antihypertensive agents include thiazide diuretics, CCBs, and ACE-Is or ARBs.
    - Diuretics, ACE-Is, ARBs, CCBs, and beta-blockers have been shown to prevent CVD compared with placebo.
      - ACE-Is were notably less effective in preventing HF and stroke compared with CCBs in black patients. ARBs may be better tolerated than ACE-Is in black patients, with less cough and angioedema, but they offer no proven advantage over ACE-Is in preventing stroke or CVD in this population; thiazide diuretics (especially chlorthalidone) or CCBs are the best initial choice for single-drug therapy in this population.
    - ARBs are reasonable if an ACE-I is not tolerated for treatment of HTN for those with CKD stage 3, or for stage 1 or 2 with albuminuria.
- The 2019 ACC/AHA guideline on the primary prevention of CVD recommends using BP-lowering medications in hypertensive adults: with an estimated 10-year ASCVD risk ≥ 10% and a SBP ≥ 130 mm Hg or DBP ≥ 80 mmHg; with diabetes and a BP > 130/80 mm Hg; or with an estimated 10-year ASCVD risk < 10% and a SBP ≥ 140 mm Hg or DBP ≥ 90 mmHg (*Arnett et al 2019*). A target BP of < 130/80 mmHg is recommended for most patients.
- The American Diabetes Association position statement on DM and HTN *(de Boer et al 2017)* recommends that most patients with DM and HTN be treated to a goal BP of < 140/90 mm Hg. Lower BP targets such as < 130/80 mm Hg may be appropriate for individuals at high risk of CVD.
  - Treatment for HTN should include drug classes demonstrated to reduce CV events in patients with DM: ACE-Is, ARBs, thiazide diuretics, or dihydropyridine CCBs.
  - Patients with BP ≥ 160/100 mm Hg should have prompt initiation of 2 drugs or a single-pill combination of drugs demonstrated to reduce CV events in patients with DM.
  - An ACE-I or ARB, at the maximum tolerated dose indicated for BP treatment, is the recommended first-line treatment for HTN in patients with DM and urine albumin-to-creatinine ratio ≥ 30 mg/g creatinine.

- The American Academy of Pediatrics clinical practice guideline for high BP in children and adolescents *(Flynn et al 2017)* recommends that the treatment goal with nonpharmacologic and pharmacologic therapy should be a reduction in SBP and DBP to < 90th percentile and < 130/80 mm Hg in adolescents ≥ 13 years old.
  - In hypertensive children and adolescents who have failed lifestyle modifications, clinicians should initiate pharmacologic treatment with an ACE-I, ARB, long-acting CCB, or thiazide diuretic.
  - Children and adolescents with CKD, HTN, and proteinuria should be treated with an ACE-I or ARB.
- Various other guidelines and position statements place ARBs as first-line therapy in patients with DM and microalbuminuria; with stable CAD and HTN; and after an MI. ARBs have demonstrated clinical benefit and reductions in morbidity and mortality in these populations *(Amsterdam et al 2014, Go et al 2014, Rosendorff et al 2015, Weber et al 2014).*
  - Due to differences in the activity of the RAAS, ARBs are often less effective as HTN monotherapy in black patients (African or Caribbean descent). Alternative first-line options for these patients include CCBs and thiazide diuretics *(Weber et al 2014).*
- HF guidelines recommend evidence-based maximally tolerated doses of ACE-Is or ARBs, and beta blockers and/or diuretics, as needed, for first-line treatment in patients with HFrEF (NYHA Class I to IV; Stage C) (*Yancy et al 2013, Yancy et al 2016, Yancy et al 2017).*
- Key recommendations from the 2016 and 2017 Focused Update of the ACC/AHA/HFSA HF guidelines related to ACE-Is, ARBs, and ARNI in Stage C HFrEF include the following (*Yancy et al 2016, Yancy et al 2017):*
  - The clinical strategy of inhibition of the RAAS with ACE-Is or ARBs or ARNI in conjunction with evidence-based beta blockers, and aldosterone antagonists in selected patients, is recommended for patients with chronic HFrEF to reduce morbidity and mortality. (Sacubitril/valsartan is recommended with a lower level of evidence than ACE-Is and ARBs.)
  - The use of ACE-Is is beneficial for patients with prior or current symptoms of HFrEF to reduce morbidity and mortality.
  - The use of ARBs to reduce morbidity and mortality is recommended in patients with prior or current symptoms of chronic HFrEF who are intolerant to ACE-Is because of cough or angioedema.
  - In patients with chronic symptomatic HFrEF NYHA Class II or III who tolerate an ACE-I or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality.
  - ARNI therapy should not be administered concomitantly with ACE-Is or within 36 hours of the last dose of an ACE-I.
  - ARNI therapy should not be administered to patients with a history of angioedema.

SAFETY SUMMARY

- In July 2018, the FDA first issued a recall of several valsartan products that exceeded acceptable levels of a probable carcinogen, N-nitrosodimethylamine (NDMA). In October 2018, the presence of another impurity, N-nitrosodiethylamine (NDEA), was also discovered in certain valsartan products. Since then, voluntary recalls of other valsartan-, losartan-, and irbesartan-containing products have been announced due to nitrosamine impurities. NDMA is also found in water and certain foods, and has been shown to increase risk of cancer in animal studies. To provide context on the risk, the FDA has stated that if 8,000 people took 320 mg daily of the recalled valsartan for 4 years, one additional cancer case may occur over the course of the 8,000 people's lifetimes. To mitigate potential drug shortages, the FDA has announced interim limits for the nitrosamine impurities in ARBs, temporarily allowing distribution of medications that have between 0.96 and 9.82 parts per million of NDMA, to help ensure that an adequate supply is available on the market. In March 2019, the FDA announced that it expects that adequate supplies of losartan without nitrosamine impurities will be available in approximately 6 months. The FDA website is maintaining an updated list of recalled products and should be consulted to determine if a specific manufacturer and lot is recalled. *(FDA drug safety alert 2019)*.

Boxed Warnings

- Use during pregnancy should be avoided. When pregnancy is detected, ARBs should be discontinued as soon as possible. Drugs that act directly on the RAAS can cause injury and death to the developing fetus.

Contraindications

- ARBs are contraindicated in patients with DM who are also receiving Tekturna (aliskiren) therapy.
- ARB combinations containing diuretics (ie, HCTZ, chlorthalidone) are contraindicated in patients with anuria.
- Nebivolol/valsartan is additionally contraindicated in patients with severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), and severe hepatic impairment.

- Sacubitril/valsartan is contraindicated in patients with a history of angioedema related to previous ACE-I or ARB therapy, concomitant use with aliskiren in patients with diabetes, or ACE-Is in all patients. Sacubitril/valsartan should not be administered within 36 hours of switching from or to an ACE-I.

Warnings and Precautions

- In general, ARBs have warnings for fetal toxicity, hypotension (especially in volume- or salt-depleted patients), impaired renal function, and hyperkalemia/electrolyte imbalances. Treatment should be discontinued when pregnancy is detected.
  - Candesartan and olmesartan have warnings for morbidity in infants < 1 year of age.
  - Olmesartan has a unique warning for sprue-like enteropathy, which is manifested by severe, chronic diarrhea with substantial weight loss.
  - Telmisartan has a unique warning for use in patients with impaired hepatic function, as it is eliminated mostly by biliary excretion.
- Diuretics (ie, HCTZ, chlorthalidone) may alter glucose tolerance and raise levels of cholesterol, triglycerides, and serum uric acid levels (which may precipitate gout). Diuretics may cause elevations of serum calcium and monitoring is recommended in patients with hypercalcemia.
  - HCTZ may also cause an idiosyncratic reaction resulting in acute transient myopia and acute angle-closure glaucoma.
  - Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.
- Nebivolol has warnings for abrupt cessation of therapy, cardiac failure, bronchospastic diseases, thyrotoxicosis, and peripheral vascular disease.
- Amlodipine has warnings for increased angina and acute myocardial infarction, and hepatic impairment.
- Sacubitril/valsartan has additional warnings for angioedema, hypotension, a risk of decreased or impaired renal function in susceptible patients, and hyperkalemia.

Adverse Effects

- Common adverse effects with ARBs include hypotension, dizziness, back pain, and headache.
  - The most common adverse reaction with azilsartan is diarrhea.
- The CCB amlodipine may cause peripheral edema.
- The most common adverse effects reported (incidence ≥ 5%) with sacubitril/valsartan include hypotension, hyperkalemia, cough, dizziness, and renal failure. With regard to hypotension, a recent Institute for Safe Medication Practices (ISMP) Quarter Watch reported that many patients initiating therapy on sacubitril/valsartan experienced significant complications ranging from dizziness to blackouts and other consequences serious enough to require hospitalization (*ISMP Quarter Watch 2017*).
- The FDA has required post-marketing studies for sacubitril/valsartan in order to assess the incidence of angioedema in patients of African or Caribbean descent (Black patients) and the risk of cognitive dysfunction in HF patients with HFpEF (*FDA approval letter 2015*). Postmarketing reports include hypersensitivity, including rash, pruritus, and anaphylactic reactions.
- Experts have raised questions regarding the potential for impact on cognitive dysfunction due to the mechanism of action of sacubitril/valsartan, particularly in patients with Alzheimer's disease. The concern is specifically around the sacubitril component and issues with neprilysin inhibition in the brain. Theoretically, neprilysin inhibition could lead to amyloid deposits, which has been linked to dementia.
- According to pharmacodynamic studies, sacubitril/valsartan 400 mg (2 x 97/103 mg tablets) once daily increased cerebrospinal fluid amyloid-β ($A\beta_{1-38}$) concentrations after 2 weeks in healthy patients. Also, the active metabolite (LBQ657) does minimally cross the blood brain barrier. The clinical relevance of increased concentrations is unknown (*Vodovar et al 2015*).

Important Drug Interactions

- Dual blockade of the RAAS with ACE-Is, ARBs, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure).
  - Most patients receiving the combination of 2 RAAS inhibitors do not obtain any additional benefit compared to monotherapy.
  - Avoid use of aliskiren with ARBs in patients with renal impairment (glomerular filtration rate < 60 mL/min).

- In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, concomitant use of non-steroidal anti-inflammatory agents (NSAIDs) with ARBs may result in deterioration of renal function, including acute renal failure. The antihypertensive effect of ARBs may be attenuated by NSAIDs.
- Concomitant use of ARBs and potassium-sparing diuretics (eg, spironolactone, amiloride, triamterene) can increase the risk of hyperkalemia.
- ARBs may increase serum lithium concentration; lithium levels should be monitored.
- Concurrent administration of the bile acid sequestering agent, colesevelam hydrochloride, reduces the systemic exposure and peak plasma concentration of olmesartan.
- Concomitant use of telmisartan and ramipril is not recommended due to increased exposure to ramipril and ramiprilat.
- HCTZ absorption is impaired in the presence of anionic exchange resins (ie, cholestyramine and colestipol resins).
- Concomitant use of HCTZ with carbamazepine has been associated with an increased risk for symptomatic hyponatremia.
- Nebivolol should not be used with cytochrome P450 (CYP) 2D6 inhibitors.
- Amlodipine should not be coadministered with doses higher than 20 mg of simvastatin per day.
- Exposure to amlodipine is increased with CYP3A4 inhibitors.

DOSING AND ADMINISTRATION

- In general, the safety and efficacy of ARBs have not been established in severe hepatic impairment.
- ARB combination products containing diuretics are not recommended in patients with severe renal impairment.
- Some ARB combination products are not recommended as initial therapy in patients with hepatic impairment because the recommended ARB starting dose is not available in the fixed-dose combination product.
- ARB combination products containing amlodipine are not recommended as initial therapy in elderly patients or patients with severe hepatic impairment because the recommended amlodipine starting dose of 2.5 mg is not available in the fixed-dose combination product.

Table 5. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single-Entity ARBs				
Atacand (candesartan)	Tablets	Oral	HTN: Once or twice daily HF: Once daily	Initiate with 8 mg once daily in moderate hepatic impairment.
Avapro (irbesartan)	Tablets	Oral	Once daily	
Benicar (olmesartan)	Tablets	Oral	Once daily	
Cozaar (losartan)	Tablets	Oral	Once daily	Initiate with 25 mg once daily in mild to moderate hepatic impairment.
Diovan (valsartan)	Tablets	Oral	HTN: Once daily HF/post-MI: Twice daily	Safety and efficacy not established in severe renal impairment
Edarbi (azilsartan)	Tablets	Oral	Once daily	
eprosartan	Tablets	Oral	Once or twice daily	Max 600 mg per day in moderate or severe renal impairment
Micardis (telmisartan)	Tablets	Oral	Once daily	
ARB/Diuretic Combinations				
Atacand HCT (candesartan/hydrochlorothiazide)	Tablets	Oral	Once daily	
Avalide (irbesartan/hydrochlorothiazide)	Tablets	Oral	Once daily	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Benicar HCT (olmesartan/hydrochlorothiazide)	Tablets	Oral	Once daily	
Diovan HCT (valsartan/hydrochlorothiazide)	Tablets	Oral	Once daily	
Edarbyclor (azilsartan/chlorthalidone)	Tablets	Oral	Once daily	
Hyzaar (losartan/hydrochlorothiazide)	Tablets	Oral	Once daily	
Micardis HCT (telmisartan/hydrochlorothiazide)	Tablets	Oral	Once daily	
ARB/Beta Blocker Combinations				
Byvalson (valsartan/nebivolol)	Tablets	Oral	Once daily	Not recommended in moderate to severe hepatic impairment or severe renal impairment.
ARB/CCB Combinations				
Azor (olmesartan/amlodipine)	Tablets	Oral	Once daily	
Exforge (valsartan/amlodipine)	Tablets	Oral	Once daily	
Twynsta (telmisartan/amlodipine)	Tablets	Oral	Once daily	
ARB/CCB/Diuretic Combinations				
Exforge HCT (valsartan/ amlodipine/hydrochlorothiazide)	Tablets	Oral	Once daily	
Tribenzor (olmesartan/ amlodipine/hydrochlorothiazide)	Tablets	Oral	Once daily	
ARB/Neprilysin inhibitor Combination				
Entresto (sacubitril/valsartan)	Tablets	Oral	Twice daily	Reduce initial dose for: • ACE-I/ARB naïve • Prior low dose of ACE-I/ ARB before initiating sacubitril/valsartan • Severe renal or moderate hepatic impairment

Abbreviations: ACE-I = angiotensin converting enzyme-inhibitor; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; HF = heart failure; HTN = hypertension; MI = myocardial infarction
See the current prescribing information for full details

CONCLUSION

- The single-entity and combination ARB products are FDA-approved for the treatment of HTN, and most are generically available. Some ARBs have additional indications for HF, diabetic nephropathy, or CV risk reduction in certain high-risk populations.
- Evidence-based guidelines recognize the important role ARBs play in the treatment of HTN and other CV and renal diseases. The current ACC/AHA guidelines recommend a BP goal of < 130/80 mm Hg for most patients *(Arnett et al 2019, Whelton et al 2018)*.
- ARBs have demonstrated efficacy in lowering SBP and DBP in patients with HTN.
  - Head-to-head trials have not consistently demonstrated superiority of one ARB compared to another.
  - Clinical trials assessing the ARB combination products in the treatment of HTN have demonstrated that, in general, dual therapy combinations of ARBs plus either HCTZ, nebivolol, or amlodipine achieve greater reductions in BP and higher BP control rates compared to monotherapy regimens. Head-to-head trials have not consistently demonstrated superiority of one combination product over another.
  - ARBs have generally demonstrated comparable efficacy to ACE-Is across indications.

- Studies have demonstrated that the combination of 2 inhibitors of the RAAS, including an ACE-I with an ARB, provides no renal or CV benefits and increased risk of adverse events, including hyperkalemia, hypotension, and renal dysfunction. All agents in this class have safety warnings against combined use.
- All ARBs have a boxed warning for use in pregnancy and are contraindicated in patients with DM who are also receiving aliskiren therapy. Other warnings include hypotension, renal failure, and hyperkalemia.
- Common adverse effects of ARBs include hypotension, dizziness, back pain, and headache.
- Current guidelines recommend ARBs as a first-line therapy for patients with HTN, DM with microalbuminuria, stable CAD with HTN, and post-MI *(Amsterdam et al 2014, de Boer et al 2017, Go et al 2014, Rosendorff et al 2015, Weber et al 2014, Whelton et al 2018).*
  - Due to differences in the activity of the RAAS, ARBs are often less effective as HTN monotherapy in black patients; CCBs and thiazide diuretics should be used as first-line options in these patients.
- Recent guideline updates from the ACC/AHA/HFSA state that in patients with chronic symptomatic HFrEF NYHA Class II or III who tolerate an ACE-I or ARB, replacement by an ARNI is recommended to further reduce morbidity and mortality (*Yancy et al 2016, Yancy et al 2017*).

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Therapeutic Class Overview
Pulmonary Arterial Hypertension Agents

INTRODUCTION

- Pulmonary arterial hypertension (PAH), a subtype of pulmonary hypertension (PH), is a chronic, life-threatening disease that is characterized by increased resistance in the pulmonary circulation caused by progressive pulmonary artery remodeling and constriction of the pulmonary vasculature (*Buckley et al 2013, Wu et al 2013*).
  - o PH is defined as a mean pulmonary arterial pressure (mPAP) of ≥ 20 mmHg at rest. In the past, PH was hemodynamically defined by an mPAP ≥ 25 mmHg; however, this cutoff was somewhat arbitrary and targeted at avoiding the over-detection of PH (*Rubin et al 2019*).
  - o Additionally, for patients with PAH, the diagnosis requires a pulmonary vascular resistance (PVR) ≥ 3 Wood units (*Rubin et al 2019*).
  - o PAH often manifests with clinical symptoms such as shortness of breath and decreased functional capacity, and eventually leads to right heart failure and death (*Gomberg-Maitland et al 2011*).
- Early recognition of PAH is essential and the gold standard for the clinical diagnosis of PAH is right heart catheterization (*Buckley et al 2013*).
- According to the 6th World Symposium on PH, the condition is classified into 5 World Health Organization (WHO) groups (*Simonneau et al 2019*):
  - o Group 1 – PAH
  - o Group 2 – PH secondary to left heart disease
  - o Group 3 – PH secondary to lung diseases and/or hypoxia
  - o Group 4 – PH due to pulmonary artery obstructions
  - o Group 5 – PH with unclear and/or multifactorial mechanisms
- Group I encompasses PAH, including idiopathic PAH, heritable PAH, drug- and toxin-induced PAH, and PAH associated with other disorders such as connective tissue disease, portal hypertension, human immunodeficiency virus infection, congenital heart disease, and schistosomiasis (*Simonneau et al 2019*).
- In addition to the diagnostic classification, patients may be stratified according to their WHO functional capacity, which was adapted from the New York Heart Association (NYHA) classification of left heart failure. A brief description of these functional classes (FC) is as follows (*Stringham et al 2010*):
  - o Class I: No limitation of physical activity
  - o Class II: Slight limitation of physical activity
  - o Class III: Marked limitation of physical activity
  - o Class IV: Inability to carry out any physical activity without symptoms
- The prevalence of WHO Group 1 PAH has been estimated at 7 to 26 cases per million adults (*Pogue et al 2016*). The disease has a poor prognosis and an approximate mortality rate of 15% within 1 year on therapy (*McLaughlin et al 2009*). The median survival in the 1980s was 2.8 years; this had improved to 7 years in the late 2000s (*Pogue et al 2016*).
- Pulmonary artery obstruction (Group 4), including chronic thromboembolic PH (CTEPH), is a leading cause of severe PH that results from thrombus formation leading to fibrous stenosis or complete obliteration of pulmonary arteries.
  - o The incidence of CTEPH is uncertain, but in a 2017 meta-analysis, the overall pooled incidence after pulmonary embolism was 2.3% (*Ende-Verhaar et al 2017*).
- Specific agents to treat PAH primarily target 3 pathways critical to its pathobiology: the prostacyclin, endothelin, and nitric oxide pathways (*Wu et al 2013*). There are currently 10 molecular entities within 5 therapeutic classes that are Food and Drug Administration (FDA)-approved for the treatment of PAH (*Lexicomp 2019*).
  - o Drugs active within the prostacyclin pathway are the prostacyclin analogues (PCAs) or prostanoids (intravenous [IV] epoprostenol; inhaled iloprost; and IV, subcutaneous [SC], inhaled, and oral treprostinil) and a prostacyclin receptor agonist (oral selexipag).
  - o Drugs active within the endothelin pathway are the endothelin receptor antagonists (ERAs) (oral ambrisentan, oral bosentan, and oral macitentan).
  - o Drugs active within the nitric oxide pathway are the phosphodiesterase-type-5 (PDE-5) inhibitors (IV and oral sildenafil and oral tadalafil) and a soluble guanylate cyclase (sGC) stimulator (oral riociguat).

- The goals of treatment include improvement in the patient's symptoms, quality of life (QOL), and survival. The optimal therapy for a patient should be individualized, taking into account many factors including severity of illness, route of administration, side effects, comorbid illness, treatment goals, and clinician preference (*McLaughlin et al 2009*).
- Initial management of PAH includes the use of warfarin, diuretics, and/or oxygen depending on the patient's diagnosis and symptoms. Prior to the initiation of advanced therapy, patients with PAH should undergo a vasoreactivity test. Oral calcium channel blockers (CCBs) are indicated only for patients who have a positive acute vasodilator response to testing (*Galiè et al 2015[b], McLaughlin et al 2009, Taichman et al 2014*).
- For patients who do not have a positive acute vasodilator response to testing and are considered low to moderate risk based on clinical assessment, oral mono- or combination therapy with certain agents are recommended. These include ERAs, PDE-5 inhibitors, a sGC stimulator, and a prostacyclin receptor (IP) agonist. In patients with high-risk disease, continuous treatment with an IV PCA therapy (epoprostenol or treprostinil) would be recommended. Combination therapy may be considered if patients are not responding adequately to monotherapy or are not candidates for monotherapy (*Barst, 2009, Galiè et al 2015[b], McLaughlin et al 2009, Taichman et al 2014*).
- The PAH agents are FDA-approved for the treatment of patients with WHO Group I PAH; however, there are differences in the study populations for which their FDA-approvals were based (*McLaughlin et al 2009*).
- Adempas (riociguat) is a first-in-class sGC stimulator with a dual mode of action involving endogenous nitric oxide that leads to increased generation of cyclic guanosine monophosphate (cGMP) with subsequent vasodilation. This agent has the additional FDA approval for treating adults with persistent/recurrent CTEPH after surgical treatment or inoperable CTEPH. Adempas is the first and only drug to be FDA-approved in the treatment of CTEPH. Pulmonary endarterectomy is curative for CTEPH, but it is technically demanding which may limit access to its use as a treatment (*Archer 2013*).
- In PAH, prostacyclin synthase is reduced resulting in inadequate production of prostacyclin I_2, a potent vasodilator with antiproliferative effects and an inhibitor of platelet aggregation (*McLaughlin et al 2009*). The PCAs, iloprost and treprostinil, were developed as chemically stable alternatives to epoprostenol, which requires continuous IV infusion due to its lack of stability (*Asaki et al 2015*). Orenitram (treprostinil) is the first FDA-approved oral PCA. It may represent a more convenient dosage form to the other treprostinil formulations (Remodulin and Tyvaso). However, patients with more severe PAH are likely to receive infused PCA rather than oral therapy (*McLaughlin et al 2009*). Among these agents, epoprostenol IV is the only agent that has demonstrated improved patient survival in high-risk PAH patients (*Galiè et al 2015[b]*). Uptravi (selexipag) works at the same pathway as the PCAs, but activates the IP receptor, also known as the prostacyclin receptor. Orenitram and Uptravi are the only orally administered agents that work within the prostacyclin pathway (*Asaki et al 2015*).
- Endothelial dysfunction in PAH causes increased production of endothelin-1 resulting in vasoconstriction, which is mediated by the endothelin receptors, ET_A and ET_B. Stimulation of ET_A causes vasoconstriction and cell proliferation, while stimulation of ET_B results in vasodilatation, antiproliferation and endothelin-1 clearance. The ERAs (Letairis [ambrisentan], Opsumit [macitentan], and Tracleer [bosentan]) competitively bind to both receptors with different affinities. Letairis and Opsumit are highly selective for the ET_A receptor, while Tracleer is slightly selective for the ET_A receptor over the ET_B receptor. In addition, Opsumit has a pharmacologically active metabolite and is considered "tissue-targeting" because it displays high affinity and sustained occupancy at the ET receptors in human pulmonary arterial smooth muscles. However, the clinical significance of receptor affinities of the ERAs has not been established (*McLaughlin et al 2009*).
- In patients with PAH, there is also an impaired release of nitric oxide by the vascular endothelium, thereby reducing cGMP concentrations. The PDE-5 enzyme is the predominant phosphodiesterase in the pulmonary vasculature and is responsible for the degradation of cGMP. The PDE-5 inhibitors, Revatio (sildenafil) and Adcirca (tadalafil), increase the concentrations of cGMP resulting in relaxation of the pulmonary vascular bed.
- Medispan class: Cardiovascular Agents, Miscellaneous – Prostaglandin Vasodilators; Pulmonary Hypertension: Endothelin Receptor Antagonists, Phosphodiesterase Inhibitors, Prostacyclin Receptor Agonist, and Soluble Guanylate Cyclase Stimulator.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
ERAs	
Letairis (ambrisentan)	✔
Opsumit (macitentan)	-
Tracleer (bosentan)	✔ *
PDE-5 inhibitors	
Adcirca (tadalafil)	✔ †
Revatio (sildenafil)	✔
Prostacyclin receptor agonist	
Uptravi (selexipag)	-
PCAs	
Flolan (epoprostenol)	✔
Veletri (epoprostenol)	-
Orenitram (treprostinil)	-
Remodulin (treprostinil)	✔
Tyvaso (treprostinil)	-
Ventavis (iloprost)	-
sGC stimulator	
Adempas (riociguat)	-

*Generic available for the tablet only. A generic is not available for the tablet for oral suspension formulation.
†Alyq (branded generic) and generically-named products.

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. FDA-approved Indications

Indication	Adcirca (tadalafil)	Adempas (riociguat)	Flolan (epoprostenol)	Letairis (ambrisentan)	Opsumit (macitentan)	Orenitram (treprostinil)	Remodulin (treprostinil)	Revatio (sildenafil)	Tracleer (bosentan)	Tyvaso (treprostinil)	Uptravi (selexipag)	Veletri (epoprostenol)	Ventavis (iloprost)
Treatment of PAH (WHO Group I) to improve exercise ability and delay clinical worsening				✔ *				✔ §	✔ †				
Treatment of PAH (WHO Group I) to improve exercise ability and capacity	✔ ¶		✔ ≠			✔ ¶¶	✔ ₴			✔ Ω		✔ ₳	
Treatment of PAH (WHO Group I) to delay/reduce risks of disease progression and reduce risk of hospitalization					✔ **						✔ ‡		

Treatment of PAH (WHO Group I) to improve exercise capacity, to improve WHO FC, and to delay clinical worsening		✔											
Treatment of PAH (WHO Group I) to improve a composite endpoint of exercise tolerance, symptoms, and lack of deterioration													✔ ¥
For patients who require transition from epoprostenol, to reduce the rate of clinical deterioration; risks and benefits of each drug should be carefully considered prior to transition							✔						
Treatment of persistent/recurrent CTEPH (WHO Group 4) after surgical treatment or inoperable CTEPH to improve exercise capacity and WHO FC		✔											
Treatment of PAH (WHO Group I), in combination with tadalafil to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability				✔ *									
Treatment of PAH (WHO Group I) in pediatric patients aged ≥ 3 years with idiopathic or congenital PAH to improve pulmonary vascular resistance, which is expected to improve exercise ability									✔				

Abbreviations: CTEPH=chronic thromboembolic pulmonary hypertension; FC=functional class; NYHA=New York Heart Association, PAH=pulmonary arterial hypertension, WHO=World Health Organization.

*Studies establishing effectiveness included predominantly patients with WHO FC II to III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%).

§The delay in clinical worsening was demonstrated when Revatio was added to background epoprostenol therapy. Studies establishing effectiveness were short-term (12 to 16 weeks) and included predominately patients with NYHA FC II to III symptoms and idiopathic etiology (71%) or associated with connective tissue disease (25%).

†Studies establishing effectiveness included predominately patients with WHO FC II to IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%).

¶Studies establishing effectiveness included predominately patients with NYHA FC II to III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).

≠Studies included predominately patients with NYHA FC III to IV symptoms and etiologies of idiopathic or heritable PAH (49%) or PAH associated with connective tissue diseases (51%).
¶¶The study that established effectiveness included predominantly patients with WHO FC II to III symptoms and etiologies of idiopathic or heritable PAH (75%) or PAH associated with connective tissue disease (19%). As the sole vasodilator, the effect on exercise is about 10% of the deficit, and the effect, if any, on a background of another vasodilator is probably less than this.
Ƨ Studies establishing effectiveness included predominately patients with NYHA FC II to IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), and PAH associated with connective tissue diseases (19%).
ΩStudies establishing effectiveness included predominately patients with NYHA FC III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).
₳Studies establishing effectiveness included predominately patients with NYHA FC III to IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.
**Effectiveness was established in a long-term study in PAH patients with predominantly WHO FC II to III symptoms treated for an average of 2 years. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).
‖Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominately patients with WHO FC II to III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%).
¥Studies establishing effectiveness included predominately patients with NYHA FC III to IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with connective tissue diseases (23%).
‡Effectiveness was established in a long-term study in PAH patients with WHO FC II to III symptoms. Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue diseases (29%), and PAH associated with congenital heart disease with repaired shunts (10%).

(*Prescribing information: Adcirca 2017, Adempas 2018, Flolan 2018, Letairis, 2018, Opsumit 2019, Orenitram 2017, Remodulin 2018, Revatio 2019, Tracleer 2019, Tyvaso 2017, Uptravi 2017, Veletri 2018, Ventavis 2017*)

NOTE: Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Adcirca (tadalafil)

- Adcirca was evaluated in the PHIRST study, a 16-week, randomized, double-blind, placebo-controlled trial consisting of 405 patients with predominantly WHO FC II or III symptoms. Treatment with Adcirca significantly improved exercise capacity, as measured by the 6MWD and reduced clinical worsening compared to placebo (*Galiè et al 2009*). In a 52-week extension trial, PHIRST-2, the improvements in 6MWD observed at the end of PHIRST appeared to be maintained through week 52 of PHIRST-2 (68 weeks total). In addition, 34% of patients enrolled in PHIRST-2 experienced an improvement in WHO FC compared to baseline of the PHIRST trial (*Oudiz et al 2012*).

Adempas (riociguat)

- The efficacy and safety of Adempas were evaluated in CHEST-1, a multinational, multicenter, double-blind,16-week trial in 261 adult patients with CTEPH. The majority of patients were WHO FC II (31%) or class III (64%). The primary endpoint of CHEST-1 was change from baseline in 6MWD after 16 weeks. Secondary endpoints included changes from baseline in pulmonary vascular resistance (PVR), N-terminal pro-brain natriuretic peptide (NT-proBNP) level, WHO FC, time to clinical worsening, Borg dyspnea score, QOL variables, and safety. Improvements in walking distance occurred beginning at week 2. At week 16, the placebo adjusted mean increase in 6MWD within the Adempas group was 46 m (95% confidence interval [CI], 25 m to 67 m; $p < 0.001$) (*Ghofrani et al 2013[a]*).
  - An open-label, non-comparative, extension study (CHEST-2) included 237 patients who completed CHEST-1. CHEST-2 consisted of an 8-week, double-blind dose-adjustment phase, followed by an open-label study phase that continued until Adempas received official approval and became commercially available. At the March 2013 cut-off date, 211 patients (89%) were receiving ongoing treatment, and 179 (76%) had received over 1 year of treatment. The safety profile of Adempas in CHEST-2 was similar to CHEST-1, with no new safety signals. Improvements in 6MWD and WHO FC observed in CHEST-1 persisted for up to 1 year in CHEST-2. In the observed population at 1 year, mean±standard deviation (SD) 6MWD had changed by 51±62 m (n = 172) versus CHEST-1 baseline (n = 237), and WHO FC had improved, stabilized, or worsened in 47, 50, or 3% of patients (n = 176) versus CHEST-1 baseline (n = 236). Of patients treated for 1 year in CHEST-2, 145 (92%) out of 157 were continuing to receive monotherapy, and 12 (8%) patients were receiving additional PH-specific medication (8 [5%] were receiving ERAs and 4 [3%] were receiving prostanoids). No patient required additional treatment with both an ERA and prostanoid at 1 year (Simmoneau et al 2015). An exploratory analysis noted a significant association with overall survival for

6MWD and NT-proBNP concentration at baseline (p = 0.0199, and 0.0183, respectively), and at follow-up (p = 0.0385, and 0.0068, respectively). Additionally, short-term improvements were associated with long-term survival and worsening-free survival. At 2 years, the overall survival rate was 93% (95% CI, 89 to 96%) and the rate of clinical worsening-free survival was 82% (95% CI, 77 to 87%) (*Simonneau et al 2016*). Due to lack of a control group and because certain outcomes were considered exploratory, data from this study must be interpreted cautiously.

- The efficacy and safety of Adempas were also evaluated in PATENT-1, a multinational, multicenter, double-blind, 12-week trial in 443 adult patients with PAH as defined by PVR > 300 dyn*sec*cm^{-5} and a PAP_{mean} > 25 mmHg. In this study, 50% of the patients were treatment-naïve with respect to PAH therapy, 44% were pre-treated with an ERA, and 6% were pretreated with a PCA (inhaled, oral, or SC). Patients were randomized to 1 of 3 treatment groups: placebo (n = 126), an exploratory capped titration arm of Adempas 1.5 mg 3 times daily (n = 63), or a capped maximum dose of Adempas 2.5 mg 3 times daily (n = 254). The primary endpoint of PATENT-1 was change from baseline in 6MWD after 12 weeks in the Adempas 2.5 mg group compared to placebo. Secondary endpoints included changes from baseline in PVR, NT-proBNP level, WHO FC, time to clinical worsening, Borg dyspnea score, QOL variables, and safety. At week 12, the placebo-adjusted mean increase in 6MWD within the Adempas 2.5 mg treatment group was 36 m (95% CI, 20 m to 52 m, p < 0.001). The group receiving the capped dose at 1.5 mg was excluded from the efficacy analysis (*Ghofrani et al 2013[b]*).
  - An open-label, non-comparative, extension study (PATENT-2) included 396 patients who completed PATENT-1. PATENT-2 consisted of an 8-week, double-blind dose-adjustment phase, followed by an open-label study phase that continues until all patients have transitioned to the commercially available drug. A total of 197 patients received Adempas monotherapy and 199 received Adempas in combination with an ERA or prostanoid, or both. The primary objective of the study was to assess the safety and tolerability of long-term Adempas treatment. Assessments took place at entry to PATENT-2, at weeks 2, 4, 6, 8, and 12, and every 3 months thereafter. At the March 2013 data cut-off, 324 patients (82%) were receiving ongoing treatment and 84% had received 1 year or more of treatment. Mean treatment duration was 95 weeks (median 91 weeks), and cumulative treatment exposure was 718 patient-years (Rubin et al 2015). An exploratory analysis concluded that there was a significant association between overall survival and 6MWD, NT-proBNP concentration, and WHO FC at baseline (p = 0.0006, 0.0225, and 0.0191, respectively), and at follow-up (p = 0.021, 0.0056, and 0.0048, respectively). Additionally, short-term improvements were associated with long-term survival and worsening-free survival. The estimated survival rate was 97% (95% CI, 95 to 98%) and rate of clinical worsening-free survival was 88% (95% CI, 85 to 91%) at 1 year and 79% (95% CI, 74 to 82%) at 2 years (*Ghofrani et al 2016*). Certain outcomes were considered exploratory, so data from this study must be interpreted cautiously.

Flolan (epoprostenol)

- The safety and efficacy of chronically-infused Flolan were evaluated in 2 similar, open-label, randomized trials of 8 to 12 weeks' duration comparing Flolan plus conventional therapy (eg, anticoagulants, oral vasodilators, diuretics, digoxin, oxygen) with conventional therapy alone in idiopathic or heritable PAH (NYHA Class II to IV) patients (n = 106). The average Flolan dose was 9.2 ng/kg/min at the trials' end. A statistically significant improvement was observed in the 6MWD in patients receiving Flolan plus conventional therapy for 8 to 12 weeks compared with those receiving conventional therapy alone. Improvements were noted as early as week 1. Increases in exercise capacity were accompanied by statistically significant improvement in dyspnea and fatigue, as measured by the Chronic Heart Failure Questionnaire and the Dyspnea Fatigue Index, respectively.
- The efficacy of chronically-infused Flolan in PAH and scleroderma spectrum of diseases (NYHA Class II to IV) was evaluated in an open-label, randomized, 12-week trial (n = 111) comparing Flolan plus conventional therapy with conventional therapy alone. The mean Flolan dose was 11.2 ng/kg/min at the end of week 12. Statistically significant improvement was observed in the 6MWD in patients receiving continuous Flolan plus conventional therapy for 12 weeks compared to those receiving conventional therapy alone. Increases in exercise capacity were accompanied by statistically significant improvement in dyspnea and fatigue, as measured by Borg Dyspnea Index and Dyspnea Fatigue Index. At week 12, the NYHA FC improved in 41% of patients treated with Flolan plus conventional therapy compared to none of the patients treated with conventional therapy alone. However, the majority of patients in both treatment groups showed no change in FC, with 4% of the Flolan plus conventional therapy group and 27% of conventional therapy group alone worsening.

Letairis (ambrisentan)

- The safety and efficacy of Letairis in the treatment of PAH were established in the ARIES trials. ARIES-1 and ARIES-2 were 12-week, randomized, double-blind, placebo-controlled trials that compared Letairis to placebo in 394 patients. Compared to placebo, treatment with Letairis resulted in a significant increase in exercise capacity as measured by 6MWD (*Galiè et al 2008[a]*). ARIES-E was the open-label extension study for ARIES-1 and ARIES-2. After 1 year of treatment, there was an improvement in 6MWD in the 2.5, 5 and 10 mg Letairis groups (25, 28 and 37 m, respectively). After 2 years of treatment, the improvement was sustained in the 5 and 10 mg groups (23 and 28 m), but not the 2.5 mg group (7 m) (*Oudiz et al 2009*).
- ARIES-3 was a long-term, open-label, single-arm, safety, and efficacy study of Letairis in patients with PH receiving Letairis 5 mg once daily for 24 weeks. The primary endpoint was change from baseline in 6MWD at week 24. Secondary efficacy endpoints included change in plasma NT-proBNP, Borg Dyspnea Index, WHO FC, time to clinical worsening of PAH, survival and adverse events (AEs). A total of 224 patients with PH due to idiopathic and familial PAH (31%), connective tissue disease (18%), chronic hypoxemia (22%), chronic thromboembolic disease (13%), or other etiologies (16%) were enrolled, and 53% of patients received stable background PAH therapies. After 24 weeks of therapy, there was an increase in 6MWD of 21 m (95% CI, 12 to 29), and a decrease in NT-proBNP of -26% (95% CI, -34 to -16%) observed in the overall population compared to baseline. However, increases in 6MWD were not observed in several non-Group 1 PH subpopulations. Peripheral edema, headache, and dyspnea were the most common AEs (*Badesch et al 2012*).
- The AMBITION trial (n = 610) was a double-blind, randomized, Phase 3/4 trial, which compared combination treatment with Letairis plus Adcirca to monotherapy with each in patients with WHO FC II or III symptoms. The study protocol was amended during the trial resulting in 17% of the initial protocol patients being excluded from the analysis, and treatment was administered significantly longer in the combination group vs. monotherapy groups (p = 0.03). Results demonstrated that patients receiving combination therapy had significantly fewer clinical failure events (defined as death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response) compared to patients receiving individual monotherapy (combination vs. pooled-monotherapy group, hazard ratio [HR] 0.5; 95% CI, 0.35 to 0.72; p < 0.001). Primary event outcomes were primarily driven by hospitalization. No significant differences were observed in terms of change in FC or all-cause death. The most common AEs that occurred more often with combination treatment included peripheral edema, headache, nasal congestion, anemia, and bronchitis (*Galiè et al 2015[a]*). Based on results from the AMBITION trial, the FDA-approved Letairis in combination with Adcirca to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability.

Opsumit (macitentan)

- The efficacy and safety of Opsumit on progression of PAH were demonstrated in a multicenter, Phase 3, event-driven, placebo-controlled trial (SERAPHIN) in 742 patients with symptomatic PAH (WHO FC II, III, or IV) with or without concomitant use of oral PDE-5 inhibitors, oral or inhaled PCAs, CCBs, or L-arginine for the 3 month period prior to randomization. Patients were randomized to placebo (n = 250), Opsumit 3 mg once daily (n = 250), or Opsumit 10 mg once daily (n = 242). The mean treatment durations were 85.3, 99.5, and 103.9 weeks in the placebo, Opsumit 3 mg, and Opsumit 10 mg groups, respectively. The primary study endpoint was time to the first occurrence of death, a significant morbidity event (defined as atrial septostomy, lung transplantation, initiation of IV or SC PCAs), or other worsening of PAH (defined as a sustained ≥ 15% decrease from baseline in 6MWD, worsening of PAH symptoms as determined by worsening of WHO FC, and need for additional treatment of PAH) during the double-blind treatment plus 7 days. Pre-specified secondary endpoints included change from baseline to month 6 in the 6MWD and percentage of patients with improvement in WHO FC. Other critical pre-specified secondary endpoints were time to PAH death or PAH hospitalization. The primary endpoint occurred in 46.4%, 38%, and 31.4% of the patients in the placebo, Opsumit 3 mg, and Opsumit 10 mg groups, respectively. Opsumit 10 mg once daily therapy resulted in a 45% reduction compared to placebo (HR, 0.55; 97.5% CI, 0.39 to 0.76; p < 0.001) in the occurrence of the primary endpoint to the end of the double-blind treatment. The beneficial effect of Opsumit 10 mg was primarily due to its reduction in clinical worsening (*Pulido et al 2013*).
  - In a sub-group analysis of the effect of Opsumit on hospitalizations, there were 117 (46.8%), 104 (41.6%), and 90 (37.2%) patients in the placebo, Opsumit 3 mg and 10 mg groups, respectively, who were hospitalized for any cause at least once during double-blind treatment, and they experienced a total of 171, 159, and 135 all-cause hospitalizations, respectively. Compared with that of placebo, the risk of all-cause hospitalization with Opsumit 3 mg was reduced by 18.9% (HR, 0.811; 95% CI, 0.623 to 1.057; p = 0.1208) and with Opsumit 10 mg by 32.3% (HR,

0.677; 95% CI, 0.514 to 0.891; p = 0.0051). Compared with placebo, the rate of PAH-related hospitalization was reduced by 44.5% in the Opsumit 3 mg group (p = 0.0004) and by 49.8% in the Opsumit 10 mg group (p < 0.0001). The mean number of annual hospital days for PAH-related hospitalizations was reduced by 53.3% in the Opsumit 3 mg arm (p = 0.0001) and by 52.3% in the Opsumit 10 mg arm (p = 0.0003). Due to the exploratory nature of this endpoint and small population, data from this study must be interpreted cautiously (*Channick et al 2015*).

Remodulin (treprostinil)

- The safety and efficacy of Remodulin were evaluated in 2 identical 12-week, multi-center, randomized, placebo-controlled, double-blind trials in a total of 470 patients with NYHA Class II, III, and IV PAH. Remodulin was administered SC at an average dose of 9.3 ng/kg/min. The effect on the 6MWD was small and did not achieve statistical significance at 12 weeks. For the combined populations, the median change from baseline for patients on Remodulin was 10 m and the median change from baseline on placebo was 0 m from a baseline of approximately 345 m. Remodulin significantly improved the Borg dyspnea score during the 6-minute walk test. Remodulin also consistently improved indices of dyspnea, fatigue, and signs and symptoms of PH. However, these results were difficult to interpret in the context of incomplete blinding to treatment assignment resulting from infusion site symptoms.

Orenitram (treprostinil)

- The efficacy and safety of Orenitram were evaluated in 3 multi-center, randomized, placebo-controlled, double-blind trials in 349 patients (FREEDOM-M), 350 patients (FREEDOM-C), and 310 patients (FREEDOM-C2).
  - FREEDOM-M compared twice daily administration of Orenitram with placebo in patients newly diagnosed with PAH and not receiving any background PAH treatment. The dose titration was based on patient's clinical response and tolerability. The primary endpoint was change in 6MWD over 12 weeks. The Orenitram group showed a significant improvement in 6MWD of 23 m (p = 0.0125). More than 50% of patients had an improvement of ≥ 20 m, and over 30% of patients had an improvement of > 50 m (*Jing et al 2013*). Orenitram demonstrated AEs typical of prostacyclin treatments (*Waxman 2013*).
  - FREEDOM-C and FREEDOM-C2 failed to meet the primary endpoint of improved 6MWD (*Tapson et al 2012, Tapson et al 2013*).

Revatio (sildenafil)

- The safety and efficacy of Revatio were evaluated in the SUPER-1 study, a 12-week, randomized, double-blind, placebo-controlled trial consisting of 278 patients with predominantly WHO FC II or III symptoms. Compared to placebo, Revatio significantly improved exercise capacity, as measured by the 6MWD, WHO FC symptoms and hemodynamics (*Galiè et al 2005*). In a 3-year extension study (SUPER-2), 46% of patients increased 6MWD relative to SUPER-1 baseline, 18% decreased 6MWD from baseline, 19% had died and 17% discontinued treatment or were lost to follow-up (*Rubin et al 2011*). The addition of Revatio to epoprostenol was evaluated in PACES, a 16-week, randomized, double-blind, placebo-controlled trial consisting of 267 patients receiving epoprostenol with predominantly WHO FC II or III symptoms. Revatio added to epoprostenol improved exercise capacity, hemodynamic measurements and time to clinical worsening more than epoprostenol plus placebo (*Simonneau et al 2008*).

Tracleer (bosentan)

- Tracleer was originally FDA-approved in PAH patients with WHO FC III and IV symptoms based on the results from 2 randomized, double-blind, placebo-controlled trials in 32 (Study 351) and 213 (BREATHE-1) patients treated for 16 and 12 weeks, respectively. In both studies, significant increases in the 6MWD were observed in all Tracleer groups compared to placebo. Tracleer was also associated with a significant reduction in dyspnea during walk tests and a significant improvement in WHO FC symptoms (*Channick et al 2001, Rubin et al 2002*). The FDA-approved indication was subsequently expanded to include patients with WHO FC II symptoms based on the results of the EARLY study consisting of 168 patients. In this 26-week study, treatment with Tracleer resulted in an increase in the 6MWD of 11.2 m compared to a decrease of 7.9 m in the placebo group; however, the difference was not statistically significant. The study did show a significant delay in clinical worsening and a lower incidence of worsening FC symptoms in the Tracleer group compared to placebo (*Galiè et al 2008[b], McLaughlin et al 2006*).
  - The results of an open-label extension phase of the EARLY trial suggested that the majority of patients exposed to long-term Tracleer therapy maintained or improved their FC. Approximately 20% of patients discontinued treatment because of AEs, which were most commonly PAH worsening (defined as death or initiation of IV or SC PCAs) and

elevated liver enzymes. Due to lack of a control group, data from this study must be interpreted cautiously (*Simmoneau et al 2014*).

- The COMPASS-2 trial (n = 334) was a prospective, double-blind, randomized controlled trial consisting of symptomatic PAH patients ranging from WHO FC II to IV who were taking stable Revatio doses (mean dose, 60 mg) for ≥ 3 months. Patients were randomized to Tracleer 125 mg twice daily plus Revatio or placebo plus Revatio for 16 weeks. There was no difference in the primary endpoint, time to the first morbidity/mortality event (defined as time to all-cause death, hospitalization for worsening PAH, initiation of IV prostanoid, atrial septostomy, lung transplant, or worsening PAH). There were also no significant differences in the individual measures of the primary endpoint; however, observed benefits were seen in terms of the mean 6MWD test. A high drop-out rate was observed during the trial; therefore, study power was reduced (*McLaughlin et al 2015*).

Tyvaso (treprostinil)

- The safety and efficacy of Tyvaso were evaluated in TRIUMPH I, a 12-week, multi-center, randomized, placebo-controlled, double-blind trial in WHO Group I PAH (98% NYHA Class III) patients who were receiving either Tracleer or Revatio (n = 235) for at least 3 months prior to study initiation. Patients received either placebo or Tyvaso in 4 daily treatments with a target dose of 9 breaths (54 mcg) per session. The primary endpoint, 6MWD, was measured at peak exposure (10 to 60 minutes post dose) and 3 to 5 hours after Tracleer or 30 to 120 minutes after Revatio. Patients receiving Tyvaso had a placebo-corrected median change from baseline in peak 6MWD of 20 meters (m) at week 12 ($p < 0.001$). The 6MWD measured at trough exposure (measured 4 hours after dosing) improved by 14 m.
- In a long-term follow-up of patients who were treated with Tyvaso in the pivotal study and the open-label extension (n = 206), Kaplan-Meier estimates of survival at 1, 2, and 3 years were 97%, 91%, and 82%, respectively. Of note, these observations were uncontrolled and therefore cannot be compared to the control group to determine the long-term effect of Tyvaso on mortality.

Uptravi (selexipag)

- The safety and efficacy of Uptravi were evaluated in the GRIPHON study (n = 1,156), a randomized, double-blind, placebo-controlled trial consisting of patients with predominantly idiopathic PAH, and WHO FC II or III symptoms. The median duration of treatment varied from 1.2 to 1.4 years for placebo and Uptravi, respectively, and treatment end was defined as 7 days after the last day of treatment intake. Compared to placebo, Uptravi significantly reduced the composite endpoint signifying the time to progression of PAH, defined as all-cause death or a PAH complication (27% vs. 41.6%; HR, 0.6; 99% CI, 0.46 to 0.78; $p < 0.001$); however, there were no differences in mortality between groups. The reduction in PAH complications was primarily driven by a reduction in disease progression (17.2% vs. 6.6%) and PAH-related hospitalization (18.7% vs. 13.6%). The safety of Uptravi compared to other agents in class is not clear. The GRIPHON pre-specified sub-group analysis did not stratify AEs by background treatment, but the study allowed stable doses of PDE-5 inhibitors and/or an ERA which accounted for approximately 80% of patients within the placebo baseline group. Those AEs that occurred significantly more often with Uptravi treatment included headache, diarrhea, jaw pain, nausea, myalgia, vomiting, extremity pain, flushing ($p < 0.001$ for all AEs), anemia ($p = 0.05$), and hyperthyroidism ($p = 0.004$) (*Sitbon et al 2015*).
- Frost and colleagues demonstrated that transitioning patients from inhaled treprostinil to Uptravi was effective and safe (*Frost et al 2018*). Of 34 enrolled patients, 32 (94.1%) stopped inhaled treprostinil and were receiving Uptravi, with 28 patients (82.4%) meeting all criteria for sustained treatment transition. In general, patients remained clinically stable throughout therapy and reported improved outcomes.

Veletri (epoprostenol)

- Please refer to the clinical efficacy summary for Flolan above.

Ventavis (iloprost)

- The efficacy of Ventavis was evaluated in a 12-week, randomized, multicenter, double-blind, placebo-controlled trial consisting of 203 patients with NYHA Class III PAH (majority), Class IV PAH, or CTEPH. Patients received 2.5 or 5 mcg of Ventavis 6 to 9 times daily during waking hours. The difference in the primary composite endpoint (10% increase in 6MWD 30 minutes after dose, improvement by at least one NYHA class compared to baseline, and no death or deterioration of PH) was statistically significant (19% vs. 4% placebo, $p = 0.0033$). The results for the CTEPH patients were not included in the aforementioned results, since there was inadequate evidence of benefit in this

patient population. The placebo-corrected difference in the 6MWD in Ventavis patients at 12 weeks was 40 m ($p < 0.01$).

- The safety of Ventavis was evaluated in a prospective, 2 year, open-label study with 63 PAH patients. Patients received Ventavis 2 to 4 mcg 6 to 9 times daily. Thirty-six patients completed at least 630 days of therapy, 19 patients dropped out prematurely, and 8 patients died. AEs were mild to moderate, the most common of which were cough and flushing. Two-year survival was found to be 87% [95% CI, 76% to 98%] (*Olschewski et al 2010*).

Meta-analyses and systematic reviews

- The results of a meta-analysis of 18 randomized controlled trials (n = 4,363) suggested that all oral PAH therapies confer a therapeutic benefit. More specifically, the findings showed:
  - PDE-5 inhibitors were associated with a statically significant reduction in mortality (relative risk [RR], 0.22; 95% CI, 0.07 to 0.71; p = 0.011), while other drugs only showed a trend toward reducing mortality.
  - Compared with placebo, ERAs, PDE-5 inhibitors, and riociguat significantly reduced clinical worsening, ameliorated WHO function class, and increased 6MWD. Oral prostanoids only showed a mild effect on 6MWD (19.88 m; 95% CI, 10.12 to 29.64, p = 0), and did not have any effect on reducing mortality and clinical worsening. Additionally, oral prostanoids significantly increased the incidence of treatment discontinuation due to AEs (RR, 3.41; 95% CI, 2.06 to 5.63; p = 0) (*Zheng et al 2014[a]*).
- A meta-analysis of 14 randomized controlled trials (n = 2,244) that evaluated the improvement in overall survival with use of oral, SC, IV, and inhaled PCAs, suggested the following:
  - Only IV PCAs showed a survival benefit (RR, 0.36; 95% CI, 0.16 to 0.79; p = 0.011), while oral (RR, 0.73; 95% CI, 0.32 to 1.66; p = 0.446), inhaled (RR, 0.28; 95% CI, 0.05 to 1.67; p = 0.162), and SC administration (RR, 0.91; 95% CI, 0.38 to 2.20; p = 0.837) did not show a benefit.
  - Overall mortality in the 14 studies was 3.30% (74 of 2,244 patients) with 2.52% (30 of 1,189 patients) mortality in the PCA-treated group and 4.17% (44 of 1,055 patients) mortality in the placebo group. The cumulative RR estimate of death showed a significant reduction of 44% (RR, 0.56; 95% CI, 0.35 to 0.88; p = 0.01), and no heterogeneity ($I^2 = 0.0\%$; p = 0.84) was detected among studies (*Zheng et al 2014[b]*).
- The results of a meta-analysis of 21 randomized controlled trials (n = 5,105) suggested that there was a reduction in the number of combined clinical worsening events (defined as all-cause mortality, lung or heart-lung transplant, hospitalization for PAH, and escalation of treatment) in patients with PAH with oral treatments, but showed less favorable effects on life expectancy in the short-term follow-up. Results demonstrated:
  - All classes reduced clinical worsening compared to placebo, including oral prostanoids (odds ratio [OR], 0.616; 95% CI, 0.419 to 0.906; p = 0.014), ERAs (OR, 0.504; 95% CI, 0.409 to 0.621; p < 0.001), PDE-5 inhibitors (OR, 0.468; 95% CI, 0.329 to 0.664; p < 0.001), and Adempas (OR, 0.277; 95% CI, 0.098 to 0.782; p = 0.015).
  - There were no significant reductions in mortality with any class versus placebo (*Zhang et al 2015*).
- A meta-analysis of 5 randomized controlled trials (n = 962) of < 16 weeks duration in adults and children treated with an sGC stimulator determined the following (all comparisons are vs. placebo):
  - sGC stimulators improve PAP in patients with PAH (who are treatment naïve or receiving a prostanoid or ERA) or those with recurrent or inoperable CTEPH.
  - Pooled analysis showed a mean difference in 6MWD of 30.13 m (95% CI, 5.29 to 54.96; $I^2 = 64\%$). On subgroup analysis, for PAH, there was no effect on 6MWD (11.91 m; 95% CI, -44.92 to 68.75; $I^2 = 77\%$), and for CTEPH, sGC stimulators improved 6MWD by a mean difference of 45 m (95% CI, 23.87 to 66.13; $I^2 = 0\%$).
  - The secondary outcome of mortality showed no change on pooled analysis.
  - Although pooled results demonstrated an increase (improvement) in WHO FC (OR, 1.53; 95% CI, 0.87 to 2.72; $I^2 = 49\%$), the results did not reach statistical significance. Also, there was no effect on clinical worsening (OR, 0.45; 95% CI, 0.17 to 1.14; $I^2 = 54\%$) or a reduction in MAP (−2.77 mmHg; 95% CI, −4.96 to −0.58; $I^2 = 49\%$). The pooled analysis did not show any significant difference in serious AEs (OR, 1.12; 95% CI, 0.66 to 1.90; $I^2 = 39\%$).
  - sGC stimulators should not be taken by people also receiving PDE-5 inhibitors or nitrates due to the risks of hypotension, and there is currently no evidence supporting their use in pulmonary hypertension associated with left heart disease (*Wardle et al 2016*).
- Several additional meta-analyses have been conducted evaluating ERAs, PDE-5 inhibitors, and PCAs. Notable observations in meta-analyses include the following:
  - Survival benefit was seen more with IV PCAs, especially in patients with more severe disease, compared with other routes such as oral and inhalation (*Ryerson et al 2010*).

- ERAs (Letairis and Tracleer) may have a somewhat lower effect on exercise tolerance in patients with connective tissue diseases, whereas PDE-5 inhibitors (Revatio and Adcirca) and the PCA epoprostenol showed consistent effects regardless of the presence or absence of connective tissue diseases (*Kuwana et al 2013*).
- Combination therapy appears to improve exercise capacity and reduce the risk of clinical worsening in PAH patients compared with monotherapy (*Zhu et al 2012*).
- Favorable effects on clinical events were not predicted by changes in the 6MWD (*Savarese et al 2012*). In addition, pulmonary hemodynamics correlated with exercise capacity, but not with clinical events (*Savarese et al 2013*).
- According to an Agency for Healthcare Research and Quality meta-analysis, prostacyclin analogues showed a statistically significant improvement in mortality. In addition, all drug classes improved 6MWD, but comparisons between agents were inconclusive. Combination therapy also improved 6MWD compared with monotherapy, but comparisons between specific regimens were inconclusive. Patients taking ERAs and PDE-5 inhibitors had a lower risk of hospitalization than those taking placebo, while the reduction in patients taking PCAs compared with placebo was similar, but not statistically significant (*McCrory et al 2013*).
- A meta-analysis including 15 RCTs comparing combination and monotherapy for the treatment of PAH found that the absolute risk reduction of clinical worsening was relatively constant beyond a 6 to 12-month treatment duration, and cast doubt on the need for trials of longer duration for measuring treatment efficacy in this population (*Lajoie et al 2017*).
- A Cochrane review of PDE-5 inhibitors for pulmonary hypertension concluded that these agents have clear beneficial effects in Group 1 PAH (*Barnes et al 2019*). For Group 2 PAH, there appears to be some benefit; however, it is unclear which type of left heart disease stands to benefit from therapy. Additionally, there is no clear benefit for PDE-5 inhibitors in PAH secondary to lung disease or CTEPH.

CLINICAL GUIDELINES

- Several published clinical guidelines on PAH are available.
  - The Chest Guideline and Expert Panel Report on pharmacologic therapy for PAH provides several options for initial and subsequent therapy (*Taichman et al 2014*).
    - Initial therapy: For patients in WHO FC II or III, monotherapy with an ERA, PDE-5 inhibitor, or sGC stimulator is recommended. In WHO FC III patients with evidence of rapid progression or markers of poor prognosis, a parenteral prostanoid should be considered. For patients in WHO FC IV, a parenteral PCA is recommended; however, if patients are unable or unwilling to manage a parenteral product, an alternative is an inhaled PCA combined with an ERA.
    - Subsequent therapy: For patients in WHO FC III who have evidence of progression or markers of poor prognosis, addition of an inhaled or parenteral prostanoid should be considered. In patients in WHO FC III or IV, if clinical status is unacceptable, a second (and if needed, a third) class of PAH therapy can be added.
  - The European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines for the diagnosis and treatment of PH (*Galiè et al 2015[b]*) provide several options for both monotherapy and combination therapy of PAH.
    - Monotherapy: For patients in WHO FC II, recommendations include an ERA, a PDE-5 inhibitor, an sGC stimulator, or a prostacyclin receptor agonist. For patients in WHO FC III, the same medications may be used, and another option is a PCA. PCAs (eg, epoprostenol) are generally preferred for patients in WHO FC IV.
    - Initial drug combination therapy: Only the combination of Adcirca and Letairis has a category I recommendation for patients in WHO FC II and III; this combination also has a category IIb recommendation for patients in WHO FC IV. Other double- and triple-therapy combinations are also options, including other ERA and PDE-5 inhibitor combinations (WHO FC II, III, and IV) and some combinations of oral therapies with parenteral PCAs (WHO FC III and IV).
    - Sequential drug combination therapy: Several options are provided for sequential combination therapy. Oral combinations are commonly recommended for patients in WHO FC II and III, including Opsumit added to Revatio, Adempas added to Tracleer, and Uptravi added to an ERA and/or a PDE-5 inhibitor. Other oral combinations and combinations of oral therapies with inhaled or parenteral agents may also be used in patients in WHO FC II, III, and/or IV, but in most cases these recommendations are not as strong.
  - A 2018 scientific statement on the evaluation and management of right-sided heart failure from the American Heart Association (AHA) summarizes data for the use of prostacyclin analogs, PDE-5 inhibitors, and endothelin receptor

agonists in patients with PAH (*Konstam et al 2018*). However, specific recommendations concerning the use of these agents in the PAH population are not provided in this document.
  - Reputable society groups agree that evidence supporting pediatric treatment is lacking. The AHA and American Thoracic Society (ATS) published a guideline on pediatric PH. This guideline states that in pediatric patients with lower-risk PAH, oral therapy with either a PDE-5 inhibitor or an ERA is recommended, and in pediatric patients with higher-risk PAH, IV or SC PCAs should be initiated without delay (*Abman et al 2015*). An expert consensus statement from the European Pediatric Pulmonary Vascular Disease Network, the International Society of Heart and Lung Transplantation, and the German Society of Pediatric Cardiology reaffirm the AHA/ATS guideline. Additionally, early combination therapy with oral PAH drugs in treatment-naïve children who are FC II or III may be considered (*Hansmann et al 2016*).

SAFETY SUMMARY

- sGC Stimulator
  - Adempas has a boxed warning due to embryo-fetal toxicity. It is contraindicated in pregnancy because it may cause fetal harm when administered to pregnant women.
  - Females can only receive Adempas through the Adempas REMS Program, a restricted distribution program that requires enrollment and certification of prescribers, patients, and pharmacies. The program also requires females of reproductive potential to comply with pregnancy testing and contraception requirements.
  - Adempas is contraindicated in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias.
  - Additional contraindications for Adempas include co-administration with nitrates or nitric oxide donors and PDE-inhibitors (specific and non-specific).
  - Warnings and precautions for Adempas include symptomatic hypotension, bleeding, and pulmonary edema in patients with veno-occlusive disease (if confirmed, treatment should be discontinued).
  - The most common AEs associated with Adempas include headache, dyspepsia and gastritis, dizziness, nausea, diarrhea, hypotension, vomiting, anemia, gastroesophageal reflux disease, and constipation.
- ERAs
  - The ERAs (Letairis, Opsumit, and Tracleer) have boxed warnings for embryo-fetal toxicity and/or risks of teratogenicity due to the potential for fetal harm when administered to women who are or may become pregnant.
  - The Letairis and Opsumit REMS programs, respectively, are designed in the same manner as the Adempas REMS program described above.
  - The Tracleer Access Program (T.A.P.) program has been re-listed as the Tracleer REMS program. As a requirement of the REMS, healthcare professionals who prescribe or dispense Tracleer must enroll and comply with the requirements. Requirements include monthly reviews of pregnancy tests in women of reproductive potential, and liver enzymes and bilirubin in all patients. All patients must understand the risks and complete an enrollment form.
  - Letairis has an additional contraindication for idiopathic pulmonary fibrosis (IPF).
  - Tracleer has an additional boxed warning for risks of hepatotoxicity and birth defects. Throughout treatment and for 1 month after stopping Tracleer, females of reproductive potential must use 2 reliable methods of contraception unless the patient has had a tubal sterilization or had an intrauterine device (IUD) inserted.
  - Drug Reaction with Eosinophilia and Systematic Symptoms (DRESS), anaphylaxis, rash, and angioedema have been reported with Tracleer.
  - Warnings and precautions for Adcirca and Revatio include prolonged erection (for more than 4 hours), hearing loss, and vision loss (in 1 or both eyes), all of which require immediate medical attention.
  - Pulmonary edema/fluid retention has been reported during postmarketing surveillance of Letairis and Tracleer. Fluid retention may occur within weeks after starting Letairis and is more common when Letairis is used in combination with Adcirca than with Letairis or Adcirca alone.
  - Use of Opsumit and Tracleer should be avoided in patients taking potent inhibitors or inducers of CYP3A.
  - Decreases in sperm count, decreased hemoglobin and hematocrit levels, and pulmonary edema (associated with pulmonary veno-occlusive disease (PVOD) have been observed in patients taking ERAs.
- PDE-5 Inhibitors
  - All PDE-5 inhibitor products have a contraindication for use in patients on nitrates as well as a warning with concomitant alpha blocker use due to resulting hypotension. The patient should allow 48 hours to elapse between

the last dose of Adcirca and taking nitrates. Additionally, Revatio and Adcirca are contraindicated for concomitant use with the sGC stimulator, Adempas.
  - In August 2012, the prescribing information for Revatio was updated with a warning stating that the use of Revatio in pediatric patients is not recommended due to increased mortality associated with higher doses and noted that lower doses are not effective in improving exercise capacity. The FDA clarified the warning related to pediatric use of Revatio in March 2014, stating it was not intended to suggest that Revatio never be used in children. The FDA acknowledged there may be situations in which the benefit-to-risk profile may be acceptable in individual children, for example, when other treatment options are limited, in which case Revatio can be used with close monitoring (FDA Drug Safety Communication, 2014).
  - Co-administration of Revatio or Adcirca with potent CYP3A inhibitors is not recommended. Co-administration of Adcirca with potent CYP3A inducers is not recommended.
  - Blood pressure lowering effects are increased when Adcirca is taken with alcohol.
  - Revatio and Adcirca are generally well tolerated with headaches, myalgia, flushing, and dyspepsia being the most common AEs reported for both products.
  - Stevens-Johnson syndrome and exfoliative dermatitis have been reported with Adcirca, and anaphylactic reaction, anaphylactic shock and anaphylactoid reaction have been reported with Revatio.
  - Vision loss, including permanent vision loss because of non-arteritic anterior ischemic optic neuropathy has been reported with the use of PDE-5 inhibitors.
- Prostacyclin Receptor Agonist
  - Uptravi has a warning/precaution to consider PVOD if acute pulmonary edema develops.
  - Uptravi is not recommended in patients with severe hepatic impairment (Child-Pugh Class C) and has not been studied in dialysis patients (or with eGFR < 15 mL/min/1.73m^2).
  - Concomitant administration of Uptravi is contraindicated with strong inhibitors of CYP2C8 (eg, gemfibrozil).
  - The most common AEs reported with Uptravi are headache, diarrhea, jaw pain, nausea, myalgia, vomiting, pain in extremity, and flushing. These AEs are more frequent during the dose titration phase.
- PCAs
  - Orenitram is contraindicated for use in patients with severe hepatic impairment (Child-Pugh Class C).
  - Flolan and Veletri are contraindicated in patients with heart failure due to severe left ventricular dysfunction. Additionally, Veletri is contraindicated in patients with pulmonary edema, stating that the development of pulmonary edema during dose initiation may be associated with pulmonary veno-occlusive disease.
  - Orenitram and Tyvaso both carry a warning/precaution related to an increased risk of bleeding, particularly in patients receiving anticoagulants. Additional warnings and precautions for Tyvaso include symptomatic hypotension, possible Tyvaso dose changes when inhibitors or inducers of CYP2C8 are added or withdrawn, and a possible increase in exposure or a decrease in tolerability with hepatic or renal impairment. Orenitram should be avoided in patients with blind-end pouches (diverticulosis).
  - The safety of Tyvaso and Ventavis has not been established in patients with significant underlying lung disease (eg, asthma, chronic obstructive pulmonary disease, acute pulmonary infections). Patients with acute pulmonary infections who are taking Tyvaso should be carefully monitored to detect any worsening of lung disease and loss of drug effect. Ventavis can induce bronchospasm.
  - Hypotension leading to syncope has been observed with Ventavis. It should not be administered in patients with a systolic blood pressure below 85 mmHg.
  - Flolan and Ventavis carry additional warnings and precautions regarding pulmonary edema. If signs of pulmonary edema occur, treatment should be stopped because this could be a sign of pulmonary venous hypertension or pulmonary veno-occlusive disease.
  - With Flolan, Orenitram, Remodulin, and Veletri, abrupt withdrawal (including interruptions in drug delivery) or sudden large reductions in the dose can worsen PAH symptoms (or cause rebound PH in patients taking Flolan).
  - Flolan carries additional warnings and precautions that include vasodilation reactions and an increased risk of bleeding.
  - Flolan, Remodulin, and Veletri are administered via an indwelling central venous catheter. This route of administration is associated with blood stream infections (BSI) and sepsis, which may be fatal. During long-term follow-up, sepsis was reported at a rate of 0.3 infections per patient per year in patients treated with Flolan. In an open-label study of IV Remodulin using an external infusion pump (n = 47), there were 7 catheter-related line infections during approximately 35 patient years, or about one BSI event per 5 years of use. A Centers for Disease Control and Prevention survey of 7 sites that used IV Remodulin for the treatment of PAH found approximately one

BSI event per 3 years of use. In an open-label study of an implantable pump (n = 60), there were 2 BSIs related to the implant procedure during approximately 265 patient-years. Continuous SC infusion (undiluted) is the preferred mode of administration of Remodulin. VELTERI was associated with chills/fever/sepsis/flu-like symptoms in 25% of patients in controlled trials for idiopathic or heritable PAH.

- Remodulin and Tyvaso exposure may increase or decrease when administered with strong inhibitors or inducers of CYP2C8.
- AEs reported with Tyvaso include cough, headache, throat irritation/pharyngolaryngeal pain, nausea, flushing, and syncope. AEs with Remodulin include infusion site pain, infusion site reaction, headache, diarrhea, nausea, rash, jaw pain, vasodilation, dizziness, edema, pruritus, and hypotension. The most common AEs reported with Orenitram include headache, diarrhea, nausea, and flushing.
- AEs associated with Ventavis include vasodilation (flushing), increased cough, headache, trismus, insomnia, nausea, hypotension, vomiting, increased alkaline phosphatase, flu syndrome, back pain, tongue pain, palpitations, syncope, increased gamma-glutamyl transpeptidase, muscle cramps, hemoptysis, and pneumonia.
- The most common AEs reported with Flolan and Veletri include dizziness, jaw pain, nausea, vomiting, headache, hypotension, flushing, and musculoskeletal pain.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Adcirca (tadalafil)	Tablet: 20 mg	Oral	Daily	Dividing the dose over the course of the day is not recommended.
Adempas (riociguat)	Tablet: 0.5, 1, 1.5, 2, and 2.5 mg	Oral	Three times daily	Patients who smoke may tolerate higher doses. If they stop smoking, dose decreases may be required. Lower starting doses should be considered in patients unable to tolerate the hypotensive effects and patients receiving strong CYP and P-gp/BCRP inhibitors. Adempas may be crushed and mixed with water or soft foods immediately before administration. Discontinue at least 24 hours prior to administering a PDE-5 inhibitor. Pregnancy test required prior to treatment initiation and monthly during treatment.
Flolan (epoprostenol)	Powder for injection: 0.5 and 1.5 mg	IV	Continuous infusion; Initiate infusion through a central venous catheter at 2 ng/kg/min; increase in increments of 1 to 2 ng/kg/min at intervals of at least 15 minutes based on clinical response	Abrupt withdrawal or sudden large reductions in infusion rates should be avoided. Continuous chronic infusion is administered through a central venous catheter. Temporary peripheral IV infusion may be used until central access is established.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Letairis (ambrisentan)	Tablet: 5 and 10 mg	Oral	Once daily (with or without tadalafil daily); titrate at 4-week intervals	Doses > 10 mg once daily have not been studied. Tablets should not be split, crushed, or chewed. Pregnancy test required prior to treatment initiation and monthly during treatment.
Opsumit (macitentan)	Tablet: 10 mg	Oral	Once daily	Doses > 10 mg once daily are not recommended.
Orenitram (treprostinil)	Extended-release tablet: 0.125, 0.25, 1, 2.5 mg, and 5 mg	Oral	Twice or 3 times daily; maximum dose is determined by tolerability; titrate not more than every 3 to 4 days as tolerated	Should be taken with food. Tablets should be swallowed whole. Coadministration with CYP2C8 inhibitors (eg, gemfibrozil) and the presence of mild hepatic impairment require a lower starting dose.
Remodulin (treprostinil)	Multi-dose vials for injection: 1, 2.5, 5, 10 mg/mL	SC, IV	Continuous infusion; initial dose for patients new to therapy: 1.25 ng/kg/min; increase in increments of 1.25 to 2.5 ng/kg/min at weekly intervals, depending on clinical response	SC is preferred, although administration via a central IV line can be performed if SC administration is not tolerated. An implantable IV infusion pump has recently been approved for use with Remodulin (Implantable System for Remodulin or ISR). Refer to the pump manufacturer's manual for specific instructions for use.
Revatio (sildenafil)	Tablet: 20 mg Powder for oral suspension: 10 mg/mL Solution for injection: 10 mg/12.5 mL	Oral, IV	Oral: 3 times daily approximately 4 to 6 hours apart Injection: IV bolus 3 times daily	Doses above 20 mg 3 times daily are not recommended. Revatio 10 mg injection dose is predicted to be the equivalent of a 20 mg oral dose. Revatio injection is for continued treatment of patients who are temporarily unable to take oral treatment. Oral suspension expires within 60 days of reconstitution.
Tracleer (bosentan)	Tablet: 62.5 and 125 mg Tablet for oral suspension: 32 mg	Oral	Twice daily (age and weight based dosing) Concurrent ritonavir: Once daily or every other day in patients who have been receiving ritonavir for ≥ 10 days; discontinue Tracleer at least 36 hours prior to initiation	Tablets for oral suspension should be dispersed in a minimal amount of water immediately before administration. Pregnancy test required prior to treatment initiation, monthly during treatment, and one month after stopping. Initiation should be avoided in patients with aminotransferases > 3x ULN. Doses > 125 mg twice daily do not have

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			of ritonavir; resume Tracleer 10 days following ritonavir initiation	additional benefit sufficient to offset the increased risk of hepatotoxicity.
Tyvaso (treprostinil)	Inhalation solution (solution, refill, and starter solution): 0.6 mg/mL (1.74 mg per 2.9 mL)	Inhale	3 breaths per treatment session, 4 times a day (4 hours apart); titrate by an additional 3 breaths per session in 1 to 2 week intervals; maximum: 9 breaths per treatment session, 4 times daily	Inhalation system consists of an ultrasonic, pulsed delivery device and its accessories.
Uptravi (selexipag)	Tablet: 200, 400, 600, 800, 1000, 1200, 1400, and 1600 mcg Titration pack: 200/800 mcg	Oral	Twice daily; titrate dose weekly	Swallow tablets whole. Food may improve tolerability.
Veletri (epoprostenol)	Powder for injection: 0.5 and 1.5 mg	IV	Continuous infusion; Initiate infusion at 2 ng/kg/min; increase in increments of 2 ng/kg/min at intervals of at least 15 minutes based on clinical response If symptoms persist or recur after improving, increase in increments of 1 to 2 ng/kg/min at intervals of at least 15 minutes	Abrupt withdrawal or sudden large reductions in infusion rates should be avoided. Continuous chronic infusion is administered through a central venous catheter. Temporary peripheral IV infusion may be used until central access is established.
Ventavis (Iloprost)	Inhalation solution: 10 and 20 mcg	Inhale	Administered 6 to 9 times per day (no more than once every 2 hours); maximum: 9 times daily	Ventavis is intended to be inhaled using the I-neb Adaptive Aerosol Delivery (AAD) System. The 20 mcg/mL concentration is for patients who are maintained at the 5 mcg dose and who have repeatedly experienced extended treatment times, which could result in incomplete dosing. Vital signs should be monitored while initiating Ventavis.

Abbreviations: CYP = cytochrome P450; IV = intravenous; P-gp/BCRP = P-glycoprotein/breast cancer resistance protein; SC = subcutaneous

CONCLUSION

- Pulmonary arterial hypertension (PAH) is a life-threatening disorder that is associated with a poor prognosis.
- There are 5 classes of drugs that are used in the management of PAH, including endothelin receptor antagonists (ERAs), phosphodiesterase (PDE)-5 inhibitors, a prostacyclin analog (PCA), a prostacyclin receptor agonist, and a soluble guanylate cyclase (sGC) stimulator.
- All of the PAH agents have shown improved pulmonary hemodynamics and exercise capacity in PAH patients as compared to placebo. Their effects on mortality have not been adequately demonstrated.
- Most trials for PAH have been relatively short-term trials (12 to 18 weeks) that evaluated changes in exercise capacity using the 6-minute walk distance (6MWD) as a primary endpoint. However, recently there has been a preference toward longer, event-driven trials that evaluate composite clinical worsening events (*LeVarge et al 2015*). Published event-driven trials include SERAPHIN, GRIPHON, AMBITION, and COMPASS-2 (*Galiè et al 2015[a], McLaughlin et al 2015, Pulido et al 2013, Sitbon et al 2015*).
- Clinical trials have demonstrated the safety and efficacy of the individual PAH agents; however, there is limited data comparing the agents within classes or between classes. Data are conflicting regarding the benefits of combination vs. monotherapy (*Barst, 2009, McLaughlin et al 2009, Galiè et al 2015[b], Taichman et al 2014*). Two recent trials evaluating this include the AMBITION and COMPASS-2 trials. The AMBITION trial has demonstrated that combination treatment with Letairis and Adcirca resulted in reduced disease progression and hospitalization in mainly FC II and III PAH patients compared to monotherapy (*Galiè et al 2015[a]*). However, the COMPASS-2 trial demonstrated no difference between Tracleer plus Revatio versus Revatio monotherapy for most endpoints with the exception of the mean 6MWD test (*McLaughlin et al 2015*).
- Adempas is the first and only drug to be FDA-approved in the treatment of CTEPH. Pulmonary endarterectomy can be curative for CTEPH, but it is technically demanding which may limit access to its use as a treatment. Adempas is dosed 3 times daily, which is more frequent than several other oral treatments for PAH.
- The ERAs (Letairis, Opsumit, and Tracleer) competitively bind to both receptors with different affinities. Letairis and Opsumit are highly selective for the ET_A receptor, while Tracleer is slightly selective for the ET_A receptor over the ET_B receptor. In addition, Opsumit has a pharmacologically active metabolite and is considered “tissue-targeting” because it displays high affinity and sustained occupancy at the ET receptors in human pulmonary arterial smooth muscles. However, the clinical significance of receptor affinities of the ERAs has not been established.
- The PDE-5 inhibitors (Adcirca and Revatio) are generally well tolerated; the most common side effects include headache, myalgia, flushing, dizziness, and gastrointestinal upset. Both products are contraindicated for use in patients on nitrates and have warnings about their use in patients on alpha-adrenergic inhibitors. Use of Adcirca with potent CYP3A inhibitors or inducers may significantly alter serum levels of Adcirca and is not recommended. Use of Adcirca in patients who are using an sGC stimulator may potentiate the hypotensive effects of sGC stimulators and is not recommended. Use of Revatio with potent CYP3A inhibitors is not recommended as they may significantly alter serum levels of Revatio.
- In addition to the oral tablet formulation, Revatio is available in an oral suspension formulation and an intravenous formulation.
- Adcirca is taken once a day compared to 3 times a day with Revatio.
- Orenitram is the first oral PCA approved by the FDA. The PCAs are frequently reserved for more severe forms of PAH. As the first oral option in this subclass for treatment of PAH, Orenitram may offer a more convenient alternative dosage form leading to earlier PCA initiation in treatment. Orenitram is dosed twice daily and requires dosage titration every 3 to 4 days. Orenitram did not demonstrate added benefit when added to other vasodilator therapy.
- Uptravi is a first-in-class prostacyclin receptor agonist, which works within the same pathway as Orenitram. Based on results from the GRIPHON trial, Uptravi has reduced disease progression and hospitalization. This is in contrast to Orenitram, which has only improved exercise tolerability. Unlike Orenitram, Uptravi has also demonstrated efficacy when combined with a PDE-5 inhibitor and/or an ERA. The safety of Uptravi compared to other oral agents in the class is not clear. The GRIPHON pre-specified sub-group analysis did not stratify AEs by background treatment, but the study allowed stable doses of PDE-5 inhibitors and/or an ERA throughout the trial. Background treatment was used by approximately 80% of patients within the placebo baseline group. Those AEs reported significantly more often with Uptravi treatment include headache, diarrhea, jaw pain, nausea, myalgia, vomiting, extremity pain, flushing, anemia, and hyperthyroidism (*Sitbon et al 2015*). Based on indirect trial evidence, the proportion of patients discontinuing Uptravi vs. placebo (14% vs. 7%) due to AEs in the GRIPHON trial was higher than those within the

Orenitram labeling vs. placebo (4% vs. 3%) (*Orenitram prescribing information 2014, Sitbon et al 2015*). Overall, it is not clear how the Uptravi safety profile compares to other agents in class due to different study populations. Head-to-head trials are needed to confirm safety risks and differences.

- The 2014 CHEST Guideline and Expert Panel Report update identifies PDE-5 inhibitors, ERAs, the oral PCA, and the sGC stimulator as viable alternatives in treating PAH adults with varying severity levels (FC II to IV) based primarily on consensus opinions (*Taichman et al 2014*).
- The 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) guideline stratifies PAH treatment by low-, intermediate-, or high-risk patients. In adult patients with low or intermediate risk (FC II to III), initial monotherapy or initial oral combination therapy is recommended. Based on the AMBITION trial, guidelines state that initial combination treatment with ambrisentan plus tadalafil has proven to be superior to initial monotherapy with ambrisentan or tadalafil in delaying clinical failure. In adult patients with high risk (FC IV), initial combination therapy including IV PCAs is recommended, with epoprostenol IV considered first-line due to the mortality benefits in trials (*Galiè et al 2015[b]*).
- Reputable society group guidelines agree that there is a lack of randomized trials in pediatric patients, making it difficult to deliver strong guidelines (*Abman et al 2015, Galiè et al 2015[b], Hansmann et al 2016*). The 2015 American Heart Association and American Thoracic Society guidelines recommend oral therapy with either a PDE-5 inhibitor or an ERA in lower-risk PAH pediatric patients. In pediatric patients with higher-risk PAH, IV and SC PCAs should be initiated immediately with a goal to transition patients to oral or inhaled therapy after the patient is asymptomatic and stable (*Abman et al 2015*). The 2015 ESC/ERS guidelines recommend that pediatric treatment follows adult guidelines, taking risks into account (*Galiè et al 2015[b]*). The European Pediatric Pulmonary Vascular Disease Network, the International Society of Heart and Lung Transplantation, and the German Society of Pediatric Cardiology reaffirm much of the aforementioned guidance, but also stipulate that early combination therapy with 2 oral PAH drugs in treatment-naïve children who are FC II or III may be considered (*Hansmann et al 2016*).
- A 2018 scientific statement on the evaluation and management of right-sided heart failure from the American Heart Association (AHA) summarizes data for the use of prostacyclin analogs, PDE-5 inhibitors, and endothelin receptor agonists in patients with PAH (*Konstam et al 2018*). However, specific recommendations concerning the use of these agents in the PAH population are not provided in this document.

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Therapeutic Class Overview
Omega-3 Fatty Acids

INTRODUCTION

- The independent relationship of triglycerides (TGs) to the risk of future cardiovascular disease (CVD) events has long been controversial (*Miller et al 2011*).
- Rich sources of omega-3-fatty acids come from fatty fish and plant sources, and fish oil contains eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).
  - Omega-3-fatty acids can reduce TG levels by approximately 27 to 45% (*Jellinger et al 2017*).
  - Select clinical trials suggest that relatively high doses of omega-3-fatty acids, in the form of fish, fish oils, or high-linolenic acid oils, reduce the risk for major coronary events in persons with established coronary heart disease; however, the overall body of literature does not offer convincing evidence that fish oil supplements are beneficial for preventing CVD or improving outcomes (*Abdelhamid et al 2018, National Cholesterol Education Program [NCEP] 2002, Smith et al 2011, Manson 2019*).
  - A 2018 large-scale randomized controlled trial (RCT) with Vascepa (icosapent ethyl) demonstrated a significant reduction in cardiovascular events when added to statin therapy in patients with elevated TG levels despite statin therapy (*Bhatt et al 2018*).
- The scope of this review will focus on Lovaza (omega-3-acid ethyl esters), Vascepa (icosapent ethyl), and Epanova (omega-3-carboxylic acids), which are all prescription omega-3 fatty acids Food and Drug Administration (FDA)-approved as adjunct therapy to diet to reduce TGs in adults with severe (≥ 500 mg/dL) hypertriglyceridemia.
  - Lovaza (omega-3-acid ethyl esters) is available as a 1 gram soft-gelatin capsule, containing approximately 375 mg and 465 mg of DHA and EPA, respectively.
  - Vascepa (icosapent ethyl) is available as a soft-gelatin capsule, containing icosapent ethyl, an esterified formulation of EPA. Vascepa contains ≥ 96% EPA (*LexiComp 2019*).
  - Epanova (omega-3 carboxylic acids) coated, soft-gelatin capsules contain at least 850 mg of polyunsaturated fatty acids, including multiple omega-3 fatty acids (predominantly EPA and DHA). Epanova was approved by the FDA in 2014, but has not been marketed to date (*Anon 2019*).
  - Omtryg and Triklo (omega-3-acid ethyl esters) have been discontinued.
  - Of note, there are several over-the-counter products containing omega-3 fatty acids that are marketed as nutritional supplements. These products do not have FDA-approved indications and may not contain the same amount of the active ingredient (*LexiComp 2019*).
- Omega-3 fatty acids have the potential to be used off-label for the treatment of coronary arteriosclerosis, familial combined hyperlipidemia, heart failure, and hyperlipidemia with TG levels < 500 mg/dL (*Micromedex 2019*).
- The 2018 American College of Cardiology/American Heart Association (ACC/AHA) Guideline on the Management of Blood Cholesterol provides recommendations based on a patient's overall atherosclerotic CVD (ASCVD) risk to guide appropriate treatment. Primary therapies in reducing ASCVD risk are adherence to a heart-healthy lifestyle and statin therapy. Omega-3 fatty acids and fibrates are recommended in patients with TGs ≥ 500 mg/dL, but neither agent is considered a low-density lipoprotein cholesterol (LDL-C)-lowering drug (*Grundy et al 2018*). Recent ACC/AHA recommendations on non-statin use do not consider the use of omega-3 fatty acids as they did not include therapies for severe hypertriglyceridemia (*Lloyd-Jones et al 2016, Lloyd-Jones et al 2017*).
- The National Lipid Association recommends omega-3 fatty acids, fibric acid derivatives, or niacin as first-line agents for patients with TG levels ≤ 1000 mg/dL. These agents may also be considered for patients with contraindications or intolerance to statin therapy (*Jacobson et al 2015*).
- The Endocrine Society Clinical Practice Guidelines state that omega-3 fatty acids, fibrates, and niacin may be considered as monotherapy or in combination with statins in patients with TG levels that are moderate (200 to 999 mg/dL, based on the Endocrine Society criteria) to severe (1000 to 1999 mg/dL, based on the Endocrine Society criteria) (*Berglund et al 2012*).
- The American Association of Clinical Endocrinologists and American College of Endocrinology recommend prescription omega-3 fatty acids 2 to 4 g for severe hypertriglyceridemia (TG > 500 mg/dL) (*Jellinger et al 2017*).
- Medi-Span Class: Antihyperlipidemics – Misc.

Table 1. Medications Included Within Class Review

Drug*	Generic Availability
Epanova (omega-3-carboxylic acids)†	-
Lovaza (omega-3-acid ethyl esters)*	✔
Vascepa (icosapent ethyl)	-

Omtryg and Triklo (omega-3-acid ethyl esters) are no longer marketed.
*Lovaza was initially marketed in the United States as Omacor.
†Epanova was approved by the FDA in 2014; no product launch date is available.

(*Drugs@FDA 2019 Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019; Anon 2019; Reliant Pharmaceuticals 2007*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Epanova (omega-3-carboxylic acids capsule)	Lovaza (omega-3-acid ethyl esters capsule)	Vascepa (icosapent ethyl capsule)
Adjunctive treatment to diet to reduce TG levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia	✔	✔	✔

(*Prescribing information: Epanova 2017, Lovaza 2019, Vascepa 2017*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- There are currently no head-to-head efficacy trials comparing Epanova (omega-3-carboxylic acids), Lovaza (omega-3-acid ethyl esters), or Vascepa (icosapent ethyl). One study compared the effects of an acylglycerol omega-3 formulation, which is often available in non-prescription omega-3 supplements to Lovaza. In this double-blind (DB) trial in patients with TG concentrations of 150 to 500 mg/dL, 120 patients were randomized to 5563 mg acylglycerol omega-3 daily, Lovaza 4 g daily, or placebo (olive oil). Both omega-3 groups had decreased TG concentrations compared with placebo ($p < 0.001$), but no difference was found between active treatments (28% reduction with acylglycerol omega-3 and 22% with Lovaza; $p = 0.785$). Because patients included in this study had mild to moderate elevations in TG levels at baseline, it is unclear if the acylglycerol omega-3 formulation would have similar results in patients with severe hypertriglyceridemia (*Hedengran et al 2015*).
- The EVOLVE study was a 12-week, DB, placebo (olive oil)-controlled, RCT that evaluated the safety and lipid-altering efficacy of Epanova (omega-3-carboxylic acids) in 399 adult patients with average serum TG concentrations of ≥ 500 mg/dL but < 2000 mg/dL at screening (1 and 2 weeks before random assignment). Patients were either treatment-naïve for dyslipidemia or using a stable (for at least 6 weeks before the first qualifying lipid measurement) dosage of a statin, cholesterol absorption inhibitor (CAI), or their combination. They were randomized to 1 of 4 treatment groups: placebo (olive oil) (n = 99), or Epanova 2 g (n = 100), 3 g (n = 101), or 4 g (n = 99). The Epanova 3 g group demonstrated a lower TG reduction than the other two active treatment groups. Treatment with Epanova 2 g and Epanova 4 g compared to placebo led to statistically significant reductions in fasting TG levels ($p < 0.01$ and $p < 0.001$, respectively) and in non-high-density lipoprotein cholesterol (HDL-C) levels ($p < 0.05$ and $p < 0.01$, respectively). However, there was a statistically significant increase in LDL-C levels in both active treatment groups ($p < 0.001$ for both) (*Kastelein et al 2014*).
- The ESPRIT trial was a 6-week, DB, parallel-group trial of 647 diet-stable patients with fasting TG levels ≥ 200 mg/dL and < 500 mg/dL (treated with a maximally tolerated dose of statin or statin with ezetimibe) and at high risk for CVD who were randomized to receive placebo (olive oil) capsules (n = 216), Epanova 2 g daily (n = 215), or Epanova 4 g daily (n

= 216) to assess the TG and non-HDL-C lowering efficacy of adding Epanova to existing statin therapy. Compared to placebo, both the Epanova 2 g and 4 g treatment groups demonstrated significant reductions in non-HDL-C levels ($p < 0.05$ for both) and TG levels ($p < 0.001$ for both). LDL-C was significantly increased compared to placebo in the Epanova 2 g group only ($p < 0.025$) (*Maki et al 2013*).

- Lovaza (omega-3-acid ethyl esters) and Vascepa (icosapent ethyl) (studied under the investigational name, AMR-101) were consistently associated with decreases in TG levels from baseline compared to placebo in studies of hypertriglyceridemia (*Ballantyne et al 2012, Bays et al 2011, Bays Maki et al 2010, Bays McKenny et al 2010, Calabresi et al 2000, Calabresi et al 2004, Davidson et al 2007, Durrington et al 2001, Eritsland et al 1996, GISSI-Prevenzione Investigators 1999, Johansen et al 1999, Koh et al 2012, Macchia et al 2013, Maki et al 2008, Maki et al 2010, McKeone et al 1997, Nilsen et al 2001, Nordoy et al 1998, Peters et al 2012, Pownall et al 1999, Risk and Prevention Study Collaborative Group et al 2013, Roth et al 2009, Stalenhoef et al 2000, Van Dam et al 2001*).
- In select placebo-controlled trials, Lovaza (omega-3-acid ethyl esters) was associated with an increase in LDL-C levels from baseline compared to placebo (*Bays Maki et al 2010, Calabresi et al 2000, Calabresi et al 2004, Koh et al 2012, Maki et al 2010, Pownall et al 1999, Roth et al 2009, Stalenhoef et al 2000*).
- Lovaza (omega-3-acid ethyl esters) was generally associated with an additive decrease in TGs and total cholesterol (TC) levels when added to a regimen containing a statin or a fibric acid derivative (*Bays Maki et al 2010 COMBOS, Bays McKenny et al 2010, Davidson et al 2007, Durrington et al 2001, Maki et al 2008, Maki et al 2010 COMBOS, Nordoy et al 1998, Peters et al 2012, Roth et al 2009*).
- When compared in head-to-head trials, Lovaza (omega-3-acid ethyl esters) was associated with similar decreases in cholesterol parameters from baseline compared to fenofibrate. When compared to gemfibrozil, 1 DB RCT demonstrated similar significant decreases in TGs and an increase in HDL and LDL cholesterol concentrations. However, a second RCT demonstrated that Lovaza (omega-3-acid ethyl esters) was associated with a significantly smaller decrease in TG levels from baseline (–28.9 vs –51.2%, respectively; $p = 0.007$). TC was decreased 10.2% with Lovaza, and 13.0% with gemfibrozil ($p = 0.51$) (*Koh et al 2012, Stalenhoef et al 2000, Van Dam et al 2001*).
- In placebo-controlled trials, Vascepa (icosapent ethyl) was not associated with an increase in LDL-C levels from baseline compared to placebo (*Ballantyne et al 2012, Bays et al 2011*).
- Outcomes data with Lovaza (omega-3-acid ethyl esters) have demonstrated mixed results when evaluating reduction in the risk of cardiovascular events.
  - The GISSI-Prevenzione trial demonstrated the beneficial effects of omega-3 acid ethyl esters in patients who have experienced a recent myocardial infarction (MI); omega-3-acid ethyl esters significantly reduced the risk of death, nonfatal MI, and nonfatal stroke compared to vitamin E. Treatment with omega-3 poly unsaturated fatty acids (PUFA), but not vitamin E, significantly lowered the risk of the composite of death, nonfatal MI, and nonfatal stroke (relative risk [RR], 0.10; 95% confidence interval [CI], 0.01 to 0.18; $p = 0.048$ by 2-way analysis and RR, 0.15; 95% CI, 0.20 to 0.25; $p = 0.023$ by 4-way analysis) (*GISSI-Prevenzione Investigators 1999*).
  - An RCT comparing Lovaza (omega-3-acid ethyl esters) to dietary therapy in patients admitted for coronary artery bypass grafting demonstrated a lower incidence of vein graft occlusion in the treatment group. After 1 year of therapy, the vein graft occlusion rate per distal anastomoses was 27% in the group receiving Lovaza (omega-3-acid ethyl esters) compared to 33% in the control group (odds ratio [OR], 0.77; 95% CI, 0.60 to 0.99; $p = 0.034$) (*Eritsland et al 1996*).
  - An RCT comparing Lovaza (omega-3-acid ethyl esters) to placebo in patients who were scheduled for elective coronary angioplasty demonstrated no difference in the rate of restenosis. This event occurred in 40.6% of the treated stenoses in the Lovaza (omega-3-acid ethyl esters) group and in 35.4% of the treated stenoses in the placebo group (OR, 1.25; 95% CI, 0.87 to 1.80; $p = 0.21$) (*Johansen et al 1999*).
  - An RCT comparing Lovaza (omega-3-acid ethyl esters) to placebo in patients with an acute MI demonstrated no difference in the rate of cardiovascular events and revascularizations. Of the patients receiving Lovaza (omega-3-acid ethyl esters), 28% experienced at least 1 cardiac event compared to 24% of patients in the placebo group ($p = 0.74$). There was no significant difference between the groups concerning the number, type, or severity of cardiac events (*Nilsen et al 2001*).
  - The Risk and Prevention Study compared Lovaza (omega-3-acid ethyl esters) to placebo in patients evaluated to be at a high cardiovascular risk and demonstrated no difference in the rate of death, nonfatal MI, and nonfatal stroke. The primary endpoint occurred in 1478 of 12,505 patients included in the analysis (11.8%), of whom 733 of 6239 (11.7%) had received omega-3 PUFA and 745 of 6266 (11.9%) had received placebo (hazard ratio [HR], 0.97; 95% CI, 0.88 to 1.08; $p = 0.58$) (*Risk and Prevention Study Collaborative Group et al 2013*).

- An RCT comparing Lovaza (omega-3-acid ethyl esters) to placebo in patients with confirmed symptomatic paroxysmal atrial fibrillation (AF) that required cardioversion, who had at least 2 episodes of AF in the 6 months before randomization, or both, demonstrated no significant difference in the rate of recurrence of symptomatic AF. At 12 months, 56 of 297 participants (18.9%) in the placebo group and 69 of 289 participants (24%) in the omega-3 PUFA group had a recurrent symptomatic AF (HR, 1.28; 95% CI, 0.90 to 1.83; p = 0.17) (*Macchia et al 2013*).

- Additionally, 1 large trial (VITAL), enrolling over 25,000 participants, studied the effects of omega-3 fatty acids and vitamin D supplementation vs placebo for reduction of cardiovascular events and cancer. Enrolled patients were at least 60 years of age (at least 65 years for women) with no significant cardiovascular or cancer history. Omega-3 supplementation use provided 840 mg omega-3 fatty acids (460 mg EPA and 380 mg DHA [as Omacor]). After a median of 5.3 years, no significant reductions in cardiovascular events (HR 0.92; 95% CI, 0.80 to 1.06) or cancer (HR 1.03; 95% CI, 0.93 to 1.13) vs placebo were seen (*Manson 2019*).
- The multicenter, randomized, DB, placebo-controlled REDUCE-IT trial (N = 8179) evaluated the effect of Vascepa (icosapent ethyl) on ischemic events in patients with elevated TGs despite statin therapy and established CVD (70.7%) or other risk factors (eg, diabetes). The primary endpoint was a composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina. After a median follow-up of 4.9 years, a primary endpoint event was observed in 17.2% of patients in the Vascepa (icosapent ethyl) group vs 22.0% of patients in the placebo group (HR, 0.75; 95% CI, 0.68 to 0.83; p < 0.001). The number needed to treat to avoid 1 primary endpoint event was 21 (95% CI, 15 to 33). Vascepa (icosapent ethyl) was also associated with a significant reduction in the key secondary endpoint (composite of cardiovascular death, nonfatal MI, or nonfatal stroke; HR, 0.74; 95% CI, 0.65 to 0.83; p < 0.001) (*Bhatt et al 2018*).
- Additionally, a formulation of icosapent ethyl has been marketed in Japan since 1994 under the trade name Epadel (ethyl-eicosapentaenoic acid, the active metabolite of icosapent ethyl). Published studies have evaluated this formulation as an adjunctive therapy with estriol and statins in the cardiovascular outcomes of this agent.
  - In a prospective, observational, 48-week trial, Epadel (ethyl-eicosapentaenoic acid) 1800 mg daily added to estriol 2 mg daily was compared to estriol 2 mg daily alone. TC decreased significantly from baseline in both groups. Serum levels of TGs decreased significantly from 194.5 to 141.5 mg/dL (-27. 2%; p = 0.001) in the study group but increased slightly from 192.9 to 207.4 mg/dL (+7.5%) in the control group at week 48 in the women whose level of TGs was not < 150 mg/dL (*Kurabayashi et al 2000*).
  - In an open-label (OL) trial, 900 to 1800 mg/day of Epadel (ethyl-eicosapentaenoic acid) was administered to patients with hyperlipidemia who had been treated with statins for an average of 30 months. Serum TC and TG concentrations were significantly decreased 3 months after the administration of Epadel (ethyl-eicosapentaenoic acid) (from 5.63 to 5.02 mmol/L, p < 0.05; from 2.07 to 1.08 mmol/L; p < 0.01, respectively) (*Nakamura et al 1999*).
  - In the Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS), a prospective, OL, blinded endpoint trial, 18,645 patients were randomly assigned to receive either 1800 mg of Epadel (ethyl-eicosapentaenoic acid) daily with a statin or statin therapy alone. The primary endpoint was any major coronary event, including sudden cardiac death, fatal and non-fatal MI, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. At a mean follow-up of 4.6 years, the primary endpoint occurred less frequently in the Epadel (ethyl-eicosapentaenoic acid) group compared to the control group (262 [2.8%] vs 324 [3.5%], respectively; RR, 0.19; p = 0.011) (*Yokoyama et al 2007*).
  - Seven sub-analyses have been published of the JELIS study.
    - The reduction in cardiovascular risk was greater in the Epadel (ethyl-eicosapentaenoic acid) group compared to the control group in patients unable to attain LDL-C and/or HDL-C goals (-38% reduced risk; p = 0.007), those with peripheral artery disease (HR, 0.44; 95% CI, 0.19 to 0.97; p = 0.041), those with preexisting coronary artery disease (CAD) and a TC ≥ 250 mg/dL (8.7% vs 10.7%, respectively; HR, 0.77, 95% CI, 0.63 to 0.96; p = 0.017) and regardless of the number of cardiovascular risk factors (hypercholesterolemia, obesity, high TG or low HDL-C, diabetes, and hypertension) (p < 0.05 for all comparisons) (*Ishikawa et al 2010, Matsuzaki et al 2009, Saito et al 2008 Sasaki et al 2012*).
    - The use of Epadel (ethyl-eicosapentaenoic acid) was associated with a significantly greater decrease in CAD compared to the control group in patients with impaired glucose metabolism, but not normoglycemic patients (p = 0.048 and p = 0.062, respectively) (*Oikawa et al 2009*).
    - Adherence to ≥ 80% of the medication regimen was associated with a decreased incidence of cardiovascular endpoints compared to those exhibiting < 80% adherence to study medications (p = 0.041) (*Origasa et al 2010*).
    - The incidence of secondary stroke was lower in the Epadel (ethyl-eicosapentaenoic acid) group compared to the control group (6.8 vs 10.5%, respectively; HR, 0.80; 95% CI, 0.64 to 0.997; p = 0.047); however, there was no

difference between groups in the incidence of primary stroke (1.5 vs 1.3%, respectively; HR, 1.08; 95% CI, 0.95 to 1.22; p = 0.244) (*Tanaka et al 2008*).

- A Cochrane systematic review of 79 RCTs examined the effects of fish- and plant-based omega-3 fatty acids on CVD. Increased intake of EPA or DHA had little or no effect on all-cause mortality or cardiovascular events; however, evidence included in this review was primarily from supplement trials (*Abdelhamid et al* 2018). Another meta-analysis of omega-3 fatty acids found no evidence of reduction in coronary heart disease events or major vascular events in patients at risk for cardiovascular events (*Aung et al 2018*).

CLINICAL GUIDELINES

- The 2018 ACC/AHA guidelines emphasize adherence to lifestyle and to statin therapy before considering the addition of an LDL-lowering nonstatin drug. Omega-3 fatty acids and fibrates are recommended in patients with TGs ≥ 500 mg/dL (*Grundy et al 2018*).
- Other guidelines (National Lipid Association and the American Association of Clinical Endocrinologists/American College of Endocrinology) suggest a potential role for other lipid-lowering therapies when treating hypertriglyceridemia including fibric acid derivatives, niacin, and omega-3 fatty acids (*Jacobson et al 2015, Jellinger et al 2017*).

SAFETY SUMMARY

- Omega-3 fatty acids have precautions for use in patients with hepatic impairment and fish allergy; these agents may also prolong bleeding time. Lovaza (omega-3 acid ethyl esters) and Epanova (omega-3-carboxylic acids) may be associated with increases in LDL-C. Additionally, Lovaza has a possible association with atrial fibrillation or flutter.
- The most common adverse reactions associated with Lovaza (incidence > 3% and greater than placebo) were eructation, dyspepsia, and taste perversion.
- The most common adverse reactions with Epanova (incidence ≥ 3% and greater than placebo) were eructation, nausea, diarrhea, and abdominal pain. Additional adverse reactions include vomiting, flatulence, and taste perversion.
- The most common adverse reaction associated with Vascepa (incidence > 2% and greater than placebo) was arthralgia.

DOSING AND ADMINISTRATION

- Prior to initiating therapy, TG levels should be assessed. Other causes of TG elevation (eg, diabetes mellitus, hypothyroidism, or medications) should be identified and managed.
- Patients should be placed on an appropriate lipid-lowering diet prior to receiving treatment and should continue diet during therapy.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Epanova (omega-3-carboxylic acids)	Coated soft gelatin capsule	Oral	Once daily	Administered without regard to meals in clinical trials
Lovaza (omega-3-acid ethyl esters)	Soft gelatin capsule	Oral	Once daily or in 2 divided doses	Administered with meals in clinical trials
Vascepa (icosapent ethyl)	Soft gelatin capsule	Oral	In t2wo divided doses	Should be administered with food

See the current prescribing information for full details

CONCLUSION

- Prescription omega-3 fatty acids are approved by the FDA for the treatment of severe hypertriglyceridemia. There is a generic formulation of Lovaza (omega-3-acid ethyl esters) currently available. Although approved in 2014, Epanova has not been marketed to date.

- In patients with an elevated TG level (≥ 500 mg/dL), a fibric acid derivative or niacin should be initiated before LDL-C lowering therapy to prevent pancreatitis. Omega-3 fatty acids represent an alternative to fibric acid derivatives and niacin for the treatment of hypertriglyceridemia. Select clinical trials suggest that relatively high doses of omega-3-fatty acids, in the form of fish, fish oils or high-linolenic acid oils, will reduce the risk for major coronary events in persons with established coronary heart disease; however, the overall body of literature does not offer convincing evidence that fish oil supplements are beneficial for preventing CVD or improving outcomes.
- Clinical trials have demonstrated that prescription omega-3 acid ethyl esters can effectively lower TGs, as well as positively affect other lipid/lipoprotein parameters when used as monotherapy or in combination with fenofibrate or statins.
- In select placebo-controlled trials, both Lovaza (omega-3-acid ethyl esters) and Epanova (omega-3 carboxylic acids) were associated with an increase in LDL-C levels from baseline compared to placebo.
- In placebo-controlled trials, Vascepa (icosapent ethyl) was not associated with an increase in LDL-C levels from baseline compared to placebo.
- Select cardiovascular outcomes studies have suggested a decrease in cardiovascular outcomes with Lovaza (omega-3 acid ethyl esters) and Vascepa (icosapent ethyl); however, certain trials have demonstrated no benefit compared to a control group.
- Epanova (omega-3-carboxylic acids) is the first FDA-approved prescription omega-3 in free fatty acid form, which produces higher bioavailability than esterified forms. Unlike the other prescription omega-3 fatty acids, Epanova can be taken without regard to meals. It has a similar safety profile as the existing available products.
- The 2018 ACC/AHA guidelines emphasize adherence to lifestyle and to statin therapy before considering the addition of an LDL-lowering nonstatin drug. Omega-3 fatty acids are a reasonable addition for patients with persistently elevated severe hypertriglyceridemia, along with implementing a very low-fat diet (*Grundy et al 2018*).

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Therapeutic Class Overview
Antivirals, Topical

INTRODUCTION

- Herpes simplex virus 1 (HSV-1) and HSV-2 cause a wide variety of illnesses, including mucocutaneous infections, central nervous system infections, and infections of the visceral organs. The 2 most common cutaneous manifestations of HSV infection are orolabial and genital herpes (*Cernik et al 2008)*. The Centers for Disease Control and Prevention (CDC) estimated a prevalence of HSV-1 and HSV-2 of 47.8% and 11.9%, respectively in 2015 to 2016 among adolescents and adults 14 to 49 years of age (*CDC 2018*). Both viral subtypes can cause orolabial or genital infections and are clinically indistinguishable; however, cold sores are most often caused by HSV-1, and genital herpes is most often caused by HSV-2 (*Corey 2018*).
- Herpes simplex is typically transmitted through close contact with a person who is shedding virus at a peripheral site, at a mucosal surface, or in genital or oral secretions. Contact must involve mucous membranes or open or abraded skin. Following transmission, the initial infection is associated with systemic signs and symptoms and involves both mucosal and extramucosal sites. Initial infections are also associated with higher complication rates and have a longer duration of symptoms and viral shedding from lesions. After inoculation and initial infection, HSV settles into nerves near the spine and becomes latent. From there, the virus can travel along the nerves, back to the skin and either reactivate (ie, new blisters or lesions are formed) or shed (ie, no new blisters or lesions are formed). The exact mechanism of reactivation is not completely understood; however, the frequency depends on the severity and duration of the initial episode, the infecting serotype (ie, HSV-1 or -2), and the host. In contrast to initial infections, associated symptoms, signs, and anatomic sites of recurrent infections are typically localized to a defined mucocutaneous site. Recurrent infections may also be associated with prodromal symptoms, which can occur in the absence of lesions, and vary from mild tingling sensations to shooting pains. Recurrent labial herpes infection affects approximately one-third of the US population. Typically, patients experience 1 to 6 episodes per year (*Cernik et al 2008*).
- Genital herpes is one of the most common viral sexually transmitted infections (STIs) in the world. In the US, between the periods of 1988 to 1994 and 1999 to 2004, the overall prevalence of HSV-2, the most common cause of genital herpes, declined 17%, from 21.3% of males and females infected with the virus to 17.6%. The prevalence in men declined most dramatically, from 17.3% to 11.2%, a 35% decrease (*Xu et al 2006*). Overall HSV-2 seroprevalence in 2005 to 2010 was 15.7%, suggesting a plateau in infection rates (*Bradley et al 2014*). Most people infected with HSV-2 have not been diagnosed. Many such persons have mild or unrecognized infections but shed virus intermittently in the genital tract. After resolution of primary infection, the virus persists in the nerve roots of the sacral plexus, causing recurrent (often less severe) outbreaks.
- Before the introduction of acyclovir as an antiviral drug in the early 1980s, cutaneous HSV infection was managed with drying agents and other local care. Today, treatment options include multiple oral, intravenous, and topical antiviral agents. Oral treatments are effective in reducing symptoms, while intravenous administration may be required in immunocompromised patients and those with severe disseminated infection (*Corey 2018*). Topical antivirals have minimal clinical benefit in genital herpes, and use should be discouraged (*CDC 2015*). No antiviral agent currently available will eradicate HSV, and thus treatment is aimed at managing rather than curing the disease.
- This review will focus on the topical agents for HSV.
- Medispan class: Antivirals, Topical and Antivirals, Topical Combinations

Table 1. Medications Included Within Class Review*

Drug	Generic Availability
Denavir (penciclovir)	-
Xerese (acyclovir/hydrocortisone)	-
Zovirax (acyclovir cream)	✔
Zovirax (acyclovir ointment)	✔

*In addition to the prescription products listed in the table, Abreva (docosanol) cream is available as an over-the-counter product (brand and generic).

(*Drugs@FDA 2019*, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications†

Indication	Denavir (penciclovir)	Xerese (acyclovir/ hydrocortisone)	Zovirax (acyclovir cream)	Zovirax (acyclovir ointment)
Early treatment of recurrent herpes labialis (cold sores) to reduce the likelihood of ulcerative cold sores and to shorten the lesion healing time (age ≥ 6 years)		✔		
Management of initial genital herpes				✔
Management of non-life-threatening mucocutaneous herpes simplex virus infections in immunocompromised patients				✔
Treatment of recurrent herpes labialis (cold sores) (age ≥ 12 years)	✔		✔ *	

* In immunocompetent patients

† Indication for Abreva (docosanol): Treatment of cold sores/fever blisters on face or lips to shorten healing time and duration of symptoms (age ≥ 12 years)

(*Prescribing information: Abreva 2014, Denavir 2018, Xerese 2014, Zovirax cream 2018, Zovirax ointment 2017*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Conflicting results have been observed among clinical trials with topical antivirals.
- In 2 placebo-controlled studies evaluating the efficacy of a 5-day treatment regimen of acyclovir 5% ointment for the treatment of genital herpes, viral shedding was reduced in acyclovir-treated patients, but no difference in healing time was demonstrated between groups (*Luby et al 1984, Reichman et al 1983*). Studies evaluating the efficacy of a regimen with duration greater than 5 days showed that acyclovir 5% ointment significantly reduced the duration of viral shedding from genital lesions, mean duration of local pain or itching, mean time to healing of lesions, and duration of new lesion formation when compared to placebo (*Corey et al 1982, Kinghorn et al 1983*). These studies also showed a significant decrease with acyclovir ointment in the average time to crusting and healing of lesions and duration for all symptoms in patients with recurrent episodes.
- When the efficacy of acyclovir 5% cream was evaluated against placebo for the treatment of genital herpes, only a significant decrease in the duration of itching was seen in the acyclovir group (*Kinghorn et al 1986*).
- A Cochrane review evaluating the effectiveness and safety of the different existing treatments for first-episode genital herpes on duration of symptoms and time to recurrence found low-quality evidence which did not show that topical antivirals reduced symptom duration for patients undergoing their first episode of genital herpes (mean difference [MD] -0.61 days, 95% confidence interval [CI] -2.16 to 0.95; 3 randomized controlled trials [RCTs], 195 participants, I^2 statistic = 56%) (*Heslop et al 2016*).
- Studies involving acyclovir 5% cream for the treatment of recurrent herpes labialis have demonstrated a significantly shorter mean clinician-assessed duration of herpes labialis episodes and mean patient-assessed duration of pain when compared to placebo (*Gibson et al 1986, Raborn et al 1997, Shaw et al 1985, Spruance et al 1984, Spruance et al 2002*). However, changes in healing time of lesions and the number of episodes per month were not found to be significantly different.
- When compared to placebo, patients with herpes labialis treated with penciclovir 1% cream were shown to have significant decreases in overall healing time, resolution of lesion pain, and resolution of symptoms including itching, tingling, burning, numbness, and tenderness (*Boon et al 2000, Raborn et al 2002, Spruance et al 1997*). Patients treated with penciclovir were also shown to have a significantly higher proportion of cases healed at 6 and 8 days. In RCTs by Femiano et al and Lin et al, penciclovir 1% cream was compared to acyclovir cream (5% and 3%, respectively).

Penciclovir showed significantly shorter time to crusting. However, the percent of patients cured at 7 days was not significantly different (*Femiano et al 2001, Lin et al 2002*).

- The combination cream Xerese (acyclovir 5%/hydrocortisone 1%) was shown to reduce the occurrence of ulcerative lesions in patients with a history of herpes labialis compared to placebo in a randomized, double-blind, placebo-controlled, patient-initiated clinical trial. Acyclovir/hydrocortisone reduced the progression of cold sores to ulcerative lesions and significantly reduced the lesion area compared with acyclovir and placebo (*Hull et al 2011*). The safety of acyclovir/hydrocortisone was also demonstrated in adolescents with herpes labialis (*Strand et al 2012*). Adverse events were similar to other clinical trials of the combination cream in adults.
- The topical antivirals have not been well studied in the immunocompromised patient population. A study involving 63 hospitalized immunocompromised patients with herpes simplex virus (regardless of virus type or infection site) who received acyclovir 5% ointment or placebo demonstrated that acyclovir significantly accelerated the clearance of virus ($p = 0.0006$), as well as significantly shortened the time to resolution of pain ($p = 0.004$) and total healing ($p = 0.038$) (*Whitley et al 1984*).
- No studies have been conducted which directly compare oral and topical formulations for the treatment of genital or orolabial herpes.

CLINICAL GUIDELINES

- National guidelines published by the CDC report that the topical antiviral agents offer minimal clinical benefit for genital herpes infections and should not be recommended over the oral antiviral agents (ie, acyclovir, famciclovir, and valacyclovir) (*CDC 2015).*
- The Guidelines for Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV recommend oral antivirals for treatment of orolabial or genital herpes infections. Prophylaxis with antiviral drugs to prevent primary HSV infection is not recommended. Severe mucocutaneous HSV lesions respond best to initial treatment with intravenous (IV) acyclovir. Suppressive therapy with oral antivirals is effective in preventing recurrences and is preferred for patients who have severe or frequent HSV recurrences or who want to minimize the frequency of recurrences *(Panel on Opportunistic Infections in Adults and Adolescents with HIV 2019*).

SAFETY SUMMARY

- Topical antivirals should not be applied to the eye.
- Safety and efficacy of the topical antivirals have not been established in patients with immunosuppression, except for acyclovir ointment, which can be used in limited non-life threatening mucocutaneous HSV infections in immunocompromised patients.
- Adverse effects are mostly local in nature. Common adverse events include application site reaction, dryness, burning or stinging with application, and pruritus.
- Due to the topical application of these products, drug interactions are not likely to occur.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency
Denavir (penciclovir)	1% cream	Topical	Every 2 hours while awake
Xerese (acyclovir/hydrocortisone)	5%/1% cream	Topical	5 times daily
Zovirax (acyclovir cream)	5% cream	Topical	5 times daily
Zovirax (acyclovir ointment)	5% ointment	Topical	6 times daily

See the current prescribing information for full details

CONCLUSION

- Denavir (penciclovir), acyclovir cream and Xerese (acyclovir/hydrocortisone) are indicated for the treatment of recurrent herpes labialis. Acyclovir ointment is indicated for the initial treatment of genital herpes and in limited non-life-threatening mucocutaneous HSV infections in immunocompromised patients.

- The topical antiviral agents have demonstrated efficacy compared to placebo for their FDA-approved indications. They are generally safe with no significant drug interactions and limited adverse events.
- Head-to-head trials for the treatment of oral and/or genital herpes simplex have not consistently demonstrated superiority of one product over another. In a comparison trial in the treatment of herpes labialis, penciclovir cream resulted in a quicker time to crusting and cessation of pain compared to acyclovir; however, there was no significant difference in time to healing (*Femiano et al 2001*). Lin et al also compared penciclovir and acyclovir in the treatment of herpes labialis, and found that there was no significant difference in clinical cure rates and time to healing (*Lin et al 2002*).
- National guidelines published by the CDC report that the topical antiviral agents offer minimal clinical benefit for genital herpes infections and should not be recommended over the oral antiviral agents (ie, acyclovir, famciclovir, and valacyclovir) (*CDC 2015).* The Guidelines for Prevention and Treatment of Opportunistic Infections in Adults and Adolescents with HIV recommend oral antivirals for the treatment of orolabial or genital herpes infections *(Panel on Opportunistic Infections in Adults and Adolescents with HIV 2019*). However, no studies have been conducted which directly compare oral and topical formulations for the treatment of genital or orolabial herpes.

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Therapeutic Class Overview
Scabicides and Pediculicides

INTRODUCTION

- Scabies and pediculosis are infestations of the skin caused by ectoparasites. Scabies is caused by the parasitic mite *Sarcoptes scabiei* and often results in an intense pruritic eruption and itching. Pediculi or lice can cause infestations either on the head (*Pediculus humanus capitis*), body (*Pediculus humanus corporis*), or the pubic region (*Pthirus pubis*). These skin conditions are common causes of skin rash and pruritus (*Roos et al 2001, Wendel et al 2002*). Head lice infestation crosses all social and geographic boundaries and generally affects children, primarily females, aged three to 12 years (*Feldmeier 2012*). Scabies occur in both sexes, at all ages, and in all ethnic and socioeconomic groups; however, one epidemiologic study reported a higher prevalence in urban areas among women and children (*Chosidow 2006, Downs et al 1999*). The ideal agent for the treatment of head lice is one with high pediculicidal (capable of killing lice) and ovicidal (capable of killing eggs) activity with minimal toxicity (*Villegas et al 2012*).
- The topical agents indicated for the management of scabies and head lice are listed in Table 1. All of the agents included in this review are Food and Drug Administration (FDA)-approved for the treatment of head lice with the exception of Eurax (crotamiton), which is only indicated to treat scabies. Lindane lotion indicated to treat scabies has been discontinued; the shampoo is still available for the treatment of lice.
- The pediculicidal effects of most of these agents result from their neurotoxic effects on lice. These agents, except benzyl alcohol, cause periods of central nervous system hyperexcitation, resulting in paralysis and ultimately death of the lice. Ulesfia (benzyl alcohol) is unique in that it disables the breathing structure of the lice, resulting in asphyxiation rather than neuroexcitation. Neurotoxic insecticides rely on the nervous system to exert their effect; therefore, newborn larvae are not susceptible to these agents since they do not develop a nervous system for several days after hatching. This presents a challenge for eliminating lice with a single treatment because the infestation typically includes lice from all stages of the life cycle, including newly hatched eggs.
- RID (piperonyl butoxide, pyrethrum extract) and NIX (permethrin) are pediculicidal, but not ovicidal, and therefore require nit combing and retreatment in 7 to 10 days to eradicate the infestation. Benzyl alcohol is not ovicidal and also requires a second treatment, but resistance is unlikely due to its unique mechanism of action. Malathion is both pediculicidal and ovicidal, but it is malodorous, requires 8 to 12 hours of application and is highly flammable. Lindane is neurotoxic and is not recommended as an initial treatment option. Sklice (ivermectin) and Natroba (spinosad) are pediculicidal but not ovicidal. Topical ivermectin is approved as a single application product only.
- Some data suggest a growing resistance to permethrin in the United States, with recent studies stating that the effectiveness of permethrin has declined to 25% and resistance to pyrethrins is widespread (*Koch et al 2016, The Medical Letter 2016*). However, both the United States Centers for Disease Control and Prevention (CDC) as well as the American Academy of Pediatrics (AAP) continue to recommend permethrin as first-line therapy for treatment of both lice and scabies. Permethrin 1% or pyrethrins should be used when resistance is not suspected. Malathion (in patients who are 6 years of age or older) and benzyl alcohol (in children older than 6 months) are available as alternative agents if the first-line medications are inappropriate or ineffective. Spinosad and ivermectin might prove helpful in difficult cases, but are more costly. Lindane is no longer recommended for use as treatment of head lice (*AAP Red Book 2018, CDC 2015[a], CDC 2015[b], CDC 2016, CDC 2018, Devore et al 2015, Downs et al 1999).*
- Medispan class: Scabicides and pediculicides and scabicide combinations.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Eurax (crotamiton cream and lotion)	✔ ‡
Lindane (gamma-hexachlorocyclohexane)*	✔
Natroba (spinosad)	✔
Ovide (malathion)	✔
Permethrin (Elimite 5%, NIX 1% lice treatment†)	✔
Piperonyl butoxide and pyrethrins (RID†)	✔
Sklice (ivermectin)**	-
Ulesfia (benzyl alcohol)	-

†Over-the-counter (OTC) product is available in at least one dosage form or strength. Not all product options are listed as there are a number of OTC products available.
‡Generic Crotan (crotamiton lotion) is available; the cream is brand only.
*Lindane shampoo is available; the lotion formulation has been discontinued.
**Another product, trade name Soolantra, is available as a 1% cream and is indicated for rosacea.

(Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Eurax (crotamiton)	Lindane (gamma-hexachlorocyclohexane)	Natroba (spinosad)	Ovide (malathion)	Permethrin (Elimite, NIX)	Piperonyl butoxide and pyrethrins (RID)	Sklice (ivermectin)	Ulesfia (benzyl alcohol)
Scabies	✔				✔ §#			
Head lice		✔ *	✔ ‡	✔ †	✔ ‖#	✔ ¶	✔ ‡	✔ ‡
Pubic (crab) lice		✔ *				✔ ¶		
Body lice						✔ ¶		

*Lindane shampoo is reserved for patients who cannot tolerate or have failed first-line treatment with safer medications for the treatment of head or pubic lice.
† In patients ≥ 6 years of age
‡ In patients ≥ 6 months of age
§ Permethrin 5% cream is indicated for the treatment of scabies.
‖ Permethrin 1% lotion/cream rinse is indicated for the treatment of head lice.
In patients ≥ 2 months of age
¶ In patients ≥ 2 years of age

(Clinical Pharmacology 2019; Prescribing information: Elimite 2015, Eurax 2012, Lindane 2009, Natroba 2014, Ovide 2017, Sklice 2017, Ulesfia 2015)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Scabies

- In studies comparing various topical agents for the treatment of scabies, a higher cure rate has been reported with permethrin compared to crotamiton and Lindane (*Amer et al 1992, Haustein et al 1989, Schultz et al 1990, Taplin et al 1986b, Taplin et al 1990, Zargari et al 2006*). In the largest study (N = 467), Schultz et al reported that there was a trend towards a higher cure rate with permethrin compared to Lindane; however, the difference was not statistically significant (*Schultz et al 1990*). In a single-blind, randomized controlled trial comparing ivermectin to crotamiton (N = 340), 2 applications of ivermectin were as effective as a single application of crotamiton cream for the treatment of scabies at 2 weeks. After repeating therapy, ivermectin was superior to crotamiton cream at 4 weeks follow-up (*Goldust et al 2014*).
- Both Lindane and permethrin have also been compared to oral ivermectin for the treatment of scabies. Numerous studies have demonstrated a significantly lower cure rate after 4 weeks with Lindane compared to oral ivermectin (*Goldust et al 2013, Madan et al 2001, Mohebbipour et al 2013*). However, another study found similar efficacy between the 2 agents at days 15 and 29 after treatment (*Chouela et al 1999*). Results from another study found that after a single application, permethrin was associated with a higher cure rate compared to ivermectin (*Usha et al 2000*).
- A Cochrane review evaluated 15 studies comparing topical permethrin, topical ivermectin, and oral ivermectin for scabies (*Rosumeck et al 2018*). The meta-analysis found no clear differences in rate of complete clearance of scabies between products, with the exception of the rate of complete clearance after 1 week when comparing topical permethrin to oral ivermectin (relative risk 0.65, 95% confidence interval [CI] 0.54 to 0.78). However, at weeks 2 and 4, there was no difference in the rate of complete clearance for that comparison. Rates of adverse events were similar between all evaluated therapies.
- A meta-analysis evaluated 52 studies comparing treatments for scabies to each other or placebo. These treatments included sulfur, benzyl benzoate, lindane, malathion, crotamiton, permethrin, oral or topical ivermectin, synergized pyrethrins, or herbal treatments. The primary outcome was either clinical or microscopic cure. Secondary outcomes included persistent itching and adverse events. Results of the direct meta-analysis demonstrated permethrin to be significantly better at achieving cure than oral ivermectin, lindane and crotamiton at 1 to 2 weeks and 3 to 6 weeks. Oral ivermectin demonstrated better cure rates than lindane. For persistent itching, oral ivermectin was significantly better than benzyl benzoate and lindane; permethrin was significantly better than lindane. No significant differences between treatments were observed in adverse events. According to the network meta-analysis, the highest probability of cure at 3 to 6 weeks was associated with permethrin + oral ivermectin followed by permethrin alone and topical ivermectin. Topical ivermectin followed by permethrin were the highest ranked to reduce persistent itching. The agents with the lowest probability for adverse events were synthetic pyrethrins, malathion, and oral ivermectin. Sulfur ranked highest in the probability for adverse events followed by permethrin + oral ivermectin (*Thadanipon 2019*).

Lice

- Benzyl alcohol has been evaluated in 2 multicenter, randomized, double-blind, vehicle-controlled studies in patients (6 months of age and older) with an active head lice infestation (N = 628). In both studies, 2 applications of benzyl alcohol were associated with a significantly greater chance of treatment success (zero live lice 14 days following final treatment) compared to vehicle ($p < 0.001$). The absolute difference in treatment success rates in study I was 71.4% in favor of benzyl alcohol (95% CI, 61.8 to 85.7%) and 48.8% (95% CI, 31.1 to 62%) in study II, again in favor of benzyl alcohol. In both studies, there was a lower incidence of treatment failure associated with benzyl alcohol compared to vehicle (3.3 vs 83.6% and 14.3 vs 60.7% in studies I and II, respectively; $p < 0.001$ for both) (*Meinking et al 2010*).
- Permethrin has demonstrated a higher rate of treatment success compared to Lindane in the treatment of lice following a single application (*Brandenburg et al 1986, Bowerman et al 1987, Kalter et al 1987, Taplin et al 1986a*). Compared to the combination of pyrethrins and piperonyl butoxide, permethrin has been shown to be significantly more efficacious (*Carson et al 1988, DiNapoli et al 1988*). Carson et al reported a cure rate of 96.3% for permethrin and a cure rate of 45.2% for the combination of pyrethrins and piperonyl butoxide at 7 days following treatment ($p < 0.005$) (*Carson et al 1988*). In multiple studies, malathion has been reported to be pediculicidal and ovicidal or had higher rates of cure when compared to permethrin (*Meinking et al 2004, Meinking et al 2007, Roberts et al 2000*).
- Two identical, vehicle-controlled studies demonstrating the safety and efficacy of ivermectin lotion in the treatment of head lice were completed in 781 patients (6 months of age and older) with head lice. The 2 studies showed that a higher percentage of patients treated with ivermectin lotion, without nit combing, were treatment responders (free of live lice at day 2 and through day 8 to the final evaluation at day 15) following a single application compared to vehicle application (combined study results for day 2: 94.9 vs 31.3%, respectively; day 8: 85.2 vs 20.8%, respectively; day 15: 73.8 vs 17.6%, respectively; $p < 0.001$ for each comparison). (*Pariser et al 2012*).

- Spinosad has been evaluated in 2 randomized, active-controlled trials of 1038 patients aged 6 months or older with an active head lice infestation. Patients received spinosad without nit combing or permethrin 1% topical solution with nit combing. Fourteen days following treatment, the spinosad without nit combing treatment arm had a greater proportion of lice-free patients compared to permethrin with nit combing ($p < 0.001$ for both trials). Moreover, the majority of patients treated with spinosad required only 1 course of treatment, compared to the majority of permethrin-treated patients who required 2 courses of treatment (p values not reported) (*Stough et al 2009*).

CLINICAL GUIDELINES

Scabies

- Current treatment guidelines from the CDC and the AAP state that permethrin 5% cream is the drug of choice for children 2 months of age and older with scabies. Crotamiton is available as another option for adult patients, but frequent treatment failures have been reported with this agent. Oral ivermectin may be considered for patients who fail treatment or for those who cannot tolerate topical therapies. Lindane is not recommended due to the risk of neurotoxicity, and the lotion formulation that was FDA-approved for scabies has been discontinued (*AAP Red Book 2018, CDC 2018, Clinical Pharmacology 2019, Gunning et al 2012, Strong et al 2010, WHO 2019*).
- Crusted scabies should be treated using oral ivermectin in combination with a topical agent (*CDC 2018*).
- Household members and sexual contacts of the affected individual should be treated even if they do not have any signs of an infestation, as it can take 2 to 5 weeks for symptoms to develop. To prevent re-infestation, all patients should be treated at the same time (*CDC 2018*).
- All clothing, bedding, and towels require decontamination by laundering in hot water and drying in a hot dryer, dry-cleaning, or sealing in a plastic bag for 72 hours. The use of a fumigant or insecticide spray is not recommended (*CDC 2018*).

Lice

- The CDC and the AAP recommend permethrin 1% as first-line antiparasitic therapy for the treatment of lice. For the treatment of head lice, therapy should be initiated with permethrin 1% or pyrethrins when there is no known resistance. Malathion (in patients 6 years of age or older) and benzyl alcohol (in patients 6 months of age and older) may be used when resistance to permethrin or pyrethrins is documented or when treatment with these products fails despite their correct use. Per the AAP, spinosad and ivermectin might prove helpful in difficult cases, but the cost of these preparations should be taken into account by the prescriber. Lindane is no longer recommended by the AAP for use in treatment of head lice (*AAP Red Book 2018, CDC 2015[a], CDC 2015[b], CDC 2016, Devore et al 2015, Downs et al 1999, Gunning et al 2012*).
- All clothing, bedding, and towels should be laundered in hot water and dried in a hot dryer to avoid another infestation. Items that cannot be washed can be placed in a hot dryer for 20 to 30 minutes, dry-cleaned, or sealed in a plastic bag for 2 weeks; combs and brushes should be soaked in hot water (at least 130 degrees Fahrenheit) for 5 to 10 minutes. The use of fumigants is not recommended (*CDC 2015[a], CDC 2015[b], CDC 2016*).
- Non-pharmacological tactics should be used to treat body lice, such as laundering clothing and bedding in hot water as well as regular bathing. If the prescriber determines that pharmacological treatment is necessary, the choice of pediculicide should follow the same guidelines as used for head lice (*CDC 2015[a], Gunning et al 2012*).
- The CDC recommends permethrin 1% or the combination of piperonyl butoxide and pyrethrins as equivalent therapies for pubic lice (*CDC 2015[b]*).

SAFETY SUMMARY

- Lindane carries a boxed warning for therapy placement, neurologic toxicity, contraindications, and proper use.
  - Lindane should only be used in patients who cannot tolerate or have failed first-line treatment with safer medications.
  - Neurologic toxicity has been reported with Lindane use, including seizures and deaths; use with caution in infants, children, the elderly, individuals with other skin conditions, and individuals who weigh less than 110 pounds (50 kg).
  - Lindane is contraindicated in premature infants and individuals with known uncontrolled seizure disorders.
  - Patients should be instructed on the proper use of Lindane including amount to apply, how long to leave on, and avoiding retreatment.
- Lindane is contraindicated in patients with crusted (Norwegian) scabies and other skin conditions such as atopic dermatitis or psoriasis that may increase systemic absorption of the drug.

- Malathion lotion is contraindicated in neonates and infants because their scalps are more permeable and may have increased absorption of malathion. Malathion lotion is flammable; patients should be instructed to allow hair to dry naturally after application and avoid use of any electric heat source.
- All topical scabicide and pediculicide products are contraindicated in patients with a sensitivity or allergy to any active or inactive ingredient in the product.
- For the class, adverse events are mostly dermatological in nature.
- Lindane should be used with caution with any drug that is known to lower the seizure threshold. Drug interactions for the remaining products in this class are minimal due to the topical application.
- Products have not been evaluated in the elderly; caution should be exercised when used in this population.

Table 3. Specific Populations

Drug	Pregnancy	Nursing Mothers	Pediatrics
Eurax (crotamiton)	Category C*	Lactation information is not available from the manufacturer so it is unknown whether excreted in breast milk; use with caution.	Safety and effectiveness in pediatric patients have not been established.
Lindane (gamma-hexachlorocyclohexane)	Category C*	Enters breast milk; use is contraindicated. Discard milk for at least 24 hours after application.	Avoid use in infants and young children due to a higher incidence of adverse reactions and risk of toxicity in this age group.
Natroba (spinosad)	Category B*	Spinosad is not present in breast milk. However, Natroba also contains benzyl alcohol which may be systemically absorbed through the skin. Use only if benefits outweigh the risks and discard breast milk for at least 8 hours after use.	Should not be used in children younger than 6 months old due to risk of benzyl alcohol toxicity.
Ovide (malathion)	Category B*	Unknown whether excreted in breast milk; use with caution.	Should not be used in children younger than 6 years old.
Permethrin	Category B*	Unknown whether excreted in breast milk; due to tumorigenic potential in animal studies, consider discontinuing nursing temporarily or withholding the drug while nursing	Should not be used in children younger than 2 months old.
Piperonyl butoxide and pyrethrins	Category C*	Unknown whether excreted in breast milk; use with caution.	Should not be used in children younger than 2 years old.
Sklice (ivermectin)	Unclassified†: No studies evaluating use in pregnant women. Observational studies have not revealed adverse effects; but these studies cannot definitively rule out any drug-associated risk.	Following oral administration, it is excreted in human milk in low amounts; this has not been evaluated following topical administration.	Should not be used in children younger than 6 months old.

Drug	Pregnancy	Nursing Mothers	Pediatrics
Ulesfia (benzyl alcohol)	Category B*	Unknown whether excreted in breast milk, but benzyl alcohol may be absorbed through the skin; use with caution.	Should not be used in children younger than 6 months old.

*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women. Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Eurax (crotamiton)	Cream (Eurax), lotion (Eurax)	Topical	Apply thoroughly from chin to toes, including skin folds and under fingernails; a second application is recommended 24 hours later. A cleansing bath should be taken 48 hours after the last application.	
Lindane (gamma-hexachlorocyclohexane)	Shampoo	Topical	Apply to dry hair and leave in place for 4 minutes. Then add a small amount of water until a good lather forms and immediately rinse. Retreatment is not recommended.	
Natroba (spinosad)	Suspension	Topical	Apply to dry scalp and hair; wash off after 10 minutes. A second treatment may be applied after 7 days if live lice are still seen.	
Ovide (malathion)	Lotion	Topical	Apply to dry hair. Leave on 8 to 12 hours then shampoo and rinse. May repeat with a second application after 7 to 9 days if lice are still present.	Product is flammable; avoid smoking, open flame, and hair dryers. Allow hair to dry naturally and uncovered.
Permethrin	Cream, crème rinse, lotion	Topical	Scabies: Apply cream from head to soles of feet. Wash off after 8 to 14 hours. Application may be repeated after 14 days if live mites are still present. Lice: Apply crème rinse/lotion on the scalp and damp hair. Leave on for 10 minutes then rinse with water. May repeat after 7 days if live lice are still present.	The 5% cream formulation is approved for scabies and is available by prescription only; the 1% crème rinse and lotion are approved for head lice and are available OTC.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Piperonyl butoxide and pyrethrins	Shampoo, crème rinse	Topical	Apply to hair and scalp. Leave on for no more than 10 minutes then rinse. Treatment should be repeated after 7 to 10 days on dry hair.	If first application is applied on wet hair, reapply after 24 hours.
Sklice (ivermectin)	Lotion	Topical	Apply to dry hair and scalp. Leave on for 10 minutes then rinse with water. Wait 24 hours before using shampoo. For single use only; do not re-treat.	
Ulesfia (benzyl alcohol)	Lotion	Topical	Apply to dry hair and scalp. Leave on for 10 minutes then rinse. Repeat treatment after 7 days.	

See the current prescribing information for full details

CONCLUSION

- There are a number of effective topical scabicide and pediculicide agents available including Eurax (crotamiton), Lindane (gamma-hexachlorocyclohexane), Ovide (malathion), Natroba (spinosad), permethrin (Elimite 5%, NIX 1%), piperonyl butoxide with pyrethrins (RID), Sklice (ivermectin) and Ulesfia (benzyl alcohol). Permethrin is recommended as first-line therapy for treatment of scabies and lice, despite increasing resistance in the United States (*Downs et al 1999, CDC 2016, Devore et al 2015*).
- Topical insecticides exert their pediculicidal and scabicidal effects through their neurotoxic actions on lice. Benzyl alcohol acts via asphyxiation of the parasite rather than neuroexcitation, theoretically lowering the risk of resistance. Ivermectin and spinosad are 2 newer agents approved for the treatment of head lice. Spinosad is not extensively metabolized, and therefore, it is still present and able to exert its effect when the lice eggs hatch and the nervous system develops. This may prevent the need for a second administration if no live lice are observed several days following the initial application (*Villegas et al 2012*). Ivermectin has been approved for one-time use. Permethrin 1% and the combination of pyrethrins and piperonyl butoxide are available OTC (*CDC 2016).* Lindane, a well-known older agent, is reserved as second-line therapy and carries a boxed warning describing risk of neurotoxicity associated with its use. Other available agents offer alternative options should resistance occur, or if a patient experiences treatment failure with a first-line product (*CDC 2016, Devore et al 2015*).
- Limited direct comparisons have been completed with agents in this class. Permethrin has demonstrated a higher rate of treatment success compared to Lindane in the treatment of lice following a single application (*Brandenburg et al 1986, Bowerman et al 1987, Taplin et al 1986a*). Compared to the combination of pyrethrins and piperonyl butoxide, permethrin was more efficacious several days following treatment; however, one study found the agents to be equally effective after 14 days (*Carson et al 1988, DiNapoli et al 1988*). Numerous studies have demonstrated a significantly lower cure rate after 4 weeks with Lindane compared to oral ivermectin (*Goldust et al 2013, Madan et al 2001, Mohebbipour et al 2013*); however, one study found no difference at days 15 and 29 following treatments (*Chouela et al 1999*). In multiple studies, malathion has been reported to be pediculicidal and ovicidal when compared to permethrin (*Meinking et al 2004, Roberts et al 2000*).
- The newer agents, which include benzyl alcohol, ivermectin, and spinosad, have shown cure rates (lice-free at day 14 or 15) of 75 to 76%, 71 to 76% and 84.6 to 86.7%, respectively, although there is limited published literature confirming these results.
- A comparison of the overall success rates for the topical scabicide products shows 89 to 100% success with permethrin, 65 to 92% with Lindane, and 60 to 88% with Eurax. A meta-analysis demonstrated permethrin to be significantly better at achieving cure than oral ivermectin, lindane and crotamiton at 1 to 2 weeks and 3 to 6 weeks (*Thadanipon 2019*). Current clinical guidelines recommend permethrin 5% as the drug of choice for the treatment of scabies. Lindane is not recommended due to its toxicity, and the lotion formulation that was approved for scabies has been discontinued; the

shampoo formulation is only approved for lice and should be reserved for patients who have exhausted medication options that pose less risk. For crusted scabies, oral ivermectin should be co-administered with a topical agent.

- Overall, topical pediculicides are effective in eradicating head lice, but generally do not have any effect on ova (nits). The guidelines from CDC and AAP recommend permethrin 1% or the combination of pyrethrins and piperonyl butoxide for head lice when resistance is not suspected (*AAP Red Book 2018, CDC 2016, Devore et al 2015*). Retreatment of head lice usually is recommended because most approved pediculicides are not completely ovicidal. Spinosad and malathion are the only ovicidal medications for the treatment of head lice, but the need for re-treatment has been reported (*CDC 2016*). Lindane is no longer recommended by the AAP for the treatment of head lice (*Devore et al 2015*).
- Body lice can be managed with nonpharmacological tactics such as laundering clothes and bedding in hot water and regular bathing. Should pharmacological treatment be necessary, the choice of pediculicide should follow the same guidelines as used for head lice (*CDC 2015[a], Gunning et al 2012*).
- The CDC recommends permethrin or the combination of piperonyl butoxide and pyrethrins as equivalent therapies for pediculosis pubis (*CDC 2015[b]*).

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INTRODUCTION

- Atopic dermatitis, also referred to as atopic eczema, is a chronic, highly pruritic, and relapsing inflammatory skin condition. The prevalence of atopic dermatitis is estimated to be between 15% to 30% in children and 2% to 10% in adults; approximately 18 million children and adults have atopic dermatitis in the United States *(Berke et al 2012, Eichenfield et al 2014a, Food and Drug Administration [FDA] presentation 2015)*. Atopic dermatitis is one of the most common skin disorders in children with more than 90% of cases starting before the age of 5 years *(Eichenfield et al 2014a)*.
- The pathogenesis of atopic dermatitis can be explained by impaired epidermal barrier function due to structural and functional abnormalities in the skin as well as a cutaneous inflammatory response to environmental factors *(Weston & Howe 2018)*. Pruritus is one of the most common symptoms of atopic dermatitis, and it is an essential feature which provokes a vicious "itch-scratch" cycle that compromises the epidermal barrier which results in water loss, xerosis, microbial colonization, and secondary infection *(Castro 2008)*. The clinical manifestations of atopic dermatitis vary according to age and disease activity; however, almost all patients with atopic dermatitis report dry skin. The infantile and childhood stages are characterized by pruritic, red, crusted lesions and generally involve the face, neck, and extensor skin surfaces *(Eichenfield et al 2014a)*. The adult stage of atopic dermatitis is more lichenified and localized to the flexural folds of the extremities *(Eichenfield et al 2014a)*.
- Diagnosis of atopic dermatitis is based on a constellation of clinical symptoms. There is no optimal long-term maintenance treatment for atopic dermatitis, and there is no known cure. The general approach for the treatment of atopic dermatitis involves elimination of exacerbating factors, restoring the skin's abnormal barrier function, hydrating the skin, and controlling active disease with topical anti-inflammatory agents *(Eichenfield et al 2014b, Schneider et al 2013, Tollefson et al 2014)*.
- Patients with atopic dermatitis should avoid exacerbating factors including excessive bathing, low humidity environments, emotional stress, xerosis, and exposure to detergents. Thick creams with low water content or ointments which have zero water content protect against xerosis and should be utilized. Antihistamines are utilized as an adjunct in patients with atopic dermatitis to control pruritus and eye irritation. Sedating antihistamines (eg, diphenhydramine, hydroxyzine) appear to be more effective than non-sedating ones (eg, fexofenadine, loratadine) *(Eichenfield et al 2014b)*. However, evidence supporting their use is weak due to lack of controlled trials.
- Topical corticosteroids are considered to be the standard of care for the treatment of atopic dermatitis *(Eichenfield et al 2014b, Schneider et al 2013, Tollefson et al 2014)*. Low- to high-potency topical corticosteroids are utilized 1 or more times daily for the treatment of acute flares, as well as intermittently to prevent relapses. One large trial showed that twice-daily application of topical corticosteroids was no more effective than once-daily application *(Krakowski et al 2008)*. There are tolerability and safety concerns regarding the use of topical corticosteroids including skin atrophy, striae, and telangiectasia, which may limit long-term use of these agents. These adverse reactions occur more frequently when topical corticosteroids are used on sensitive areas of thin skin including skin folds and the face or neck *(Eichenfield et al 2014b, Krakowski et al 2008, Schneider et al 2013)*.
- Immunosuppressive agents for atopic dermatitis include Elidel (pimecrolimus) and Protopic (tacrolimus). The exact mechanism of action in atopic dermatitis is not known. Elidel and Protopic inhibit calcineurin, a calcium-dependent phosphatase, by binding with high affinity to immunophilin-12 (FKBP-12), which is theorized to be the primary mode of inflammation reduction in atopic dermatitis *(Clinical Pharmacology 2019)*. Protopic and Elidel provide immunosuppression via inhibition of T-cell activation.
- There are some concerns regarding the long-term safety of these agents. On January 19, 2006, the FDA approved updated labeling for the agents *(FDA press release 2006)*. This updated labeling was a result of cancer-related adverse events (AEs) with the use of these medications. The labeling includes a boxed warning about a possible risk of cancer and a medication guide for patients to ensure that they are aware of this concern. The labeling clarifies that these medications are recommended for use as second-line treatments and are not recommended in children under 2 years of

age. A definitive causal link between the topical immunosuppressants and the incidence of malignancy has not been established.

- Eucrisa (crisaborole) is a non-steroidal, topical treatment for atopic dermatitis that works by way of phosphodiesterase (PDE)-4 inhibition. Inflammation is associated with elevated PDE-4 enzyme activity and overactive PDE-4 has been shown to contribute to the signs and symptoms of atopic dermatitis *(Zane et al 2016)*. Eucrisa enhances cellular control of inflammation by inhibiting PDE-4 and its ability to degrade intracellular cyclic adenosine monophosphate (cAMP), thereby suppressing the release of cytokines *(Paller et al 2016)*. The novel boron chemistry of Eucrisa additionally enables synthesis of a low molecular weight compound that facilitates effective penetration through human skin *(Paller et al 2016)*.
- Medispan Class: Immunosuppressive Agents – Topical; Phosphodiesterase 4 (PDE4) Inhibitors – Topical; Macrolide Immunosuppressants - Topical

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Elidel (pimecrolimus)	✔
Protopic (tacrolimus)	✔
Eucrisa (crisaborole)	-

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Elidel (pimecrolimus)	Protopic (tacrolimus)	Eucrisa (crisaborole)
Second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adults and children 2 years of age and older, who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable.	✔		
Second-line therapy for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.		✔ *	
Topical treatment of mild to moderate atopic dermatitis in patients 2 years of age and older			✔

*Both 0.03% and 0.1% ointment for adults and only 0.03% ointment for children 2 to 15 years of age.

(*Prescribing information: Elidel 2017, Eucrisa 2017, Protopic 2018*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Elidel and Protopic

- The FDA approval of Elidel cream was based on 3 randomized, double-blind, vehicle-controlled, Phase III studies in patients 3 months to 17 years of age with mild to moderate atopic dermatitis (N = 589). Two of these 3 trials support the use of Elidel cream in patients 2 years of age and older with mild to moderate atopic dermatitis. Two other identical, 6-

week, vehicle-controlled, Phase III trials were conducted in pediatric patients 2 to 17 years of age (N = 403). These studies showed significant clinical response based on physician's global evaluation for Elidel-treated patients compared to patients in the vehicle group. These studies are outlined in the manufacturer product labeling.

- The FDA approval of Protopic ointment was based on 3 randomized, double-blind, vehicle-controlled, Phase III studies in patients with moderate to severe atopic dermatitis. One of the studies was conducted in pediatric patients (N = 351) ages 2 to 15 years, and the other 2 studies were conducted in adult patients (N = 632). The primary efficacy endpoint was met by all 3 studies with a significantly greater percentage of patients achieving at least 90% improvement based on the physician's global evaluation of clinical response in the Protopic group compared to the vehicle group ($p < 0.001$). There was some evidence that Protopic 0.1% ointment may provide more efficacy than the 0.03% ointment in adult patients who had severe disease at baseline. There was no difference in efficacy between the Protopic strengths in the pediatric study. These studies are outlined in the manufacturer product labeling.
- Elidel and Protopic have been directly compared in clinical trials. One trial compared Elidel 1% to Protopic 0.03% in patients 2 to 17 years of age (N = 141) and found no difference in the incidence of application site reactions between the topical immunomodulators in the 6-week study *(Kempers et al 2004)*. However, itching was reported at a significantly higher rate in the Protopic group. In 2 other clinical trials, Protopic 0.1% was compared to Elidel in adult patients over 6 weeks. Patients treated with Protopic had a significantly greater improvement in the Eczema Area Severity Index (EASI) score compared to those treated with Elidel (*Abramovits et al 2008, Fleischer et al 2007*). The success in therapy based on the Investigator Global Atopic Dermatitis Assessment, improvement in percent body surface area (BSA) affected, and improvement in signs and symptoms of atopic dermatitis in face and neck were all statistically significant for the Protopic group in both studies *(Abramovits et al 2008, Fleischer et al 2007)*. There were no differences in AEs between the groups.
- A meta-analysis of 3 randomized clinical trials showed that both adults and children in the Protopic-treated group had a significantly greater improvement in EASI score at week 6 as compared to the Elidel group *(Paller et al 2005)*. The most common AEs in all studies were local application site reactions including burning and stinging *(Paller et al 2005)*.
- A meta-analysis of 25 randomized controlled trials (N = 6897) showed that Protopic 0.1% was equally efficacious as potent topical corticosteroids and more efficacious than mild topical corticosteroids for the treatment of atopic dermatitis *(Ashcroft et al 2005)*. Additionally, Elidel was found to be less effective than potent topical corticosteroids *(Ashcroft et al 2005)*. Individual clinical trials have reported conflicting results *(Bieber et al 2007, Doss et al 2009, Doss et al 2010)*.
- A meta-analysis and systematic review assessed the effectiveness of topical immunomodulators compared to topical corticosteroids and/or placebo (N = 7378) *(El-Batawy et al 2009)*. In terms of overall comparison, Elidel was found to be more effective than vehicle at 3 and 6 weeks. However, a long-term study that was included in this review did not find any difference between these 2 groups at 6 and 12 months. Also, betamethasone valerate, a potent topical corticosteroid, was found to be significantly more effective in adults (3 weeks) than Elidel in the treatment of moderate to severe atopic dermatitis. Although this meta-analysis showed that Elidel seems to be less effective than topical corticosteroids, Elidel would be efficacious in areas where topical corticosteroids may not be recommended such as the face and sensitive areas including skin folds. Pooled analysis of Protopic trials demonstrated that Protopic was more effective than vehicle *(El-Batawy et al 2009)*. When compared to mild potency topical corticosteroids like hydrocortisone acetate, Protopic was more efficacious. However, when compared to moderate potency topical corticosteroids, Protopic 0.03% was significantly less effective than topical corticosteroids, and Protopic 0.1% was equal in effectiveness to the topical corticosteroids. Overall, Protopic was found to be more effective than mild topical corticosteroids and equally effective as moderately potent topical corticosteroids *(El-Batawy et al 2009)*.
- A systematic review of 20 randomized controlled trials (N = 6288) showed that Protopic was more efficacious than placebo or mild topical corticosteroids for the treatment of atopic dermatitis *(Chen et al 2010)*. Additionally, Elidel was more efficacious than placebo and equally efficacious as mild topical corticosteroids for the treatment of atopic dermatitis. In this review, 3 trials comparing Elidel to Protopic were identified. While 2 of the trials did find Protopic to be significantly more efficacious, no significant difference was found in the third trial.
- A retrospective cohort evaluated initial cancer diagnosis in patients with a diagnosis of atopic dermatitis or eczema and found that while exposure to Elidel or Protopic was not associated with an increase in overall cancer rates, exposure to these agents was associated with an increased risk of T-cell lymphoma ($p < 0.001$ and $p = 0.01$, respectively). However, after the exclusion of 4 cases due to physician suspected T-cell lymphoma prior to exposure, the risks were only significant for patients exposed to Protopic and not Elidel ($p < 0.001$, $p = 0.086$, respectively) *(Hui et al 2009)*.

Eucrisa

- The safety and efficacy of Eucrisa were demonstrated in 2 identically designed, randomized, Phase III, double-blind, vehicle-controlled trials in a total of 1522 patients with mild to moderate atopic dermatitis and ≥ 5% treatable BSA *(Eucrisa formulary submission dossier 2016, Paller et al 2016)*. The primary endpoint of success was defined as the proportion of subjects at Day 29 who were clear or almost clear with a ≥ 2-grade improvement from baseline by the Investigator's Static Global Assessment (ISGA) scale. More patients receiving Eucrisa vs vehicle achieved the primary endpoint of ISGA success (Study AD-301: 32.8% vs 25.4%, p = 0.038; Study AD-302: 31.4% vs 18.0%, p < 0.001), with a greater percentage achieving clear/almost clear overall (51.7% vs 40.6%, p = 0.005; 48.5% vs 29.7%, p < 0.001). In addition, Eucrisa-treated patients achieved greater ISGA score improvements and improvement in pruritus earlier (both p < 0.001).
  - An open-label extension trial of AD-301 and AD-302 evaluated the safety of Eucrisa in 517 patients with mild to moderate atopic dermatitis for 48 weeks. Patients underwent an average of 6 treatment periods and used an average of 133 grams of ointment/month. Most treatment-emergent AEs were mild (51.2%) or moderate (44.6%) and were considered unrelated to treatment with Eucrisa (93.1%). The most commonly observed AEs (≥ 1% of patients) included atopic dermatitis flares (3.1%), application site pain (2.3%), and application site infection (1.2%). Most patients (77.8%) did not require rescue medications. Children and adolescents made up 48% of those patients that initiated rescue therapies (*Eichenfield et al 2017*).

CLINICAL GUIDELINES

- Treatment guidelines generally agree that a stepwise approach to treatment is needed. Nonpharmacological therapies (ie, lukewarm baths, skin moisturizers, etc.) are followed by topical corticosteroids and/or topical calcineurin inhibitors. Low to high potency topical corticosteroids are the standard of care, and strength is selected based on severity, duration of treatment, location of exacerbation, and age of the patient. Elidel and Protopic are topical calcineurin inhibitors that are recommended as second-line therapy in patients who fail or cannot tolerate corticosteroids. Eucrisa has not yet been added to the guidelines *(Eichenfield et al 2014a, Eichenfield et al 2014b, Schneider et al 2013, Sidbury et al 2014, Tollefson et al 2014)*.

SAFETY SUMMARY

Elidel and Protopic

- Boxed warning: Although a causal relationship has not been established, rare cases of malignancy (eg, skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors.
  - Avoid continuous long-term use, in any age group, and limit application to areas of involvement with atopic dermatitis.
  - Both agents are not indicated for use in children less than 2 years of age. Only Protopic 0.03% ointment is indicated for use in children 2 to 15 years of age; Elidel is indicated for children 2 years and older and adults.
- Key Warnings/Precautions:
  - Do not use on malignant or pre-malignant skin conditions.
  - Resolve bacterial or viral infections at the treatment site.
  - While using avoid exposure to sunlight.
  - Do not use in immunocompromised patients.
- AEs: Application site irritation and reactions such as skin burning, itching, redness, and rash. Hypersensitivity reactions can also occur.
- A 5-year, open-label, multicenter study evaluated the use of Elidel in 2418 infants compared to topical corticosteroids *(Sigurgeirsson et al 2015)*. The primary endpoint was safety; the secondary endpoint was long-term efficacy defined as a score of 0 to 5 on the Investigator's Global Assessment (IGA). Topical corticosteroids included low potency such as hydrocortisone 1% or medium potency such as hydrocortisone butyrate 0.1%. For safety, no differences between the groups were observed for growth rate or bacterial or viral infections. More Elidel patients reported bronchitis (p = 0.02), infected eczema (p < 0.001), impetigo (p = 0.045), and nasopharyngitis (p = 0.04). Serious infections and infestations were similar between the groups. Two malignancies occurred in the corticosteroid-treated group, and one benign tumor was reported in the Elidel-treated group. Over the 5-year period, 88.7% and 92.3% of the Elidel- and corticosteroid-treatment groups, respectively, reported overall IGA treatment success. Significant attrition occurred with only 69.4% and 72.1% of Elidel- and corticosteroid-treated patients completing the study.

Eucrisa

- Contraindications: Known hypersensitivity to Eucrisa or any component of the formulation

- Warnings/precautions:
  - Hypersensitivity reactions, including contact urticaria, have occurred in patients treated with Eucrisa. Hypersensitivity should be suspected in the event of severe pruritus, swelling, and erythema at the application site or at a distant site. If signs and symptoms of hypersensitivity occur, Eucrisa should be discontinued immediately and appropriate therapy initiated.
- AEs:
  - In pivotal studies AD-301 and AD-302, 1012 patients (2 to 79 years of age) with mild to moderate atopic dermatitis were treated with Eucrisa twice daily for 4 weeks. The AE reported by ≥ 1% of Eucrisa-treated patients (45/1012 [4%] vs. 6/499 [1%] of vehicle-treated patients) was application site pain, referring to skin sensations such as burning or stinging. Less common (< 1%) AEs in patients treated with Eucrisa included contact urticaria.
  - No safety signals were identified from vital signs or laboratory assessments in the pivotal studies or in the 48-week, long-term safety extension study *(Eucrisa formulary submission dossier 2016, Paller et al 2016)*.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Elidel (pimecrolimus)	Cream (1%)	Topical	Two times daily (applied as a thin layer)	Do not use in children less than 2 years of age. Do not use with occlusive dressings since occlusion may promote systemic exposure. Safety has not been evaluated. If signs and symptoms persist beyond 6 weeks, patients should be re-examined by their health care provider to confirm the diagnosis. Continuous long-term use should be avoided, and application should be limited to areas of involvement.
Protopic (tacrolimus)	Ointment (0.03% and 0.1%)	Topical	Two times daily (applied as a thin layer)	Do not use in children less than 2 years of age. Do not use with occlusive dressings since occlusion may promote systemic exposure. Safety has not been evaluated. If signs and symptoms persist beyond 6 weeks, patients should be re-examined by their health care provider to confirm the diagnosis. Continuous long-term use should be avoided, and application should be limited to areas of involvement.
Eucrisa (crisaborole)	Ointment (2%)	Topical	Two times daily (applied as a thin layer)	Safety and effectiveness in pediatric patients below the age of 2 years have not been established.

See the current prescribing information for full details

CONCLUSION

- The topical calcineurin inhibitors, Elidel (pimecrolimus 1% cream) and Protopic (tacrolimus 0.03% and 0.1% ointment), are indicated as second-line therapies for the short-term and non-continuous chronic treatment of atopic dermatitis (Elidel: mild to moderate atopic dermatitis; Protopic: moderate to severe atopic dermatitis) in non-immunocompromised adults and children (Elidel: ≥ 2 years of age; Protopic: 0.03% and 0.1% in adults, 0.03% in patients 2 to 15 years of age) who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable. The FDA added another agent to the atopic dermatitis armamentarium with the approval of Eucrisa (crisaborole) ointment for the topical treatment of mild to moderate atopic dermatitis in patients ≥ 2 years of age.
- The topical anti-inflammatory agents work by way of several mechanisms of action; however, the exact mechanism of action in atopic dermatitis is not known. Elidel and Protopic inhibit calcineurin, a calcium-dependent phosphatase, by binding with high affinity to immunophilin-12 (FKBP-12). Protopic and Elidel provide immunosuppression via inhibition of T-cell activation, which is theorized to be the primary mode of inflammation reduction in atopic dermatitis. Eucrisa is a non-steroidal treatment option with a novel mechanism of action. In patients with atopic dermatitis, PDE-4 activity increases circulating inflammatory cells resulting in increased cytokine production. It is believed that Eucrisa enhances cellular control of inflammation by inhibiting PDE-4 and its ability to degrade intracellular cAMP, thereby suppressing the release of cytokines *(Clinical Pharmacology 2019, Paller et al 2016)*.
- Several head-to-head studies comparing the efficacy of the calcineurin inhibitors have been conducted. A meta-analysis of 3 studies directly comparing Elidel and Protopic evaluated the change from baseline in EASI score at week 6 of treatment *(Paller et al 2005)*. Results favored treatment with Protopic, and AEs between the groups were similar. Another meta-analysis evaluating Elidel, Protopic, topical corticosteroids, and vehicle preparations demonstrated a significantly greater change in EASI score in patients using Protopic compared to patients using Elidel in addition to better Investigator Global Atopic Dermatitis Assessment in patients with moderate to severe disease *(Ashcroft et al 2005)*. Protopic was found to be more effective than mild topical corticosteroids and equally effective as moderately potent topical corticosteroids *(El-Batawy et al 2009)*.
- Concerns regarding the long-term safety of the topical calcineurin inhibitors have been addressed in the guidelines and position papers outlined in this review. In 2005, the FDA released a Public Health Advisory to communicate the potential risk of cancer of these products to healthcare providers and patients. The FDA has advised that Elidel and Protopic be used only as labeled and asked providers and patients to consider these agents only as second-line therapies; new labeling was approved in early 2006 *(FDA press release 2006)*. Topical calcineurin inhibitors may be associated with immunosuppression or malignancy.
- Eucrisa demonstrated short-term efficacy over vehicle ointment in 2 identically designed, 28-day, Phase III, randomized, double-blind trials; more patients receiving Eucrisa vs vehicle achieved the primary endpoint of ISGA success, with a greater percentage of Eucrisa-treated patients achieving clear/almost clear overall. Over 28 days, application site pain was the most commonly reported AE. Unpublished data gleaned from the 48-week, long-term study revealed no significant safety signals.
- Current guidelines for the treatment of atopic dermatitis recommend the use of topical corticosteroids as first-line treatment and recommend the use of topical Elidel or Protopic in those patients intolerant or unresponsive to corticosteroids or in whom corticosteroids are contraindicated or when corticosteroid-sparing measures may be desired. Eucrisa has not yet been added to the guidelines *(Eichenfield et al 2014a, Eichenfield et al 2014b, Schneider et al 2013, Sidbury et al 2014, Tollefson et al 2014)*.

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Therapeutic Class Overview
Antiemetics

INTRODUCTION

- Nausea, the sensation of anticipating vomiting, may occur with or without concomitant dyspepsia, other gastrointestinal (GI) symptoms, or vomiting, which is the forceful expulsion of gastric contents (*Longstreth 2018*).
- Chemotherapy-induced nausea and vomiting (CINV) is often viewed as the most severe and distressing form of nausea and vomiting (n/v) that occurs in patients with cancer. Additional causes of n/v in this population include surgery, opioid therapy, and radiation (*Hesketh, 2018; Hesketh 2017[a]*).
- Normal function of the upper GI tract involves interactions between the gut and the central nervous system (CNS), with the motor function of the GI tract being controlled at the level of the parasympathetic and sympathetic nervous systems, enteric brain neurons, and smooth muscle cells (*Longstreth 2018*).
- Three distinct types of CINV have been defined, including (*Hesketh 2018, Hesketh 2017[a]*):
  - Acute emesis, which most commonly begins within 1 to 2 hours of chemotherapy and usually peaks in the first 4 to 6 hours
  - Delayed emesis, occurring beyond 24 hours after chemotherapy
  - Anticipatory emesis, occurring prior to treatment as a conditioned response in patients who have developed significant n/v during previous cycles of chemotherapy
- Approximately one-third of surgical patients have nausea, vomiting, or both after receiving general anesthesia, with increased risk associated with the female gender, nonsmoker status, previous history of postoperative n/v (PONV), and use of postoperative opioids (*Longstreth 2018*).
- Nausea and/or vomiting caused by radiation therapy (RT) is generally less severe than that caused by chemotherapy. The pathophysiology of radiation-induced n/v (RINV) remains unclear, but it is thought to be similar to that caused by chemotherapy (*Feyer et al 2019*).
- Nausea with or without vomiting is common in early pregnancy. Severe vomiting resulting in dehydration and weight loss is termed hyperemesis gravidarum and occurs less frequently. The treatment goals in patients with nausea and vomiting of pregnancy (NVP) are to reduce symptoms through changes in diet/environment and by medication, to correct consequences or complications of n/v such as dehydration, and to minimize the fetal effects of NVP treatment (*American College of Obstetrics and Gynecologists [ACOG] 2018, Smith et al 2019*).
- The mechanism of action for the 5-hydroxytryptamine (5-HT3, or serotonin) agents results from the blockade of 5-HT3 receptors in both the gastric area and the chemoreceptor trigger zone in the CNS. By blocking these receptors, these medications disrupt the signal to vomit and reduce the sensation of nausea (*Mannix et al 2006*).
- The substance P/neurokinin 1 (NK1) receptor antagonists cross the blood brain barrier and occupy the NK1 receptors in the brain, leading to reduced symptoms of n/v.
- Synthetic delta-9-tetrahydrocannabinol (THC) is the active ingredient in the THC derivative agents, also known as the cannabinoids. Cannabinoid receptors have been discovered in neural tissues, and these receptors may play a role in mediating the antiemetic effects of cannabinoids such as dronabinol and nabilone. These agents, like other cannabinoids, have the potential to be abused and produce psychological dependence. Both dronabinol and nabilone may produce alterations in mood (euphoria, detachment, depression, anxiety) and alterations in reality (distorted perceptions of objects and time and hallucinations).
- The mechanism of action of Diclegis and Bonjesta (doxylamine succinate/pyridoxine hydrochloride [HCl]) are unknown (*Diclegis and Bonjesta prescribing information*).
- The 5-HT3 receptor antagonists are Food and Drug Administration (FDA)-approved for the treatment of CINV, PONV, and/or RINV, although the medications and various dosage forms of each agent differ slightly with respect to these indications.
- The substance P/NK1 receptor antagonists are currently FDA-approved for the prevention of CINV. In addition, aprepitant is approved for the prevention of PONV.
- The combination product, Akynzeo, contains palonosetron, a 5-HT3 receptor antagonist, and a substance P/NK1 receptor antagonist: netupitant in the oral formulation and fosnetupitant in the injectable formulation. This agent is approved for prevention of acute and delayed n/v associated with initial and repeat courses of cancer chemotherapy.

- Diclegis and Bonjesta are fixed-dose combination products of doxylamine succinate, an antihistamine, and pyridoxine HCl, a vitamin B6 analog. Diclegis and Bonjesta are indicated for the treatment of NVP in women who do not respond to conservative management. It should be noted that these agents have not been studied in hyperemesis gravidarum.
  - The combination of doxylamine and pyridoxine was previously available in the United States under the brand name Bendectin. However, this product was removed from the market in 1983 due to law suits alleging teratogenicity despite scientific evidence of the safety and efficacy of the medication. A meta-analysis (MA) of controlled studies on outcome of pregnancies exposed to Bendectin reported no increase in the incidence of birth defects (*Smith et al 2019*).
- The scope of this review will focus on the agents outlined in Table 1 for their respective FDA-approved indications as related to CINV. Other agents including anticholinergic agents, antihistamines, glucocorticoids, and dopamine receptor antagonists may also be effective antiemetics; however, they have been excluded from this review.
- Medispan Therapeutic Class: 5-HT3 Receptor Antagonists; Substance P/NK1 Receptor Antagonists; Antiemetics – Miscellaneous; Antiemetic Combinations – Two Ingredient.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Akynzeo (palonosetron/netupitant) capsule	–
Akynzeo (palonosetron/fosnetupitant) injection	–
Aloxi (palonosetron) IV solution	✔
Anzemet (dolasetron) tablets¥	–
Bonjesta (doxylamine succinate/pyridoxine HCl) 20 mg extended-release tablets	–
Cesamet (nabilone) capsule	–
Cinvanti (aprepitant) IV emulsion	–
Diclegis (doxylamine succinate/pyridoxine HCl) 10 mg delayed-release tablets	✔ §
Emend (aprepitant) oral suspension	–
Emend (aprepitant) capsule, combination pack	✔
Emend (fosaprepitant) IV solution	–‖
granisetron injection, tablets	✔ ‡
Marinol (dronabinol) capsule	✔
ondansetron injection	✔ ‡
Sancuso (granisetron) transdermal patch	–
Sustol (granisetron) extended-release subcutaneous injection	–
Syndros (dronabinol) oral solution	–
Varubi (rolapitant) tablet†	–
Zofran (ondansetron) oral solution, tablet	✔ ‡
Zofran ODT (ondansetron) ODT	✔ ‡
Zuplenz (ondansetron) oral soluble film	–

Abbrv: IV=intravenous, ODT=orally disintegrating tablet
‡Generic available in at least 1 dosage form and/or strength.
§Actavis received FDA approval for generic Diclegis on August 19, 2016; however, it is not yet marketed.
‖Sandoz received FDA approval for generic Emend injection on September 24, 2012. However, patents will likely protect Emend injection from generic competition until March 4, 2019, pending patent litigation.
¥ Listed as discontinued on FDA Orange Book; however, per the manufacturer Validus Pharmaceuticals on February 12, 2019, the product is currently on backorder but not discontinued.
†The FDA Web site shows the IV rolapitant product as discontinued. The manufacturer of IV rolapitant suspended further distribution of the product in February 2018 due to reports of anaphylaxis, anaphylactic shock, and other serious hypersensitivity reactions associated with its use.

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	5-HT$_3$ Receptor Antagonists				Substance P/NK$_1$ Receptor Antagonists			THC Derivatives		Combination Products	
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Aprepitant	Fosaprepitant	Rolapitant	Dronabinol	Nabilone	Palonosetron/ netupitant (oral) fosnetupitant (IV)	Doxylamine succinate/ pyridoxine HCl
Anorexia in patients with AIDS											
Anorexia associated with weight loss in adults with AIDS								✔			
CINV											
N/V associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments								✔	✔		
Highly emetogenic cancer chemotherapy (HEC) – prevention of acute n/v associated with initial and repeat courses in adults				✔							
Prevention of acute and delayed n/v associated with initial and repeat courses of HEC including high-dose cisplatin in patients ≥ 6 months of age					✔ * (oral suspension)	✔ *					
Prevention of acute n/v associated with initial and repeat courses of emetogenic chemotherapy, including HEC in pediatric patients aged 1 month to < 17 years				✔							
Prevention of acute and delayed n/v associated with initial and repeat courses of HEC, including high-dose cisplatin, in adults					✔ * (IV emulsion)						
Prevention of delayed n/v associated with initial and repeat courses of emetogenic cancer chemotherapy, including HEC							✔ *				
Prevention of acute and delayed n/v associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, HEC in combination with dexamethasone										✔ (capsule)	
Prevention of acute and delayed n/v associated with initial and repeat courses of HEC in combination with dexamethasone										✔ ¥ (IV)	

Indication	5-HT$_3$ Receptor Antagonists				Substance P/NK$_1$ Receptor Antagonists			THC Derivatives		Combination Products	
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Aprepitant	Fosaprepitant	Rolapitant	Dronabinol	Nabilone	Palonosetron/ netupitant (oral) fosnetupitant (IV)	Doxylamine succinate/ pyridoxine HCl
Prevention of acute and delayed n/v associated with initial and repeat courses of HEC, including high-dose cisplatin, in patients ≥ 12 years of age					✔ * (capsule)						
Prevention of delayed n/v associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, HEC							✔ *				
Prevention of n/v associated with HEC including cisplatin ≥ 50 mg/m^2			✔ (tablet, ODT, oral solution, oral soluble film)								
Prevention of n/v associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin		✔ (injection, tablets)									
Prevention of n/v associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin, in patients ≥ 6 months of age			✔ (injection)								
Moderately emetogenic cancer (MEC) chemotherapy – prevention of n/v associated with initial and repeat courses in adults				✔	✔ * (IV emulsion)						
Prevention of n/v in patients receiving MEC and/or HEC for up to 5 consecutive days		✔ (TD)									
Prevention of n/v associated with initial and repeat courses of MEC			✔ (tablet, ODT, oral solution, oral soluble film)								
Prevention of n/v associated with MEC, including initial and repeat courses in ages ≥ 2 years	✔										

Indication	5-HT$_3$ Receptor Antagonists				Substance P/NK$_1$ Receptor Antagonists			THC Derivatives		Combination Products	
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Aprepitant	Fosaprepitant	Rolapitant	Dronabinol	Nabilone	Palonosetron/ netupitant (oral) fosnetupitant (IV)	Doxylamine succinate/ pyridoxine HCl
Prevention of n/v associated with initial and repeat courses of MEC, in patients ≥ 6 months of age					✔ (oral suspension)						
Prevention of acute and delayed n/v associated with initial and repeat courses of MEC or anthracycline and cyclophosphamide combination chemotherapy regimens.		✔ * (ER injection)									
Prevention of delayed n/v associated with initial and repeat courses of MEC in patients ≥ 6 months of age						✔ *					
Prevention of n/v associated with initial and repeat courses of MEC in patients ≥ 12 years of age					✔ * (capsule)						
NVP											
Treatment of NVP in women who do not respond to conservative management											✔
PONV											
Prevention of PONV for up to 24 hours following surgery; efficacy beyond 24 hours has not been demonstrated; as with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that n/v will occur post-operatively. In patients where n/v must be avoided postoperatively, Aloxi injection is recommended even where the incidence of PONV is low				✔							
Prevention of PONV in adults			✔ (tablet, ODT, oral solution)		✔ (capsule)						
Prevention of PONV; as with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that n/v will occur post-operatively. In patients where n/v must be avoided postoperatively, this drug is recommended even where the incidence of PONV is low.		✔ (injection)	✔ (injection†, oral soluble film)								

Indication	5-HT$_3$ Receptor Antagonists				Substance P/NK$_1$ Receptor Antagonists			THC Derivatives		Combination Products	
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Aprepitant	Fosaprepitant	Rolapitant	Dronabinol	Nabilone	Palonosetron/ netupitant (oral) fosnetupitant (IV)	Doxylamine succinate/ pyridoxine HCl
RINV											
Prevention of n/v associated with RT, including TBI and fractionated abdominal RT		✔ (tablets)									
Prevention of n/v associated with radiotherapy in patients receiving either TBI, single high-dose fraction to the abdomen, or daily fractions to the abdomen			✔ (tablet, ODT, oral solution, oral soluble film)								

Abbrv: 5-HT3 = serotonin (5-hydroxytryptamine) 3 receptor, AIDS = acquired immunodeficiency syndrome, ER = extended release, HEC = highly emetogenic cancer chemotherapy, MEC = moderately emetogenic cancer chemotherapy, n/v = nausea/vomiting, NVP = nausea and vomiting of pregnancy, NK1 = neurokinin 1, ODT = orally disintegrating tablet, PONV = postoperative nausea and vomiting, RINV = radiation-induced nausea and vomiting, RT = radiation therapy, TBI = total body irradiation, TD = transdermal patch, THC = delta-9-tetrahydrocannabinol

* When used in combination with other antiemetic agents.

† For patients who do not receive prophylactic ondansetron injection and experience n/v postoperatively, ondansetron injection may be given to prevent further episodes.

¥ Not studied for prevention of n/v associated with anthracycline plus cyclophosphamide chemotherapy.

(*Prescribing information: Akynzeo 2018, Aloxi 2018, Anzemet tablets 2018, Bonjesta 2018, Cesamet 2015, Cinvanti 2018, Diclegis tablets 2018, Emend capsules and oral suspension 2017, Emend for injection 2018, granisetron injection 2018, granisetron tablets 2018, Marinol 2017, ondansetron injection 2018, Sancuso 2017, Sustol 2017, Syndros 2018, Varubi 2018, Zofran tablets ODT oral solution 2017, Zuplenz 2017*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Anorexia in patients with AIDS

- A 2015 MA (N = 6,462; 79 trials) evaluated the efficacy and safety of cannabinoids in various conditions, including appetite stimulation in HIV/AIDS. Most trials were of low to moderate quality and compared cannabinoids to usual care, placebo, or no treatment across trials. Compared with placebo, cannabinoids were associated with a higher proportion of patients demonstrating a complete n/v response (47% vs 20%; odds ratio [OR], 3.82; 95% confidence interval [CI], 1.55 to 9.42; 3 trials), reduction in pain (37% vs 31%; OR, 1.41; 95% CI, 0.99 to 2.00; 8 trials), and a greater average reduction in numerical rating scale pain assessment (on a 0 to 10 point scale; weighted mean difference [WMD], -0.46; 95% CI, -0.80 to -0.11; 6 trials). A total of 4 trials evaluated dronabinol for appetite stimulation in 255 patients with HIV infection or AIDS, key outcomes are outlined below (*Abrams et al 2003, Timpone et al 1997, Whiting et al 2015):*
  - Data from 1 small study (n = 139, of which only 88 were evaluable) demonstrated that a large proportion of patients experienced weight gain of ≥ 2 kg within 6 weeks vs placebo (OR, 2.2; 95% CI, 0.68 to 7.27). An active comparison trial found that megestrol acetate was associated with greater weight gain than dronabinol and that combining dronabinol with megestrol acetate did not lead to additional weight gain.
- A 2013 MA of 7 trials, mostly of poor quality, found similar results as *Whiting et al*. Randomized controlled trials (RCTs) included any cannabis intervention and were of a short duration, ranging from 21 to 84 days. Patients had a mean weight gain in the dronabinol group of 0.1 kg, compared with a weight loss of 0.4 kg in the placebo group (*Lutge et al 2013*).

CINV

- For the management of CINV, MAs and head-to-head trials have demonstrated that the cannabinoids, dronabinol and nabilone, are more effective compared to placebo and may be more effective than prochlorperazine and metoclopramide. There are no published clinical trials comparing dronabinol to nabilone for CINV. The effectiveness of Syndros (dronabinol) oral solution for its FDA-approved indications was based on studies of dronabinol capsules.
- In a study by *Lane et al,* the combination of dronabinol plus prochlorperazine significantly reduced the mean duration of vomiting per episode compared to either agent administered with placebo (*Lane et al 1991*).
- Dolasetron has been shown to be an effective therapy in the treatment of CINV in comparative studies with palonosetron, ondansetron, and placebo (*Eberhart et al 2004, Eisenberg et al 2003, Karamanlioglu et al 2003, Lofters et al 1997, Meyer et al 2005, Walker et al 2001*).
- Granisetron and ondansetron are generally recognized as equally efficacious in treating CINV and PONV. Various studies may show slight benefits of 1 over another, but this has not been a consistently proven outcome (*Billio et al 2010, Dabbous et al 2010, del Giglio et al 2000, Dempsey et al 2004, Gan et al 2005, Jaing et al 2004, Kalaycio et al 1998, Lacerda et al 2000, Orchard et al 1999, White et al 2006*).
- Sancuso (granisetron) patch was non-inferior to orally administered granisetron for CINV (*Boccia et al 2011*).
- Palonosetron was reported to be more effective than other medications in the class as well as placebo, particularly at preventing delayed emesis (*Aapro et al 2005, Billio et al 2010, Botrel et al 2011, Dong et al 2011, Eisenberg et al 2003, Gralla et al 2003, Kaushal et al 2010, Likun et al 2011, Massa et al 2009, Suzuki et al 2016, Chow et al 2018*).
- The safety and efficacy of Sustol (granisetron) were evaluated in a pivotal Phase 3, double-blind (DB), double-dummy, multicenter (MC), RCT in adults receiving HEC or MEC (*Raftopoulos et al 2015[a], Raftopoulos et al 2015[b]*). In the modified intention-to-treat population, both granisetron ER 5 mg and 10 mg were noninferior to palonosetron in preventing acute CINV after HEC and MEC. The FDA-approved dose of granisetron ER 10 mg was non-inferior to palonosetron in preventing delayed CINV after MEC and was not superior in preventing delayed CINV after HEC (*Raftopoulos et al 2015[a], Raftopoulos et al 2015[b]*).
- All of the 5-HT3 receptor antagonists have been shown to be equally effective in preventing acute CINV in separate MAs and are superior to placebo (*Billio et al 2010, del Giglio et al 2000, George et al 2009, Singhal et al 2012, Tang et al 2012*). A 2016 MA comparing ondansetron to other 5-HT3 receptor antagonists used for CINV found that ondansetron exhibited similar efficacy to granisetron, but greater efficacy than dolasetron for acute vomiting; palonosetron exhibited greater efficacy than ondansetron for delayed nausea and acute and delayed vomiting (*Simino et al 2016*).
- A 2016 Cochrane review found that 5-HT3 receptor antagonists are effective in children who receive emetogenic chemotherapy. Granisetron or palonosetron may be more effective than ondansetron, and the addition of dexamethasone improves vomiting symptoms (*Phillips et al 2016*).

- A randomized, DB, non-inferiority study comparing single-dose palonosetron 20 mcg/kg to multi-dose ondansetron 150 mcg/kg x 3 doses for the prevention of CINV in pediatric patients, aged 0 to 17 years, receiving MEC or HEC found that palonosetron was non-inferior to ondansetron in the acute phase (0 to 24 hours post chemotherapy) (*Kovacs et al 2016*). A randomized, DB study in pediatric patients, aged 0 to 18 years, receiving HEC found complete response rates were not significantly different during the acute phase between palonosetron 5 mcg/kg, 10 mcg/kg and ondansetron 150 mcg/kg x 3 doses *(Tan et al 2018).* Palonosetron 10 mcg/kg was superior to ondansetron and palonosetron 5 mcg/kg in the delayed phase. In a randomized, open-label study, palonosetron was found to be non-inferior and cost-effective in comparison to ondansetron for the prevention of acute CINV in children (2 to 18 years of age) with cancer (*Jain et al* 2018).
- A randomized, DB study in patients receiving HEC found that when used as part of combination therapy with dexamethasone and aprepitant, palonosetron IV was not more efficacious than granisetron IV at overall prevention of CINV. Combination therapy with palonosetron was, however, more efficacious than granisetron in controlling CINV in the delayed phase (24 to 120 hours post chemotherapy) (*Suzuki et al 2016*).
- One MC, DB, RCT evaluated dexamethasone compared to aprepitant in the prophylaxis of delayed CINV in patients with breast cancer who received chemotherapy containing anthracyclines and cyclophosphamide and the same antiemetic prophylaxis regimen. The primary endpoint was rate of complete response (ie, no vomiting or rescue treatment) from days 2 to 5 after chemotherapy. The results showed similar efficacy and toxicity between dexamethasone and aprepitant in the prevention of delayed emesis (*Roila et al 2014*).
- Aprepitant has been shown to be effective for the treatment of CINV as monotherapy and in combination with various 5-HT3 antagonists and/or dexamethasone (*Herrington et al 2008, Rapoport et al 2010, Yeo et al 2009, Herrstedt et al 2005, Warr et al 2005, Gralla et al 2005, De Wit et al 2004, Poli-Bigelli et al 2003, Hesketh et al 2003, Martin et al 2003, Gore et al 2009, Jordan et al 2009, Grunberg et al 2009*).
- In combination regimens with granisetron and dexamethasone, rolapitant has been shown to be more effective than placebo for the prevention of CINV due to MEC and HEC in clinical trials (*Rapoport et al 2015, Schwartzberg et al 2015*). In combinations with 5-HT3 antagonists and dexamethasone, addition of rolapitant has also been shown to be more effective at preventing CINV over multiple cycles of MEC or HEC, when compared to similar combinations without rolapitant (*Rapoport et al 2016*).
- The fixed-dose combination palonosetron and netupitant + dexamethasone has been shown to be significantly superior to each agent administered individually for CINV prevention following MEC (*Aapro et al 2014*); however, results from another study for CINV prevention revealed similar efficacy between the fixed-dose combination and each agent administered individually with dexamethasone (*Gralla et al 2014*).
- In a small study, *Meiri et al* reported that dronabinol and ondansetron were similarly effective for the management of delayed CINV, but combination therapy with these 2 agents was not more effective than either agent alone (*Meiri et al 2007*).
- In a large MA (13 dronabinol studies and 16 nabilone studies), treatment with cannabinoids was more effective for complete control of nausea in the first 24 hours of chemotherapy compared to alizapride, chlorpromazine, domperidone, haloperidol, metoclopramide, prochlorperazine, or thiethylperazine (relative risk [RR], 1.38; 95% confidence interval [CI], 1.18 to 1.62; number needed to treat [NNT] = 6) and for complete control of vomiting (RR, 1.28; 95% CI, 1.08 to 1.51; NNT = 8). Of note, cannabinoids were not more effective compared to other agents when the chemotherapy regimen was of very high- or very low-emetogenic risk (*Tramèr et al 2001*).
- In a second MA, authors concluded that with regard to antiemetic efficacy, dronabinol was no more effective compared to placebo (RR, 0.47; 95% CI, 0.19 to 1.16; p = 0.1) but was more effective compared to neuroleptics (RR, 0.67; 95% CI, 0.47 to 0.96; NNT = 3.4). Nabilone was not more effective than neuroleptics (RR, 0.88; 95% CI, 0.72 to 1.08; P = 0.21). With regard to patient preference and tolerability, cannabinoids were preferred over other study agents (RR, 0.33; 95% CI, 0.24 to 0.44; p < 0.00001; NNT = 1.8) (*Machado Rocha et al 2008*).
- In a MA of 23 RCTs (11 dronabinol studies and 12 nabilone studies), compared to placebo, treatment with cannabinoids resulted in a higher chance of reporting complete absence of n/v (RR, 2.9; 95% CI, 1.8 to 4.7; 3 studies); however, patients were more likely to withdraw due to an adverse event compared to placebo (2 trials; RR, 6.9; 95% CI, 1.96 to 24) and compared to prochlorperazine (RR, 3.9; 95% CI, 1.3 to 12; 5 studies). The proportion of patients who reported absence of n/v was not different between cannabinoids and prochlorperazine (*Smith et al 2015*).

NVP

- FDA-approvals of Diclegis and Bonjesta (doxylamine succinate/pyridoxine HCl) were based on 1 DB, randomized, multi-center, placebo-controlled study that evaluated the safety and efficacy of doxylamine succinate/pyridoxine HCl in pregnant adult women in the gestational age range of 7 to 14 weeks with n/v. Patients (N = 298) were randomized to 14 days of placebo or 2 tablets daily at bedtime and up to a maximum dose of 4 tablets of doxylamine succinate/pyridoxine HCl. Doxylamine succinate/pyridoxine hydrochloride treatment resulted in a statistically significant improvement in both the symptom and quality of life domains of the Pregnancy Unique-Quantification of Emesis (PUQE) score. There was a 4.8 point mean decrease from baseline in the symptom domain PUQE score at day 15 in the doxylamine succinate/pyridoxine HCl group compared to 3.9 point decrease in the placebo group (p = 0.006). For quality of life, there was also a 2.8 point mean increase from baseline in the score at day 15 in the Diclegis group compared to a 1.8 point decrease in the placebo group (P = 0.005) (*Koren et al 2010*).
  - A follow-up analysis of this trial was conducted in 2015 to evaluate the maternal safety of doxylamine/pyridoxine as compared to placebo. Based on the results of this analysis, doxylamine/pyridoxine was not associated with an overall increased in rate of adverse effects as compared to placebo (*Koren et al 2015*).

PONV

- In a MA, palonosetron was shown to be more effective for prevention of early and late postoperative nausea and late postoperative vomiting compared to ondansetron (*Xiong et al 2015*).
- A 2016 MA found that when compared to other 5-HT3 antagonists and NK1 antagonists, aprepitant reduces incidence of PONV, and need for rescue medications (*Singh et al 2016*).

RINV

- There are very few trials evaluating the prevention of RINV, and trials generally include patients with moderate to high risk RINV. The 5-HT3 receptor antagonists are the only agents in class which have demonstrated efficacy, and of these, only ondansetron and granisetron are FDA-approved.
- One DB, active-comparator trial compared oral ondansetron 8 mg to oral granisetron 2 mg in 34 bone marrow transplant patients receiving TBI, which is associated with high emetogenic risks. The study was only powered to demonstrate a difference between each active treatment groups and historical controls. In the intention-to-treat population, significantly more patients given granisetron (33.3%) or ondansetron (26.7%) had zero emetic episodes over 4 days, the primary efficacy end point, than those within the historical control group (0%) (p < 0.01) (*Spitzer et al 2000).*
- In a MA of 9 trials, fewer patients had residual emesis with 5-HT3 receptor antagonists compared with placebo (40% vs 57%; RR, 0.7; 95% CI, 0.57 to 0.86), and fewer required rescue medication (6.5% vs 36%; RR, 0.18; 95% CI, 0.05 to 0.60). Despite treatment, most patients did develop RT-induced nausea (70% vs 83%; RR 0.84; 95% CI, 0.73 to 0.96) (*Salvo et al 2012*).

CLINICAL GUIDELINES

- The 5-HT3 receptor antagonists are considered part of the standard of care in the management of CINV due to chemotherapeutic agents with moderate-to-high emetic risk, RINV, and PONV. Treatment of CINV, RINV or PONV generally involves the use of multiple agents that affect different receptor types (*American Gastroentrological Association [AGA], 2001, Herrstedt et al 2017, Hesketh et al 2017[b], Gan et al 2014, Gupta et al 2016, Roila et al 2010).*
- The 2016 expert opinion statement from the American Society for Enhanced Recovery (ASER) for the prophylaxis and management of PONV provides the following recommendations (*Gupta et al 2016*):
  - All patients should receive PONV prophylaxis during the perioperative period.
  - The number of risk factors should determine the number of medications used for treatment and prophylaxis for PONV.
- The 2017 American Society of Clinical Oncology (ASCO) antiemetic guidelines recommend the following for CINV (*Hesketh et al 2017[b]*):
  - For the prevention of n/v induced by HEC, a 4 drug combination of an NK1 receptor antagonist, a 5-HT3 receptor antagonist, dexamethasone, and olanzapine is recommended as first-line therapy.
  - For MEC, other than carboplatin area under the curve (AUC) ≥ 4 mg/mL/min, a 2-drug combination of a 5-HT3 receptor antagonist and dexamethasone is recommended.
  - For MEC that includes carboplatin AUC ≥ 4 mg/mL/min, a 3-drug combination of a NK1 receptor antagonist, a 5-HT3 receptor antagonist, and dexamethasone is recommended.

- For children receiving HEC or MEC, a 3-drug combination of a 5-HT3 receptor antagonist, dexamethasone, and aprepitant is recommended. A 2-drug regimen of a 5-HT3 receptor antagonist and dexamethasone can be used if aprepitant cannot be given; palonosetron and aprepitant can be used if dexamethasone cannot be given.
- Cannabinoids (eg, nabilone, dronabinol) are not listed as appropriate first-line antiemetics for any group of patients receiving chemotherapy of high to low emetic risk. These agents can be used in conjunction with standard regimens for patients who continue to have symptoms despite optimal prophylaxis (including use of olanzapine).

- The 2019 National Comprehensive Cancer Network (NCCN) antiemesis guideline recommends the following regimens for prevention of CINV depending on emetic risk (order does not imply preference) *(NCCN 2019):*
  - For high emetic risk IV chemotherapy on day 1: 1) NK-1receptor antagonist, 5-HT3 receptor antagonist, plus dexamethasone; 2) olanzapine, palonosetron, plus dexamethasone; 3) olanzapine, NK-1 receptor antagonist, 5-HT3 receptor antagonist, and dexamethasone. Additional agents depending on the regimen are used on days 2, 3, and 4.
  - For moderate emetic risk IV chemotherapy on day 1: 1) 5-HT3 receptor antagonist plus dexamethasone; 2) olanzapine, palonosetron, plus dexamethasone; 3) NK-1 receptor antagonist, 5-HT3 receptor antagonist, plus dexamethasone. Additional agents depending on the regimen are used on days 2 and 3.
  - For high to moderate emetic risk oral chemotherapy: 5-HT3 receptor antagonist started before chemotherapy and continued daily.
- The NCCN guideline recommends granisetron ± dexamethasone or ondansetron ± dexamethasone for pretreatment for RINV in patients receiving radiation therapy (upper abdomen/localized site) or total body irradiation *(NCCN 2019).*
- The 2018 ACOG Practice Bulletin for NVP recommends the following algorithm (*ACOG 2018*):
  - First-line non-pharmacologic options: Change the prenatal vitamin to 1 that contains only folic acid, ginger capsules, and P6 acupressure with wrist bands.
  - If symptoms persist, escalate to first-line pharmacologic interventions: pyridoxine (vitamin B6) monotherapy or pydridoxine in combination with doxylamine in various doses.
  - If symptoms persist, oral dimenhydrinate, oral diphenhydramine, rectal prochlorperazine, or oral/rectal promethazine may be added.
  - If there is no dehydration and symptoms persist, oral/intramuscular (IM) metoclopramide, oral ondansetron, oral/rectal/IM promethazine, or IM trimethobenzamide may be added.
  - If there is dehydration, patients should receive IV fluid replacement. If symptoms persist, IV dimenhydrinate, IV metoclopramide, IV ondansetron, or IV promethazine may be added.
    - If symptoms continue to persist, IM/IV chlorpromazine or oral/IV methylprednisolone may be added.

SAFETY SUMMARY

- The 5-HT3 receptor antagonists and substance P/NK1 receptor antagonists are contraindicated with hypersensitivity, and overall these agents are generally well-tolerated. Ondansetron is also contraindicated with apomorphine.
- The 5-HT3 receptor antagonists are generally very well-tolerated. There is a warning and general precaution for dolasetron regarding the risk of arrhythmias. Ondansetron and granisetron have QTc prolongation as a general precaution. In addition, the development of serotonin syndrome has been reported with 5-HT3 receptor antagonists. Ondansetron and granisetron may mask progressive ileus or gastric distention following abdominal surgery or in patients with CINV.
- Aprepitant and fosaprepitant are moderate inhibitors of CYP3A4 and aprepitant is an inducer of CYP2C9. Netupitant is a substrate and moderate inhibitor of CYP3A4. Rolapitant inhibits CYP2D6; therefore, dose reductions may be warranted with these agents. Aprepitant, fosaprepitant, and rolapitant are contraindicated taking CYP substrates of the respective enzymes that have a narrow therapeutic index, pimozide and thioridazine. Increased plasma concentrations may result in QT prolongation and torsades de pointes.
- Fosaprepitant, aprepitant, and rolapitant can cause serious hypersensitivity reactions, including anaphylaxis and anaphylactic shock, during or soon after infusion. If hypersensitivity reactions occur, discontinue the infusion and administer appropriate medical therapy. Do not reinitiate aprepitant, fosaprepitant, or rolapitant IV in patients who experience hypersensitivity symptoms with first-time use. Infusion site reactions have been reported with fosaprepitant IV; avoid infusion into small veins or through a butterfly catheter.
- Dronabinol and nabilone have the potential to be abused and produce psychological dependence. Both dronabinol and nabilone may produce alterations in mood and alterations in reality (distorted perceptions of objects and time and hallucinations).

- Dronabinol and nabilone are contraindicated in individuals who are allergic to cannabinoids. Syndros (dronabinol oral solution) is contraindicated in patients with hypersensitivity to alcohol and in patients who have received products containing disulfiram or metronidazole within 14 days. Syndros contains dehydrated alcohol (50%, w/w) and propylene glycol (5.5%, w/w). Disulfiram- and metronidazole-containing products should not be administered within 7 days of completing Syndros treatment.
- Consider risks and benefits of using dronabinol in patients with a history of seizures. Patients with cardiac disorders may experience cardiac effects such as hypotension, hypertension, syncope, or tachycardia with cannabinoids.
- Dronabinol and nabilone may exacerbate or unmask symptoms of mania, depression, or schizophrenia.
- Common adverse events with cannabinoids were dizziness, drowsiness, dry mouth, euphoria, and coordination disturbance.
- Syndros and Marinol both contain the same active ingredient, dronabinol, and the safety of Syndros oral solution was based on studies using dronabinol capsules. Additional warnings and precautions include:
  - Avoid dronabinol in patients with a psychiatric history or monitor patients for new or worsening psychiatric symptoms if use of dronabinol cannot be avoided.
  - Reduce the dose or discontinue if signs and symptoms of cognitive impairment occur.
  - Consider a dose reduction or discontinue in patients who develop worsening nausea, vomiting, or abdominal pain while taking dronabinol.
- Doxylamine/pyridoxine is contraindicated when used with monoamine oxidase inhibitors (MAOIs), as they intensify and prolong the adverse effects of the agent. The most common adverse effect observed with doxylamine/pyridoxine is somnolence. The warning section in the prescribing information states that activities requiring complete mental alertness, such as driving or operating heavy machinery, are not recommended (unless cleared to do so by a health care provider). Doxylamine/pyridoxine is also not recommended when using CNS depressants, such as alcohol. Doxylamine/pyridoxine has anticholinergic properties. It should be used with caution in women with asthma, increased intraocular pressure, narrow angle glaucoma, stenosis peptic ulcer, pyloroduodenal obstruction, and urinary bladder-neck obstruction. Additionally, false positive urine screening tests for methadone, opiates, and phencyclidine (PCP) have been reported with doxylamine/pyridoxine use.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
5-HT$_3$ Receptor Antagonists				
Dolasetron	Tablet	Oral	Take within 1 hour before chemotherapy.	Indicated in both pediatric (age 2 to 16 years based on adult PK data) and adults. ECG monitoring recommended in patients with renal impairment and the elderly.
Granisetron	Tablet, injection, injection ER, TD patch	Oral, IV, SC, TD	Take orally within 1 hour before chemotherapy or radiation, or twice daily. Administer patch a minimum of 24 hours before chemotherapy (up to a maximum of 48 hours) and remove a minimum of 24 hours after chemotherapy completion Administer IV or SC within 30 minutes before chemotherapy or administer IV right before induction	Injection approved for CINV in children 2 to 16 years. Tablet, injection ER, and TD patch have not studied in pediatrics. Do not use injection ER in severe renal impairment and adjust frequency in moderate renal impairment. Apply patch to upper outer arm. The patch may be worn for up to 7 days

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			of anesthesia or immediately before reversal of anesthesia. Do not administer SC injection ER more frequently than once a week.	depending on the duration of the chemotherapy regimen.
Ondansetron	Tablet, oral solution, ODT, oral soluble film, IV solution, injection	Oral, lingual, IV, IM	Oral administrations vary: (1) Give within 30 minutes before HEC or; (2) given twice daily, with the first dose given 30 minutes before the start of emetogenic chemotherapy and a subsequent dose 8 hours later; then twice daily for 1 to 2 days after the completion of chemotherapy or; (3) give 1 to 2 hours before each fraction of radiotherapy administered each day or; (4) give 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy or; (5) give 1 hour before induction of anesthesia or; (6) for pediatric patients, give 3 times daily with the first dose given 30 minutes before the start of emetogenic chemotherapy and subsequent doses 4 and 8 hours later; then 3 times daily (every 8 hours) for 1 to 2 days after completion of chemotherapy. IV administrations vary: (1) administer IV over 15 minutes beginning 30 minutes before chemotherapy and subsequent doses are given 4 and 8 hours after the first dose or; (2) administer IV over 2 to 5 minutes immediately before induction of anesthesia, or postoperatively if the patient did not receive prophylactic antiemetics and experiences nausea and/or vomiting within 2 hours after surgery or; (3) for pediatric patients administer IV over 2 to 5 min immediately prior to or following anesthesia induction, or postoperatively if the patient did not receive prophylactic antiemetics and experiences	Do not exceed 8 mg daily in patients with severe hepatic impairment (Child-Pugh score ≥10). There is no experience beyond first-day administration in these patients. Depending on indication and formulation, drug may be administered in patients aged ≥ 1 month.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			nausea and/or vomiting occurring shortly after surgery. Administer IM as a single dose.	
Palonosetron	IV solution	IV	IV administrations vary: (1) administer IV over 30 seconds, approximately 30 minutes before the start of chemotherapy or; (2) administer IV over 10 seconds immediately before the induction of anesthesia or; (3) for pediatric patients, administer IV over 15 minutes, beginning approximately 30 minutes before the start of chemotherapy	IV solution approved for prevention of CINV in pediatric patients aged ≥ 1 month.
Substance P/NK_1 Receptor Antagonists				
Aprepitant	Capsule, combination pack, oral suspension, IV emulsion	Oral, IV	Take orally within 1 hour before chemotherapy and once daily for 2 additional days or; 3 hours prior to induction of anesthesia. Administer IV over 30 minutes beginning 30 minutes before chemotherapy (for the 3-day regimen, continue capsules on day 2 and 3).	Given as part of a regimen that includes a corticosteroid and a 5-HT3 antagonist. Oral suspension approved for prevention of CINV in pediatric patients aged 6 months to < 12 years. Give with or without food. Use with caution in severe hepatic impairment.
Fosaprepitant	IV solution	IV	Adults: Administer IV over 20 to 30 minutes before chemotherapy. Administer IV over 30 minutes (12 to 17 years) or 60 minutes (6 months to <12 years) (for the 3-day regimen, continue capsules or oral suspension on days 2 and 3). Complete infusion approximately 30 minutes prior to chemotherapy	Given as part of a regimen that includes a corticosteroid and a 5-HT3 antagonist. Use with caution in severe hepatic impairment.
Rolapitant	Tablet	Oral	Administer orally within 2 hours prior to chemotherapy.	Given as part of a regimen that includes a corticosteroid and a 5-HT3 antagonist. Avoid use in severe hepatic impairment; if use cannot be avoided, monitor for adverse events.
THC derivatives				

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Dronabinol	Capsule, oral solution	Oral	Take orally 1 to 3 hours before chemotherapy and subsequent doses every 2 to 4 hours after chemotherapy for a total of 4 to 6 doses/day or; take orally twice daily, one hour prior to lunch and dinner.	If adverse effects occur and do not resolve in 1 to 3 days with continued use, consider dose reductions. In elderly, consider decreasing the initial dose to reduce risk of CNS adverse reactions. Always use calibrated oral dosing syringe for administration; if the prescribed dose is > 5 mg, it must be divided in multiple doses. Take with 6 to 8 ounces of water (oral solution).
Nabilone	Capsule	Oral	Take orally twice daily; initial dose is given 1 to 3 hours before chemotherapy and subsequent doses 2 to 3 times daily.	
Combination products				
Palonosetron/ netupitant Palonosteron/ fosnetupitent	Capsule Powder for injection	Oral IV	Oral administration: Take orally within 1 hour before chemotherapy IV administration: Infuse over 30 minutes starting 30 minutes before chemotherapy.	Given as part of a regimen that includes a corticosteroid. Do not use in severe renal or hepatic impairment.
Doxylamine succinate/ pyridoxine HCl	Tablet ER, tablet DR	Oral	Take orally at bedtime. Titrate dose to twice daily (for the 20/20 mg tablet ER) or 3 times daily (for the 10/10 mg tablet DR).	Bonjesta is available in 20/20 mg tablets ER and Diclegis is available in 10/10 mg tablets DR. Should be taken on an empty stomach with a glass of water.

Abbrv: DR = delayed release, ER = extended release, IV = intravenous, ODT = orally disintegrating tablet, PK = pharmacokinetic, SC = subcutaneously, TD = transdermal
See the current prescribing information for full details.

CONCLUSION

- Nausea and vomiting are significant problems, particularly in the treatment of cancer and following surgery. There are several classes of antiemetic drugs that may influence the neurotransmitter receptors involved in the pathway associated with n/v (*Longstreth 2018*)
- Choice of agents generally depends upon the relative emetogenic potential of the influencing agent, condition, or procedure, including chemotherapy or radiation therapy. Various formulations may be prescribed based on age of the patient, indication, and persistence of symptoms (*AGA 2001, ACOG 2018, Hesketh et al 2017[b], Longstreth 2018, Roila et al 2010; NCCN 2019*).
- Guideline recommendations vary according to indication. The 2017 ASCO antiemetic guidelines recommend a 4-drug combination of a NK1 receptor antagonist, a 5-HT3 receptor antagonist, dexamethasone, and olanzapine as first-line therapy for the prevention of CINV due to HEC. For MEC, a 2-drug combination of a 5-HT3 receptor antagonist plus dexamethasone is recommended for regimens other than carboplatin area AUC ≥ 4 mg/mL/min or a 3-drug combination of a NK1 receptor antagonist, a 5-HT3 receptor antagonist, and dexamethasone for patients treated with a regimen that includes carboplatin AUC ≥ 4 mg/mL/min (*Hesketh et al 2017[b]*). A 2016 expert opinion statement from ASER states that during the perioperative period, all patients should receive PONV prophylaxis (*Gupta et al 2016*). The clinical

consensus guidelines for NVP from the ACOG recommend pyridoxine alone or in combination with doxylamine as first-line pharmacologic therapy (*ACOG 2018*).

- The 5-HT3 antagonists are the cornerstone of therapy for acute emesis with MEC to HEC agents in the management of CINV, in addition to RINV and PONV. These agents include dolasetron, granisetron, ondansetron, and palonosetron. Ondansetron is the most well studied medication; however, trials haven't demonstrated a clear treatment leader between dolasetron, granisetron, and ondansetron. Palonosetron has a longer half-life and a higher receptor binding affinity than the other 5-HT3 receptor antagonists. Single-dose therapy with palonosetron is reported to be more effective than other medications in the class, particularly at preventing delayed emesis. There are very few trials evaluating the prevention of RINV. The 5-HT3 receptor antagonists are the only agents in this class review with demonstrated efficacy and, of these, only ondansetron and granisetron are FDA-approved. Oral formulations appear to have comparable efficacy to IV formulations in CINV. The 5-HT3 receptor antagonists are generally well tolerated, with mild headache the most frequent adverse event. Cardiac abnormalities ranging from ECG interval changes to torsade de pointes or QTc prolongation have been reported with dolasetron, granisetron, and ondansetron. In addition, the development of serotonin syndrome has been reported with 5-HT3 receptor antagonists (*Aapro et al 2005, AGA, 2001, Billio et al 2010, Botrel et al 2011, Dong et al 2011, Eisenberg et al 2003, Gan et al 2014, Gralla et al 2003, Gupta et al 2016, Herrstedt et al 2017, Hesketh et al 2017[b], Kaushal et al 2010, Kovacs et al 2016, Likun et al 2011, Longstreth 2018, Roila et al 2010, Salvo et al 2012, Simino et al 2016, Spitzer et al 2000, Suzuki et al 2016*).
  - All 5-HT3 antagonist formulations are available generically with the exception of Anzemet (dolasetron) tablets, Sancuso (granisetron) transdermal patch, Sustol (granisetron) extended-release injection, and Zuplenz (ondansetron) oral soluble film.
- The substance P/NK1 receptor antagonists are prescribed for both acute and delayed CINV, which is an advantage over first-generation serotonin antagonists that are generally effective for acute emesis only. These include aprepitant, fosaprepitant, and rolapitant. The substance P/NK1 receptor antagonists are most effective when used in combination with other agents, typically a 5-HT3 antagonist, a glucocorticoid, ± olanzapine, for patients receiving HEC. One MA concluded aprepitant reduces incidence of PONV and need for rescue medications compared to other 5-HT3 and NK1 antagonists. Aprepitant and fosaprepitant are moderate inhibitors of the CYP3A4 pathway and rolapitant inhibits CYP2D6; therefore, dose reductions may be warranted. Anaphylaxis, anaphylactic shock, and other serious hypersensitivity reactions have also been reported in patients receiving IV formulations, some requiring hospitalization (*AGA 2001, Gralla et al 2005, Grunberg et al 2011, Hesketh et al 2017[b], Herrington et al 2008, Herrstedt et al 2005, Longstreth 2018, Rapoport et al 2010, Roila et al 2010, Singh et al 2016, Warr et al 2005, Yeo et al 2009)*.
  - The only substance P/NK1 receptor antagonist formulations available generically are aprepitant capsules and combination pack.
- The THC derivatives, also referred to as the cannabinoids, have been prescribed for CINV and also have properties that may contribute to weight gain. The agents include nabilone and dronabinol. Dronabinol is also FDA-approved for anorexia associated with weight loss in adults with AIDS. In terms of CINV, these agents have a modest antiemetic activity and a relatively unfavorable adverse event profile. Side effects include vertigo, xerostomia, hypotension, and dysphoria, particularly in elderly patients. Trials have demonstrated that the cannabinoids are more effective compared to placebo and may be more effective than metoclopramide and prochlorperazine; however, no head-to-head trials have been conducted. The cannabinoids have little clinical utility. Due to the availability of other agents that are more effective and better tolerated, dronabinol and nabilone are recommended for later line therapy *(Hesketh et al 2017[b], Lane et al 1991, Longstreth 2018, Meiri et al 2007, Machado Rocha et al 2008, Tramer et al 2001)*.
  - Only Marinol (dronabinol) oral capsules are available generically.
- Combination products include Diclegis and Bonjesta (doxylamine succinate/pyridoxine) and Akynzeo (palonosetron/netupitant and palonosetron/fosnetupitant). Doxylamine succinate/pyridoxine is the only agent in this class FDA-approved for NVP and is guideline-recommended as a first-line pharmacologic therapy. Diclegis and Bonjesta vary by fixed dose strengths; however, each individual component is available over-the-counter (*ACOG 2018)*. The fixed-dose combination Akynzeo (palonosetron/netupitant) with dexamethasone has been shown to be significantly superior to each agent administered individually for CINV prevention following MEC (*Aapro et al 2014*); however, results from another study for CINV prevention revealed similar efficacy between the fixed-dose combination and each agent administered individually with dexamethasone (*Gralla et al 2014*). Netupitant is also a moderate inhibitor of the CYP3A4 pathway and clinicians should be aware of potential drug interactions.

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INTRODUCTION

- The proton pump inhibitors (PPIs) are a class of antisecretory compounds that suppress gastric acid secretion and are generally considered the most potent acid suppressants available. Parietal cells line the gastric mucosa and secrete acid into the gastric lumen in response to several stimuli. Within the parietal cell, a gastric transport enzyme known as hydrogen/potassium adenosine triphosphatase is involved in the final step in acid secretion. This enzyme, commonly referred to as the proton pump, exchanges potassium ions (K^+) for hydrogen ions (H^+) resulting in a lower gastric pH. The PPIs exert their effect by covalently binding to the proton pump and irreversibly inhibiting this ion exchange, causing an increase in gastric pH. The PPIs can only inhibit proton pumps that are actively secreting acid (*Wolfe et al, 2000*). Approximately 70% to 80% of the proton pumps will be active following a meal (*Welage, 2003*). As a result, single doses of PPIs will not completely inhibit acid secretion, and subsequent doses are required to inhibit previously inactive proton pumps and newly regenerated pumps. With regular dosing, maximal acid suppression occurs in 3 to 4 days (*Welage, 2003; Wolfe et al, 2000*).
- There are currently 6 PPIs available on the market in a variety of formulations. The PPIs include dexlansoprazole (Dexilant), esomeprazole magnesium (Nexium, Nexium IV, Nexium 24HR), esomeprazole strontium, lansoprazole (Prevacid, Prevacid Solutab, Prevacid 24HR), omeprazole (Prilosec, Prilosec OTC, Zegerid, Zegerid OTC), pantoprazole (Protonix, Protonix IV), and rabeprazole (Aciphex, Aciphex Sprinkle), of which certain formulations of rabeprazole, esomeprazole, lansoprazole, omeprazole, omeprazole with sodium bicarbonate, and pantoprazole are available generically. In addition, lansoprazole, esomeprazole magnesium, omeprazole, and omeprazole with sodium bicarbonate are available over-the-counter (OTC). The only currently available PPI combination product is naproxen/esomeprazole (Vimovo); however, combination products are outside the scope of this overview and will not be reviewed.
- All of the PPIs are substituted benzimidazole derivatives and are structurally related.
  - Omeprazole is a racemic mixture of *S*- and *R*-isomers and esomeprazole contains only the *S*-isomer of omeprazole. Following oral administration, the *S*-isomer has demonstrated higher plasma levels compared to the *R*-isomer.
  - Dexlansoprazole, the enantiomer of lansoprazole, has a dual delayed-release formulation designed to provide 2 separate releases of medication. It contains 2 types of enteric-coated granules resulting in a concentration-time profile with 2 distinct peaks: the first peak occurs 1 to 2 hours after administration, followed by a second peak within 4 to 5 hours. In addition, it can be taken without regard to meals (*Dexilant prescribing information, 2018*).
  - In August 2013, esomeprazole strontium was Food and Drug Administration (FDA)-approved without a proprietary name. Its approval was based on bioequivalence of esomeprazole strontium 24.65 mg and 49.3 mg delayed-release capsules to esomeprazole magnesium 20 and 40 mg delayed-release capsules, respectively. Shortly after its approval, the manufacturer made an authorized generic available by the same name. Both strengths of this product were discontinued for several months during 2015-2016, but reappeared on the market with a different manufacturer in September 2016.
- The PPIs primarily differ in their pharmacokinetic and pharmacodynamic properties in addition to their formulations. While some differences have been reported in head-to-head studies directly comparing the PPIs, the magnitude of these differences is generally small, and the clinical significance has not been established. When administered in equivalent dosages, the PPIs have generally demonstrated comparable efficacy to one another (*Dean, 2010*).
- In general, all PPIs are FDA-approved for the treatment of gastroesophageal reflux disease (GERD) and for the healing and maintenance of erosive esophagitis. Some of the agents also have approval for the treatment of peptic ulcer disease, the treatment of pathological hypersecretory conditions, and *Helicobacter pylori (H. pylori)* eradication as part of combination therapy with antibiotics.
- Current national and international consensus guidelines recognize the PPIs as first-line therapy for the management of dyspepsia, GERD, peptic ulcer disease, and eradication of *H. pylori.* In addition, these agents have a role in the management of Barrett's esophagus. Most currently available guidelines do not give preference to one PPI over another (*American Gastroenterological Association [AGA], 2011; Chey et al, 2017; Kahrilas et al, 2008; Katz et al, 2013; Laine et*

al, 2012; Lanza et al, 2009; Malfertheiner et al, 2012; Rosen et al, 2018; Shaheen et al, 2016; Moayyedi et al, 2017; Vakil et al, 2005). The 2016 joint European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)/North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) guideline for management of *H. pylori* in children and adolescents states that esomeprazole and rabeprazole may be preferred when available, because they are less susceptible to degradation by rapid CYP2C19 metabolizers (*Jones et al, 2017*). However, the American Academy of Pediatrics does not recommend routine use of PPIs in preterm infants for GERD due to a lack of evidence of PPI efficacy in this population as well as evidence of significant adverse effects (*Eichenwald 2018*).

- The agents included in this review are listed alphabetically by brand name in Table 1. Since there are multiple branded agents that contain the same generic component(s), the remaining tables in the review are organized alphabetically by generic name.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Aciphex (rabeprazole sodium) delayed-release tablets	✔
Aciphex Sprinkle (rabeprazole sodium) delayed-release capsules	-
Dexilant (dexlansoprazole) delayed-release capsules	-†
esomeprazole strontium, delayed-release capsules	-
esomeprazole magnesium* delayed-release capsules	✔
lansoprazole* delayed-release orally disintegrating tablets	✔
Nexium (esomeprazole magnesium) delayed-release capsules	✔
Nexium (esomeprazole magnesium) granules for delayed-release oral suspension	-
Nexium IV (esomeprazole sodium) injection	✔
Nexium 24HR* (esomeprazole magnesium) delayed-release capsules	✔
Nexium 24HR* (esomeprazole magnesium) delayed-release tablets	-
omeprazole magnesium* delayed-release capsules, tablets	✔
Prevacid (lansoprazole) delayed-release capsules	✔
Prevacid 24HR* (lansoprazole) delayed-release capsules	✔
Prevacid Solutab (lansoprazole) delayed-release orally disintegrating tablets	✔
Prilosec (omeprazole magnesium) powder for delayed-release oral suspension	-
Prilosec OTC* (omeprazole magnesium) delayed-release tablets	✔
Protonix (pantoprazole) delayed-release tablets	✔
Protonix (pantoprazole) powder for delayed-release oral suspension	-
Protonix IV (pantoprazole) injection, powder for solution	✔
Zegerid (omeprazole with sodium bicarbonate) capsules‡	✔
Zegerid (omeprazole with sodium bicarbonate) powder for oral suspension	✔
Zegerid OTC* (omeprazole with sodium bicarbonate) capsules, oral suspension	✔

*Available OTC.
†Generic 60 mg delayed-release capsule approved by the FDA for adult patients, but generic product not yet available due to patent exclusivity.
‡A branded generic product, Omeppi, which contains the same ingredients as Zegerid capsules is also available.

(*DRUGS@FDA.com, 2019; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2019; Clinical Pharmacology 2019*)

INDICATIONS

Table 2. FDA-Approved Indications

Indication	Dexlansoprazole	Esomeprazole magnesium and strontium	Esomeprazole sodium	Lansoprazole	Omeprazole magnesium	Omeprazole/ sodium bicarbonate	Pantoprazole	Rabeprazole
GERD[a]								
Maintaining healing of erosive esophagitis	✔	✔		✔	✔	✔	✔	✔
Treatment of erosive esophagitis	✔	✔	✔	✔	✔	✔	✔ c	✔
Treatment of symptomatic GERD	✔	✔		✔	✔	✔		✔
Peptic Ulcer Disease								
Healing of nonsteroidal anti-inflammatory drug (NSAID)-associated gastric ulcer				✔				
H. pylori eradication to reduce the risk of duodenal ulcer recurrence		✔ b		✔ b	✔ b			✔ b
Maintenance of healing duodenal ulcers				✔				
Risk reduction of NSAID-associated gastric ulcer		✔		✔				
Treatment of active, benign gastric ulcer				✔	✔	✔		
Treatment of active duodenal ulcers				✔	✔	✔		✔
Other								
Risk reduction of upper gastrointestinal bleeding in critically ill patients						✔		
Treatment of frequent heartburn for up to 14 days		✔ (Nexium 24HR)		✔ (Prevacid 24HR)	✔ (Prilosec OTC)	✔ (Zegerid OTC)		

Indication	Dexlansoprazole	Esomeprazole magnesium and strontium	Esomeprazole sodium	Lansoprazole	Omeprazole magnesium	Omeprazole/ sodium bicarbonate	Pantoprazole	Rabeprazole
Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome		✔		✔	✔		✔ d	✔
Risk reduction of rebleeding of gastric or duodenal ulcers following therapeutic endoscopy in adults			✔					

a Esomeprazole magnesium/sodium, lansoprazole, omeprazole, and pantoprazole are approved for pediatric patients. Dexlansoprazole and rabeprazole are indicated for patients 12 years of age or older. Esomeprazole strontium and omeprazole/sodium bicarbonate are approved for adult patients.
b As triple therapy in combination with amoxicillin and clarithromycin (esomeprazole magnesium/strontium, lansoprazole, omeprazole, and rabeprazole) or dual therapy with amoxicillin (lansoprazole) or clarithromycin (omeprazole).
c Oral formulations indicated for the short-term treatment of erosive esophagitis associated with GERD; intravenous formulation indicated for the short-term treatment (7 to 10 days) of adult patients with GERD associated with a history of erosive esophagitis.
d Intravenous and oral formulation.

(*Prescribing information: Aciphex, 2018; Aciphex Sprinkle, 2018; Dexilant, 2018; esomeprazole strontium, 2018; lansoprazole, 2018; Nexium, 2018; Nexium IV, 2018; Nexium 24HR, 2018; Prevacid, 2018; Prevacid 24HR, 2017; Prilosec suspension, 2018; Prilosec OTC, 2018; Protonix, 2018; Protonix IV, 2018; Zegerid, 2018; Zegerid OTC, 2019*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Clinical trials consistently demonstrate that the PPIs are highly effective in treating, providing symptom relief, and preventing relapse in gastric acid disorders such as GERD and peptic ulcer disease (*Armstrong et al, 2004; Bardhan et al, 2001; Bazzoli et al, 1998; Caro et al, 2001; Castell et al, 2002; Castell et al, 2005; Chan et al, 2010; Chey et al, 2003; Choi et al, 2007; Conrad et al, 2005; Delchier et al, 2000; Devault et al, 2006; Edwards et al, 2001; Fass et al, 2009; Fass et al, 2011; Fass et al, 2012; Felga et al, 2010; Fennerty et al, 2005; Fujimoto et al, 2011; Gisbert et al, 2003; Gisbert et al, 2004[a]; Gisbert, et al, 2004[b]; Goh et al, 2007; Haddad et al, 2013; Howden et al, 2002; Howden et al, 2009; Hsu et al, 2005; Kahrilas et al, 2000; Katz et al, 2007; Kinoshita et al, 2011; Klok et al, 2003; Labenz et al, 2005[a]; Labenz et al, 2005[b]; Laine et al, 2011; Lauritsen et al, 2003; Liang et al, 2017; Lightdale et al, 2006; McNicholl et al, 2012; Metz et al, 2009; Mönnikes et al, 2012; Pace et al, 2005; Pilotto et al, 2007; Pouchain et al, 2012; Ramdani et al, 2002; Regula et al, 2006; Richter et al, 2001[a]; Richter et al, 2011[b]; Scheiman et al, 2011; Schmitt et al, 2006; Scholten et al, 2003; Sharma et al, 2001; Sharma et al, 2009; Sugano et al, 2011; Tsai et al, 2004; Ulmer et al, 2003; van Pinxteren et al, 2010; Vergara et al, 2003; Wang et al, 2006; Wu et al, 2007*).
- The safety and efficacy of esomeprazole strontium have been established based on adequate and well-controlled adult studies of esomeprazole magnesium in the healing and maintenance of erosive esophagitis, symptomatic GERD, risk reduction of NSAID-associated gastric ulcer, *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence, and pathological hypersecretory conditions including Zollinger-Ellison Syndrome.
- A number of studies have compared the various PPIs to one another. While some differences have been reported, the magnitude of differences has been small and of uncertain clinical importance. In particular, the degree to which any of the reported differences would justify the selection of one versus another PPI, particularly when considering cost-effectiveness, is unclear (*Wolfe, 2017*).

GERD

- In meta-analyses and direct comparator trials, lansoprazole, omeprazole, pantoprazole, and rabeprazole have demonstrated comparable healing rates, maintenance of healing, and/or symptomatic relief of GERD (*Bardhan et al, 2001; Caro et al, 2001; Edwards et al, 2001; Klok et al, 2003; Pace et al, 2005; Sharma et al, 2001*). Furthermore, Richter et al reported that lansoprazole produced a significantly quicker and greater symptomatic relief of GERD compared to omeprazole; however, the absolute differences between the 2 treatments were small, and the clinical impact of the difference was not measured within the clinical trial (*Richter et al, 2001[b]*).
- The results of several meta-analyses and clinical trials demonstrated that esomeprazole may provide higher healing rates for erosive esophagitis and/or symptomatic relief of GERD compared to standard doses of lansoprazole, omeprazole, and pantoprazole at 4 and 8 weeks (*Castell et al, 2002; Devault et al, 2006; Edwards et al, 2001; Kahrilas et al, 2000; Klok et al, 2003; Labenz et al, 2005[a]; Labenz et al, 2005[b]; Li et al, 2017[a]; Richter et al, 2001[a]*). Subgroup analyses of 2 trials noted higher healing rates with esomeprazole in patients with more severe disease (*Labenz et al, 2005[a]; Schmitt et al, 2006*).
- Close analyses of all of these trials demonstrate that the overall differences between the various PPI agents were generally small and the clinical significance is not clear. In addition, results of these trials have not been consistently demonstrated in other clinical trials, particularly in those evaluating lansoprazole and pantoprazole (*Armstrong et al, 2004; Chey et al, 2003; Goh et al, 2007; Howden et al, 2002; Lightdale et al, 2006; Scholten et al, 2003*).

Peptic Ulcer Disease

- Meta-analyses and head-to-head trials comparing various PPIs for the treatment of peptic ulcer disease with *H. pylori* demonstrated comparable rates of eradication when paired with comparable antibiotic regimens (*Bazzoli et al, 1998;*

Choi et al, 2007; Gisbert et al, 2003; Gisbert et al, 2004[a]; Gisbert, et al 2004[b]; Ulmer et al, 2003; Vergara et al, 2003; Wang et al, 2006; Wu et al, 2007).

- Results from 2 meta-analyses suggested that both esomeprazole- and rabeprazole-based *H. pylori* regimens were more effective with regard to eradication rates compared to traditional PPI-based regimens (lansoprazole, omeprazole, and pantoprazole) (*McNicholl et al, 2012; Xin et al, 2016*).

CLINICAL GUIDELINES

- Current consensus among various national and international treatment guidelines recommend a PPI as the first-line therapy in the treatment and maintenance of healed erosive esophagitis, symptomatic GERD, dyspepsia (patients ≤ 55 years and no alarm features), and peptic ulcer disease caused by NSAID therapy. Triple and quadruple combination therapy with antibiotics and a PPI are considered first-line therapy for peptic ulcer disease caused by *H. pylori*. Most of the treatment guidelines do not recommend one PPI over another, and no treatment guideline recommends one formulation of a PPI over another (*American Gastroenterological Association, 2011; Chey et al, 2017; Kahrilas et al, 2008; Katz et al, 2013; Laine et al, 2012; Lanza et al, 2009; Malfertheiner et al, 2012; Shaheen et al, 2016; Moayyedi et al, 2017; Rosen et al, 2018*). The 2016 joint ESPGHAN/NASPGHAN guideline for management of *H. pylori* in children and adolescents states that esomeprazole and rabeprazole may be preferred when available, because they are less susceptible to degradation by rapid CYP2C19 metabolizers (*Jones et al, 2017*).
  - According to the AGA medical position statement on the management of GERD (2008) and the American College of Gastroenterology (ACG) guideline for the diagnosis and management of GERD (2013), PPIs are considered the drug of choice in the treatment of GERD with H_2-receptor antagonists as alternative agents that can be used for maintenance of GERD symptoms without erosive disease (*Kahrilas, 2008; Katz et al, 2013*). The ACG medical position statement notes that there are no major differences between the different PPIs (*Katz et al, 2013*).
  - According to joint recommendations from NASPGHAN and ESPGHAN (2018), PPIs are recommended as first-line therapy for the treatment of reflux-related erosive esophagitis in infants and children with GERD. For children with GERD with typical symptoms, a 4- to 8-week course of H_2-receptor antagonists or PPIs is recommended. Patients with asthma and typical GERD symptoms should also be treated (*Rosen et al, 2018*). The American Academy of Pediatrics does not recommend routine use of PPIs in preterm infants for GERD. The 2018 guidance highlights the lack of evidence of PPI efficacy in this population as well as evidence of significant adverse effects (*Eichenwald 2018*).
  - According to the ACG guideline for prevention of NSAID-related ulcer complications (2009), misoprostol or high-dose PPI treatment is recommended as co-therapy with anti-inflammatory analgesics in certain patients with high- and moderate-NSAID gastrointestinal risk. In patients who require both anti-inflammatory analgesics and low-dose aspirin, naproxen with either misoprostol or a PPI is also recommended (*Lanza et al, 2009*).
  - According to the ACG guideline on the management of *H. pylori* infection (2017), there are many first-line options for *H. pylori* treatment; a regimen should be based on patient allergies, previous macrolide exposure, and known *H. pylori* resistance rates. A PPI, clarithromycin, and amoxicillin or metronidazole (clarithromycin-based triple therapy) regimen for 14 days is recommended where *H. pylori* clarithromycin resistance is known to be < 15%. Alternately, bismuth quadruple therapy, consisting of a PPI, bismuth, tetracycline, and a nitroimidazole (metronidazole or tinidazole) for 10 to 14 days should be considered as a first-line therapy option for areas of high clarithromycin resistance (*Chey et al, 2017*).
  - High-dose PPIs are often used as primary long-term therapy in Zollinger-Ellison syndrome. PPIs are considered generally safe, even at high doses, and have demonstrated superior acid suppression, healing rates, and symptom relief compared with other antisecretory therapies (*Bergsland, 2018; National Institute of Diabetes and Digestive and Kidney Diseases [NIDDK] website*).
  - A 2015 clinical guideline by the ACG also recognized the use of PPIs in the management of Barrett's Esophagus; long-term PPI use will likely produce a net benefit for these patients (*Freedberg et al, 2017; Shaheen et al, 2016*).

SAFETY SUMMARY

- In general, the PPIs are well tolerated; abdominal pain, diarrhea, flatulence, headache, nausea, and vomiting are the most frequently reported adverse events.
- Long-term use of PPIs for 5 or more years has been associated with an increase in hip fractures (*Targownik et al, 2008; Islam et al, 2018*). When administered for 7 or more years, PPIs have been associated with a significantly increased risk of an osteoporosis-related fracture. At this time, there is inadequate evidence to mandate bone density studies and calcium supplementation in patients receiving chronic PPI therapy (*Freedberg et al, 2017; Kahrilas et al, 2008*).

Additional data are needed to determine the value of osteoporotic medications in patients receiving long-term PPI therapy (*Targownik et al, 2008*). The 2013 guidelines for the diagnosis and management of GERD recommend continuation of PPI therapy unless additional risk factors for osteoporosis exist (*Katz et al, 2013*).

- Contraindications of the PPIs include hypersensitivity to any component of their formulations. PPIs are also contraindicated in patients receiving rilpivirine-containing products.
- Warnings and precautions with the use of PPIs include risks of acute interstitial nephritis, cyanocobalamin deficiency, *Clostridium difficile*-associated diarrhea, bone fractures, hypomagnesemia, and fundic gland polyps. Concomitant use with clopidogrel, St. John's Wort, rifampin, high-dose methotrexate, and some antiretroviral medications (eg, protease inhibitors such as atazanavir and nelfinavir) should be avoided. Co-administration of PPIs with warfarin may increase international normalized ratio (INR) and prothrombin time; the dose of warfarin may need to be adjusted. False positive results for diagnostic investigations of neuroendocrine tumors may occur due to an increase in serum chromogranin A (CgA) levels. Cutaneous and systemic lupus erythematosus have been reported in patients taking PPIs; new onset events and exacerbations of existing autoimmune disease have occurred. Finally, symptomatic response to PPI therapy does not preclude the presence of gastric malignancy.
- The concomitant use of PPIs with thienopyridines such as clopidogrel was addressed in a consensus guideline from the American College of Cardiology Foundation, American College of Gastroenterology, and American Heart Association, which recommended PPI therapy be continued unless additional risk factors for cardiovascular disease exist (*Abraham et al, 2010*). A systematic review exploring the use of PPIs in combination with dual antiplatelet therapy that included clopidogrel showed inconclusive results for causing cardiovascular events while another systematic review showed an increase in cardiovascular events with PPIs in 1 analysis and only with pantoprazole, lansoprazole, and esomeprazole but not with omeprazole in another (*Malhotra et al, 2018; Melloni et al, 2015; Sherwood et al, 2015*). In a large, longitudinal, observational study of patients discharged after acute myocardial infarction treated with percutaneous coronary intervention, the use of clopidogrel or prasugrel in combination with a PPI was associated with statistically significantly more cardiovascular events than patients not discharged on a PPI (adjusted hazard ratio [HR], 1.38; 95% confidence interval [CI], 1.21 to 1.58). However, the authors noted that patients prescribed a concurrent PPI were more likely to be older and have more complex comorbidity profiles (*Jackson et al, 2016*).
- Recent research has demonstrated an association with PPIs and cardiovascular, renal, and neurological morbidity. PPI use interferes with acid production in endothelial lysosomes, leading to oxidative stress and accelerated cell death, and may contribute to the pathogenesis of the aforementioned morbidities (*Yepuri et al, 2016*).
  - A retrospective study using a data mining strategy identified 2.9 million patients in the general population taking PPIs for GERD. Data showed that GERD patients exposed to PPIs had a 1.16-fold increased association with myocardial infarction and a 2-fold increased association with cardiovascular mortality. H_2-receptor antagonists used for GERD were not associated with an increased cardiovascular risk (*Shah et al, 2015*). Another retrospective study in Taiwan found that PPI use was associated with an increased risk of hospitalization for ischemic stroke (HR, 1.36; 95% CI, 1.14 to 1.620; p = 0.001) within the 120-day period after PPI initiation (*Wang et al, 2017*). A systematic review of 6 nonrandomized observational studies directly comparing the effect of PPI use on either mortality (3 studies), and/or examining the relationship of PPI use with myocardial infarct, stroke, or peripheral arterial event determined that PPI use was associated with a higher risk for all-cause mortality (odds ratio [OR], 1.68; 95% CI, 1.53 to 1.84) and major cardiovascular events (OR, 1.54; 95% CI, 1.11 to 2.13). The rate of major cardiovascular events was also significantly higher in patients taking PPIs (OR, 1.54; 95% CI, 1.11 to 2.13, p = 0.01) (*Shiraev et al, 2017*).
  - In a large cohort study, 144,032 incident users of either PPIs or H_2-antagonists were followed for 5 years. Patients using PPIs had an increased risk of incident chronic kidney disease (HR, 1.26; 95% CI, 1.2 to 1.33) and increased risk of estimated glomerular filtration rate decline and end-stage renal disease as compared to H_2-antagonist users (*Xie et al, 2017*). Similar patterns were identified in another large population-based cohort study; twice-daily PPI dosing was associated with a higher risk than once-daily dosing (*Lazarus et al, 2016*). A large retrospective analysis found that PPI users had an increased risk for doubled serum creatinine levels (HR, 1.26; 95% CI, 1.05 to 1.51) and an increased risk for 30% or more decrease in estimated glomerular filtration rate (HR, 1.26; 95% CI, 1.16 to 1.36) compared to H_2-antagonist users. The risks of end-stage renal disease (HR, 2.40; 95% CI, 0.76 to 7.58) and acute kidney injury (HR, 1.30; 95% CI, 1.00 to 1.69) were also elevated with PPIs, but the risk elevations were not statistically significant. The study concluded that PPIs are associated with the risk of chronic kidney disease progression (*Klatte et al, 2017*). A retrospective analysis of claims data in Taiwan also identified an increased risk for PPI-associated chronic kidney disease in PPI-users compared to non-users (*Hung et al, 2017*). Meta-analyses evaluating the risk of chronic kidney disease have identified an increased risk for chronic kidney disease and end-

stage renal disease in PPI-users as compared to both H_2-receptor antagonists-users and non-PPI users (*Nochaiwong et al, 2018; Wijarnpreecha et al, 2017*). However, these findings are based on observational studies and were deemed as low-quality evidence by Nochaiwong et al.

- A prospective cohort study using observational data from 73,679 patients ≥ 75 years and dementia-free at baseline were analyzed. Patients on PPIs (N = 2950) had a significantly increased risk of dementia than patients not on PPIs (HR, 1.44; 95% CI, 1.36 to 1.52, p < 0.001) (*Gomm et al, 2016*). However, this finding has not been consistently replicated. A prospective cohort study of 13,684 patients enrolled in the Nurses' Health Study II did not find a significant association between PPI use and cognitive function after adjusting for H_2-antagonist use and other confounding variables (*Lochhead et al, 2017*). Additionally, a nested case-control study using data from the Finnish nationwide healthcare registers did not find an association between PPI use and Alzheimer's disease (OR, 1.03; 95% CI, 1.00 to 1.05) (*Taipale et al, 2017*). A prospective study analyzing Denmark survey data did not find an association between PPI use and cognitive decline (adjusted cognitive difference of 0.69; 95% CI, -4.98 to 3.61) (*Wod et al, 2018*). A prospective population-based cohort study (N = 3484) found no association between PPI use and dementia risk (HR, 0.87, 95% CI, 0.65 to 1.18 for 1 year of daily use; HR, 0.99, 95% CI, 0.75 to 1.30 for 3 years of daily use; HR, 1.13, 95% CI, 0.82 to 1.56 for 5 years of daily use) *(Gray et al*, 2017). An observational longitudinal study found PPIs were not associated with dementia or Alzheimer's disease. Patients on continuous and intermittent therapy had a lower risk of cognitive decline (HR, 0.78, 95% CI, 0.66 to 0.93 and HR, 0.84, 95% CI, 0.76 to 0.93, respectively) (*Goldstein et al*, *2017*).

- A recent meta-analysis found an association between gastric mucosal atrophy and long-term PPI treatment. In this analysis of 13 studies (1465 patients on long-term PPI and 1603 controls), patients on long-term PPI therapy had higher rates of gastric atrophy (OR, 1.55; 95% CI, 1.00 to 2.41) than controls. A subgroup analysis noted that omeprazole and lansoprazole groups had higher rates of gastric atrophy compared to control groups, while esomeprazole had lower rates compared to control groups (*Li et al, 2017[b]*). An increased risk of gastric cancer with long-term use of PPIs was also demonstrated in a recent meta-analysis; two studies (n = 17,158 patients) provided data for this outcome (*Islam et al, 2018*).
- A 2018 meta-analysis evaluating adverse events associated with long-term use of PPIs demonstrated an increased risk of community-acquired pneumonia (OR, 1.67; 95% CI, 1.04 to 2.67) for long-term users of PPIs, with older patients (> 60 years) and those who took higher doses of PPIs demonstrating greater risk; 7 studies (n = 868,882) provided data for this outcome (*Islam et al, 2018*).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Dexlansoprazole	Delayed-release capsule	Oral	Treatment of symptomatic, non-erosive GERD (≥ 12 years of age): Once daily for 4 weeks Treatment of erosive esophagitis (≥ 12 years of age: Once daily for up to 8 weeks Maintenance of healing of erosive esophagitis (≥ 12 years of age: Once daily for up to 6 months in adults and	Delayed-release capsules can be taken without regard to food. Delayed-release capsules can be opened and contents sprinkled onto applesauce for immediate consumption. Delayed-release capsules can be opened and contents mixed in 20 mL of water for administration in an oral syringe for immediate consumption. Refill the oral syringe with 10 mL of water twice to ensure all of the contents are delivered. Delayed-release capsules can be opened with contents mixed in 20 mL of water and withdrawn in a catheter-tip syringe and administered by nasogastric tube. Refill the syringe with 10 mL of water twice to flush the tube.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			16 weeks in patients 12 to 17 years of age	
Esomeprazole magnesium	Delayed-release capsules Delayed-release suspension (unit-dose packets) Delayed-release capsules (OTC) Delayed-release tablets (OTC)	Oral	Treatment of symptomatic GERD (≥ 12 years of age): Once daily for 4 to 8 weeks *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence: Once daily for 10 days Treatment of erosive esophagitis (≥ 12 years of age): Once daily for 4 to 16 weeks Maintenance of healing of erosive esophagitis: Once daily for up to 6 months Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome: Twice daily Risk reduction of NSAID-associated gastric ulcer: Once daily for up to 6 months Treatment of frequent heartburn (OTC): Once daily for 14 days; may repeat a 14-day course every 4 months Treatment of symptomatic GERD, short-term (1 to 11 years of age):	Should be taken at least 1 hour before meals. Capsules can be opened and contents sprinkled onto applesauce for immediate consumption. Contents can also be emptied into 60 mL catheter tipped syringe and shaken with 50 mL of water for administration via nasogastric tube. Packets for delayed-release suspension should be emptied into water (5 mL for 2.5 mg or 5 mg; 15 mL for 10 mg, 20 mg, or 40 mg), stirred, left for 2 to 3 minutes to thicken, and drank within 30 minutes. Can also be emptied into a catheter-tipped syringe for administration via nasogastric tube. Doses > 20 mg should not be exceeded in patients with severe liver impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Once daily for up to 8 weeks Treatment of erosive esophagitis (1 to 11 years of age): Once daily for 8 weeks (weight-based) Treatment of erosive esophagitis due to acid-mediated GERD (1 month to < 1 year of age): Once daily for up to 6 weeks (weight-based)	
Esomeprazole sodium	Powder for injection	IV	Treatment of symptomatic GERD with erosive esophagitis (Adults): once daily by IV injection or IV infusion Risk reduction of rebleeding of gastric or duodenal ulcers following therapeutic endoscopy in adults: IV infusion over 30 minutes followed by a continuous infusion over 3 days (72 hours) Treatment of symptomatic GERD with erosive esophagitis (1 to 17 years of age): Once daily (weight-based) by IV infusion over 10 to 30 minutes Treatment of symptomatic GERD with erosive esophagitis (1 month to < 1 year): Once daily	Should be discontinued in favor of oral therapy as soon as oral therapy is possible.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			(weight-based) by IV infusion over 10 to 30 minutes	
Esomeprazole strontium	Delayed-release capsules	Oral	Treatment of erosive esophagitis in adults: Once daily for 4 to 16 weeks Maintenance of healing of erosive esophagitis in adults: Once daily for up to 6 months Treatment of symptomatic GERD in adults: Once daily for 4 to 8 weeks Risk reduction of NSAID-associated gastric ulcer in adults: Once daily for up to 6 months *H. pylori* eradication (triple therapy) in adults: Once daily for 10 days Pathological hypersecretory conditions in adults: Twice daily	Should be taken at least 1 hour before meals. Capsule can be swallowed whole. Do not chew or crush capsule. Capsules can be opened and contents sprinkled onto applesauce for immediate consumption. Do not chew or crush granules. Contents can also be emptied into 60 mL catheter tipped syringe and shaken with 50 mL water for administration via nasogastric tube.
Lansoprazole	Delayed-release capsules Delayed-release orally disintegrating tablets Delayed-release capsules (OTC) Delayed-release orally disintegrating tablets (OTC)	Oral	Treatment of symptomatic GERD and heartburn (adults): Once daily for up to 8 weeks *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence: 2 to 3 times daily for 10 to 14 days Treatment of active duodenal ulcers: Once daily for 4 weeks	Should be taken before eating and swallowed whole. Capsules (non-OTC) can be opened and contents sprinkled into applesauce, Ensure, pudding, cottage cheese, yogurt, or strained pears. May be mixed in 60 mL apple juice, orange juice, or tomato juice for immediate consumption. Contents can also be mixed into 40 mL apple juice for administration via nasogastric tube, flushing with additional juice.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Treatment of erosive esophagitis: Once daily for up to 16 weeks Treatment of active, benign gastric ulcer: Once daily for up to 8 weeks Healing of NSAID associated gastric ulcer: Once daily for 8 weeks Maintenance of healing duodenal ulcers: Once daily for up to 12 months Maintenance of healing of erosive esophagitis: Once daily for up to 12 months Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome: Once daily Risk reduction of NSAID-associated gastric ulcer: Once daily up to 12 weeks Treatment of symptomatic GERD and erosive esophagitis (1 to 11 years of age): Once daily for up to 12 weeks (weight-based) Treatment of symptomatic	Orally disintegrating tablets should be placed on the tongue, allowed to disintegrate, and swallowed. Orally disintegrating tablets (non-OTC) may also be mixed with water (4 mL for 15 mg tablet or 10 mL for 10 mg tablet) in an oral syringe and gently shaken for oral or nasogastric tube administration.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			nonerosive GERD (12 to 17 years of age): Once daily for up to 8 weeks Treatment of symptomatic GERD with erosive esophagitis (12 to 17 years of age): Once daily for up to 8 weeks Treatment of frequent heartburn (OTC): Once daily for 14 days; may repeat a 14-day course every 4 months	
Omeprazole magnesium	Delayed-release capsules Delayed-release suspension (unit-dose packets) Delayed-release tablets and orally disintegrating tablets (OTC)	Oral	Treatment of symptomatic GERD and heartburn (adults): Once daily for 4 weeks Treatment of symptomatic GERD and erosive esophagitis due to acid-mediated GERD (1 to 16 years of age): Once daily (weight-based) for up to 4 weeks for symptomatic GERD and for up to 12 weeks for erosive esophagitis due to acid-mediated GERD *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence (adults): Once or twice daily for 10 to 14 days; an additional 10 to 18 days of therapy may be needed Treatment of active duodenal ulcers (adults):	Should be taken before eating. Capsules can be opened and contents sprinkled into applesauce for immediate consumption. Unit-dose packets should be emptied into water, stirred, left for 2 to 3 minutes to thicken, and drank within 30 minutes. Capsule contents and oral suspension can also be emptied into a catheter-tipped syringe for administration via nasogastric tube.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Once daily for 4 weeks; some patients may require an additional 4 weeks Treatment of erosive esophagitis due to acid-mediated GERD (adults): Once daily for 4 to 16 weeks Treatment of erosive esophagitis due to acid-mediated GERD (1 month to < 1 year of age): Once daily for up to 6 weeks (weight-based) Treatment of active, benign gastric ulcer (adults): Once daily for 4 to 8 weeks Maintenance of healing of erosive esophagitis due to acid-mediated GERD (adults): Once daily for up to 12 months Maintenance of healing of erosive esophagitis due to acid-mediated GERD (1 to 16 years of age): Once daily (weight-based) for up to 12 months Note: Controlled studies do not extend beyond 12 months. Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome (adults):	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Once daily Treatment of frequent heartburn (OTC): Once daily for 14 days; may repeat a 14-day course every 4 months	
Omeprazole/ sodium bicarbonate	Capsules Powder for oral suspension (unit-dose packets): Capsules (OTC): Note: all formulations are indicated for adults only. Their safety and effectiveness in pediatric patients < 18 years of age have not been established.	Oral	Treatment of symptomatic GERD (with no esophageal erosions): Once daily for 4 to 8 weeks Treatment of active duodenal ulcers: Once daily for 4 weeks; some patients may require an additional 4 weeks Treatment of erosive esophagitis: Once daily for 4 to 16 weeks Treatment of active, benign gastric ulcer: Once daily for up to 12 months Maintenance of healing of erosive esophagitis: Once daily for up to 12 months Risk reduction of upper gastrointestinal bleeding in critically ill patients: Once daily for up to 12 months Treatment of frequent heartburn (OTC): Once daily for 14 days; may repeat a 14-day course every 4 months	Should be taken on an empty stomach at least 1 hour before a meal. Capsules should be swallowed intact with only water and should never be opened. Due to sodium bicarbonate content, one 40 mg unit (capsule or powder packet) is not equivalent to two 20 mg units; therefore, two 20 mg units should not be substituted for one 40 mg unit. Packets for delayed-release oral suspension should be emptied into a small cup with one to two tablespoons of water, stirred well, and drank immediately. Can also be constituted with 20 mL water in an appropriate-sized syringe for administration via nasogastric or orogastric tube. Patients receiving continuous nasogastric or orogastric tube feedings should have these feedings suspended 3 hours before and 1 hour after omeprazole/sodium bicarbonate administration.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Pantoprazole	Delayed-release suspension (unit-dose packets) Delayed-release tablets Powder for injection	Oral, IV	Treatment of erosive esophagitis associated with GERD: Delayed-release suspension, delayed-release tablet: Once daily for up to 8 to 16 weeks Powder for injection: Once daily for 7 to 10 days Maintenance of healing of erosive esophagitis: Delayed-release suspension, delayed-release tablet: 40 mg daily for up to 12 months Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome: Delayed-release suspension, delayed-release tablet: Twice daily Powder for injection: Twice daily Treatment of erosive esophagitis (≥ 5 years of age): Delayed-release suspension, delayed-release tablet: Once daily for 8 weeks	Powder for injection should be discontinued in favor of oral therapy as soon as oral therapy is possible. Tablets can be taken with or without food and should be swallowed whole. Delayed-release oral suspension should only be administered approximately 30 minutes prior to a meal in 1 teaspoonful of applesauce (eat within 10 minutes) or apple juice (drink immediately). Can also be mixed with 10 mL apple juice in a catheter-tipped 60 mL syringe for administration via nasogastric tube or gastrostomy tube. No refrigeration required. Can be reconstituted for 2-minute or 15-minute infusion.
Rabeprazole	Delayed-release tablets Sprinkle delayed-release capsules	Oral	Treatment of symptomatic GERD: Once daily for up to 4 to 8 weeks *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence:	Take 30 minutes before a meal. For *H. pylori* regimen, take with morning and evening meals. Swallow tablets whole; do not chew, crush, or split. Contents of the Sprinkle capsules should be sprinkled on a spoonful of soft food or liquid, take the full dose within 15 minutes.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Twice daily for 7 days Healing of duodenal ulcers: Once daily after the morning meal for up to 4 weeks Healing of erosive or ulcerative GERD: Once daily for 4 to 16 weeks Maintenance of healing of erosive or ulcerative GERD: Once daily for up to 12 months Treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome: Once daily Treatment of symptomatic GERD in adolescent patients ≥ 12 years of age: Once daily for up to 8 weeks Treatment of GERD in pediatric patients 1 to 11 years of age (Aciphex Sprinkle): Once daily for up to 12 weeks (weight-based)	

See the current prescribing information for full details

CONCLUSION

- PPIs are the most potent inhibitors of gastric acid secretion available.
- All of the PPIs are FDA-approved for the treatment and maintenance of GERD and, with the exception of dexlansoprazole and omeprazole with sodium bicarbonate, for the treatment of pathological hypersecretory conditions.
- With the exception of dexlansoprazole, esomeprazole sodium, omeprazole with sodium bicarbonate, and pantoprazole, all of the PPIs are approved for the eradication of *H. pylori* to reduce the risk of duodenal ulcer recurrence.
- Dexlansoprazole, rabeprazole, esomeprazole strontium, and omeprazole with sodium bicarbonate are the only PPIs that are not FDA-approved for use in young children. Dexlansoprazole and rabeprazole are indicated in patients ≥ 12 years of age, while esomeprazole strontium and omeprazole with sodium bicarbonate are only indicated in adults.

- All orally administered PPIs are available in delayed-release oral formulations, with the exception of omeprazole with sodium bicarbonate. All oral products can be dosed once daily.
- Dexlansoprazole is uniquely formulated to release at different time intervals, at 2 different sites of the small intestine. The clinical significance of this is unknown.
- Esomeprazole magnesium, omeprazole magnesium, and pantoprazole are available as granules for a delayed-release oral suspension. Omeprazole with sodium bicarbonate is available as a powder for oral suspension. Rabeprazole is available in a sprinkle delayed-release capsule formulation.
- Esomeprazole strontium was approved in August 2013 without a proprietary name. Available generically and approved based on studies of esomeprazole magnesium, esomeprazole strontium has the same indications as esomeprazole magnesium with the exception of use in pediatric patients. It is a different salt formulation available in 2 unique strengths: 24.65 and 49.3 mg, equivalent to esomeprazole magnesium 20 and 40 mg, respectively.
- Esomeprazole magnesium, lansoprazole, omeprazole, omeprazole magnesium, and omeprazole with sodium bicarbonate are also available in OTC formulations.
- Esomeprazole sodium and pantoprazole are available in intravenous formulations for short-term use in patients unable to take medications by mouth.
- Rabeprazole, esomeprazole magnesium, esomeprazole strontium, lansoprazole, omeprazole, omeprazole with sodium bicarbonate, and pantoprazole are all available generically, however, some formulations (eg, oral suspensions) remain available only as brands.
- Current medical evidence demonstrates that PPI therapy is highly effective in treating, providing symptomatic relief, and preventing relapse in gastric acid disorders such as erosive esophagitis and symptomatic GERD.
  - Meta-analyses and direct comparator trials have demonstrated that lansoprazole, omeprazole, pantoprazole, and rabeprazole have comparable healing rates, maintenance of healing, and symptomatic relief of GERD (*Bardhan et al, 2001; Caro et al, 2001; Edwards et al, 2001; Klok et al, 2003; Pace et al, 2005; Sharma et al, 2001*).
  - Richter et al reported statistically faster and greater symptomatic relief with lansoprazole compared to omeprazole; however, the significance of these differences in clinical practice is not known (*Richter et al, 2011[b]*).
  - There is evidence through meta-analyses and several clinical trials that esomeprazole provides higher healing rates for erosive esophagitis and/or symptomatic relief of GERD compared to standard doses of lansoprazole, omeprazole, and pantoprazole (*Castell et al, 2002; Devault et al, 2006; Edwards et al, 2001; Kahrilas et al, 2000; Klok et al, 2003; Labenz et al, 2005[a]; Labenz et al, 2005[b]; Richter et al, 2001[a]*).
  - Subgroup analyses in 2 trials noted better healing rates with esomeprazole in patients with more severe disease (*Labenz et al, 2005[a]; Schmitt et al, 2006*).
  - Evidence suggests that there is no major difference in efficacy among the various PPIs for the short-term management of reflux esophagitis when administered in equivalent dosages.
  - Currently, there is a lack of head-to-head studies of dexlansoprazole with the other agents in this class.
- Clinical studies have demonstrated that PPIs are also highly effective in the treatment of peptic ulcer disease caused by chronic NSAID therapy or *H. pylori* infection when coupled with antibiotics.
  - Meta-analyses and head-to-head trials comparing PPIs to each other have shown comparable rates of eradication when administered at comparable doses and paired with comparable antibiotic regimens.
  - Results of meta-analyses suggest that regimens containing the new generation PPIs (esomeprazole and rabeprazole) may be more effective than the other PPIs at eradicating *H. pylori* (*McNicholl et al, 2012; Xin et al, 2016*).
  - Additional studies are needed before definitive conclusions can be made regarding the use of certain PPIs in specific patient populations.
- Current consensus among various national and international treatment guidelines recommend a PPI as the first-line therapy in the treatment and maintenance of healed erosive esophagitis, symptomatic GERD, dyspepsia (patients ≤ 55 years and no alarm features), and peptic ulcer disease caused by NSAID therapy. Triple and quadruple combination therapy with antibiotics and a PPI are considered first-line therapy for peptic ulcer disease caused by *H. pylori*. Most treatment guidelines do not recommend one PPI over another, and no treatment guideline recommends one formulation of a PPI over another.

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- PRILOSEC OTC product information. Procter and Gamble. Cincinnati, OH. June 2018.
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INTRODUCTION

- Inflammatory bowel disease (IBD) is a spectrum of chronic idiopathic inflammatory intestinal conditions that cause gastrointestinal symptoms including diarrhea, abdominal pain, bleeding, fatigue, and weight loss. The exact cause of IBD is unknown; however, proposed etiologies involve a combination of infectious, genetic, and lifestyle factors *(Bernstein et al 2015, Peppercorn 2018[a], Peppercorn, 2018[c]).*
- Complications of IBD include hemorrhage, rectal fissures, fistulas, peri-rectal and intra-abdominal abscesses, and colon cancer. Possible extra-intestinal complications include hepatobiliary complications, anemia, arthritis and arthralgias, uveitis, skin lesions, and mood and anxiety disorders *(Bernstein et al 2015).*
- Ulcerative colitis (UC) and Crohn's disease (CD) are 2 forms of IBD that differ in pathophysiology and presentation; as a result of these differences, the approach to the treatment of each condition often differs *(Peppercorn 2018[a]).*
- UC is characterized by recurrent episodes of inflammation of the mucosal layer of the colon. The inflammation, limited to the mucosa, commonly involves the rectum and may extend in a proximal and continuous fashion to affect other parts of the colon. The hallmark clinical symptom is bloody diarrhea often with prominent symptoms of rectal urgency and tenesmus *(Kornbluth et al 2010, Peppercorn 2018[c]).*
- CD can involve any part of the gastrointestinal tract and is characterized by transmural inflammation and "skip areas." Transmural inflammation may lead to fibrosis, strictures, sinus tracts, and fistulae *(Peppercorn 2018[b]).*
- The immune system is known to play a critical role in the underlying pathogenesis of IBD. It is suggested that abnormal responses of both innate and adaptive immunity mechanisms induce aberrant intestinal tract inflammation in IBD patients *(Geremia et al 2014).*
- Precise incidence and prevalence of CD and UC have been limited by a lack of gold standard criteria for diagnosis, inconsistent case ascertainment, and disease misclassification. The existing data suggest that the United States (U.S.) incidence rate of UC varies between 2.2 to 14.3 per 100,000 person-years and the incidence of CD varies from 3.1 to 14.6 per 100,000 person-years. As many as 3 million persons in the U.S. suffer from IBD *(Centers for Disease Control and Prevention [CDC] 2015, CDC 2018).*
- Some risk factors for IBD include age, gender, race, ethnicity, genetics, smoking status, and dietary considerations (*Peppercorn 2018[a]*).
  - The typical age of onset of IBD is between 15 and 40 years, while a second peak between ages 50 and 80 years has been noted.
  - Caucasians tend to have a higher incidence of IBD compared to Hispanic and Black populations. Additionally, ethnic and racial differences may be related to environmental and lifestyle factors as well as underlying genetic differences.
  - Genetic susceptibility to IBD is not completely understood; however, it is estimated that nearly 10 to 25% of individuals afflicted with IBD have a first-degree relative with IBD.
  - Smoking status affects CD and UC differently, being associated with an increased risk with CD and a decreased risk with UC.
  - Dietary factors have been associated as risk factors since food antigens are believed to activate an immune response. Although specific pathogenic antigens have not been conclusively identified, processed, fried, and sugar-laden foods are associated with an increased risk of developing CD and possibly UC.
- The goals for the treatment of IBD include resolution of intestinal inflammation and healing of the mucosa; elimination of symptoms while minimizing side effects; maintenance of corticosteroid-free remission; prevention of complications, hospitalization, and surgery; and maintenance of good nutritional status *(Bernstein et al 2015).*
- Current pharmacotherapy for UC includes 5-aminosalicylic acid (5-ASA) derivatives, glucocorticoids, immunomodulators (azathioprine, 6-mercaptopurine [6-MP], and methotrexate), and biologic agents (eg, Remicade [infliximab], Humira [adalimumab]) *(Micromedex 2019; Bernstein et al 2015).*
  - Choice of therapy is based on several factors, including disease severity, anatomic extent, and response to prior therapies *(Kornbluth et al 2010).*
  - Inflammation that is distal is limited to below the descending colon and within reach of topical therapy. Inflammation that extends proximal to the descending colon requires systemic medication *(Kornbluth et al 2010).*

- Although the specific Food and Drug Administration (FDA)-approved indications of the oral 5-ASA derivative preparations vary, these agents are used in the treatment and maintenance of remission of UC. The oral 5-ASA derivatives include balsalazide, mesalamine, olsalazine, and sulfasalazine (*Kornbluth et al 2010)*. Mesalamine is available in several formulations and is also the active component of balsalazide and olsalazine (*Prescribing information: Colazal 2016, Dipentum 2014)*. The 5-ASA derivatives have not shown differences in safety or efficacy; therefore, the choice of treatment agent should be based on indication, location of the disease, expected patient compliance with the regimen, patient preference, and availability of the drug *(Cheifetz 2018)*.
- Budesonide (Uceris) is available in an extended release tablet which delays the release of budesonide until it reaches the site of action (*Prescribing information: Uceris tablet 2018*). Budesonide is also available as a rectal foam (Uceris). Budesonide extended-release capsules (Entocort EC) are approved for the treatment and maintenance of remission of CD. (*Prescribing information: Entocort EC 2019*).
- Sulfasalazine (Azulfidine EN-tabs) is also FDA-approved for the treatment of rheumatoid arthritis nonresponsive to salicylates and nonsteroidal anti-inflammatory drugs (NSAIDS) and for pediatric polyarticular-course juvenile rheumatoid arthritis (*Prescribing information: Azulfidine EN-Tabs 2016)*.
- Other injectable biologic response modifiers known as monoclonal antibodies (MABs) are also approved to treat UC and/or CD including the tumor necrosis factor (TNF) inhibitors (eg, Cimzia [certolizumab pegol], Humira [adalimumab], Amjevita [adalimumab-atto], Hyrimoz (adalimumab-adaz), Cyltezo [adalimumab-adbm], Simponi [golimumab], Inflectra [infliximab-dyyb], Ixifi [infliximab-qbtx], Renflexis [infliximab-abda] and Remicade [infliximab]). In 2014, the alpha-4 beta-7 (α4β7) integrin receptor antagonist, Entyvio (vedolizumab) was approved for treatment of moderately to severely active UC and CD in adult patients who have had an inadequate response with, lost response to, or were intolerant to a TNF inhibitor or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids. In 2016, Stelara [ustekinumab] was approved for the treatment of moderate to severely active CD in adult patients who have failed or were intolerant to treatment with immunomodulators or corticosteroids, but never failed a TNF blocker or in those who have failed or were intolerant to treatment with 1 or more TNF blockers. In 2018, Xeljanz [tofacitinib] was approved for the treatment of moderately to severely active UC, as an orally administered targeted agent (*Micromedex 2019, Drugs@FDA 2019).* Additional injectable, humanized MABs are being studied for the treatment of various forms of IBD. These are reviewed in the Immunomodulators Class.
- The scope of this review will focus upon the oral and topical agents outlined in Table 1 for their respective FDA-approved, gastrointestinal-related indications.
- Medispan Therapeutic Class: Inflammatory Bowel Agents

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Apriso (mesalamine) ER capsule	-
Asacol HD (mesalamine) DR tablet	✔
Azulfidine (sulfasalazine) tablet	✔
Azulfidine EN-tabs (sulfasalazine) DR tablet	✔
Canasa (mesalamine) rectal suppository	✔
Colazal (balsalazide) capsule	✔
Delzicol (mesalamine) DR capsule	-
Dipentum (olsalazine) capsule	-
Entocort EC (budesonide) DR capsule	✔
Lialda (mesalamine) DR tablet	✔
Pentasa (mesalamine) CR capsule	-
Rowasa (mesalamine) rectal enema suspension	✔
sfRowasa (mesalamine) rectal enema suspension (sulfite-free)	-
Uceris (budesonide) ER tablet	✔
Uceris (budesonide) rectal foam	-

CR=controlled release, DR=delayed release, EC=enteric coated, ER=extended release
Asacol (mesalamine) by Warner Chilcott was discontinued by the manufacturer in the spring of 2013 due to a business decision. A generic is not currently available.
Giazo (balsalazide) 1.1 gm tablet was discontinued in 8/2018. A generic is not currently available.

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Balsalazide	Budesonide	Mesalamine	Olsalazine	Sulfasalazine
Treatment of mild to moderate active Crohn's disease involving the ileum and/or the ascending colon in patients ≥ 8 years of age		✔ (Entocort EC)			
Treatment of mildly to moderately active UC in patients ≥ 5 years of age	✔ (Colazal)†	-	✔ (Delzicol)	-	-
Treatment of moderately active UC in adults	-	-	✔ (Asacol HD)*	-	-
Induction of remission in adults with active, mild to moderate UC	-	✔ (Uceris tablet)	✔ (Lialda)	-	-
Induction of remission in adults with active mild to moderate distal UC extending up to 40 cm from the anal verge	-	✔ (Uceris rectal foam)	-	-	-
Maintenance of remission of mild to moderate Crohn's disease involving the ileum and/or ascending colon for up to 3 months in adults		✔ (Entocort EC) ***			
Maintenance of remission of UC in adults	-	-	✔ (Apriso; Delzicol; Lialda)	-	-
Maintenance of remission of UC in patients who are intolerant of sulfasalazine	-	-	-	✔	-
Induction of remission and for the treatment of patients with mildly to moderately active UC	-	-	✔ (Pentasa)	-	-
Treatment of mildly to moderately active ulcerative proctitis	-	-	✔ (Canasa)	-	-
Treatment of active mild to moderate distal UC, proctosigmoiditis or proctitis	-	-	✔ (Rowasa; sfRowasa)	-	-
Treatment of mild to moderate UC, and as adjunctive therapy in severe UC	-	-	-	-	✔ (Azulfidine; Azulfidine EN-tabs**)
Prolongation of the remission period between acute attacks of UC	-	-	-	-	✔ (Azulfidine; Azulfidine EN-tabs**)
Treatment of patients with rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs (eg, an insufficient therapeutic response to, or intolerance of, an	-	-	-	-	✔ (Azulfidine EN-tabs)

Indication	Balsalazide	Budesonide	Mesalamine	Olsalazine	Sulfasalazine
adequate trial of full doses of 1 or more NSAIDs)					
Treatment of pediatric patients with polyarticular-course juvenile rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs	-	-	-	-	✔ (Azulfidine EN-tabs)

*Safety and effectiveness of Asacol HD beyond 6 weeks have not been established.
**Azulfidine EN-tabs are specifically indicated in patients with UC who cannot tolerate sulfasalazine tablets due to gastrointestinal intolerance when the gastrointestinal intolerance is not primarily due to high blood levels of sulfapyridine and its metabolites.
***Taper to complete cessation after 3 months; continued treatment for more than 3 months has not been shown to provide substantial clinical benefit
†Safety and effectiveness of balsalazide beyond 8 weeks in children (ages 5 to 17 years) and 12 weeks in adults have not been established.

(Prescribing information: Apriso 2018, Asacol HD 2018, Azulfidine 2016, Azulfidine EN-Tabs 2016, Canasa 2017, Colazal 2016, Delzicol 2019, Dipentum 2014, Entocort EC 2019, Lialda 2018, Pentasa 2018, Rowasa 2017, sfRowasa 2017, Uceris tablet 2018, Uceris rectal foam 2016)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Oral therapy

- Multiple systematic reviews have been published evaluating randomized clinical trials of mesalamine products for UC. No significant differences in safety or efficacy between the mesalamine products have been found in the systematic reviews.
  - In a 2013 Cochrane review of 17 randomized clinical trials (N = 2925), the efficacy and safety of oral mesalamine products used for induction and maintenance of remission of UC were evaluated. The primary outcomes were failure to induce global or clinical remission or improvement, and failure to maintain global or clinical remission (relapse). Products included balsalazide, olsalazine, Pentasa, Asacol, Lialda, and 3 mesalamine products which are not available in the U.S. For the failure to induce global or clinical remission in mild to moderately active UC endpoint, there was no significant difference between the 5-ASA formulations (balsalazide, Pentasa, olsalazine, Lialda, mesalamine, and 5-ASA micropellets) and the comparator group (Asacol and 2 mesalamine formulations) (11 studies, N = 1968, 50% vs 52%, pooled relative risk [RR] 0.94, 95% confidence interval [CI], 0.86 to 1.02, $I^2 = 0\%$, p = 0.11). For failure to induce global or clinical remission or improvement, a total of 8 studies with 1647 patients were evaluated, and results demonstrated that there was no difference between the 5-ASA products (balsalazide, Pentasa, olsalazine, Lialda, and 5-ASA micropellets) and the 5-ASA comparators (Asacol, 2 mesalamine formulations, and Pentasa) (30% vs 35%, pooled RR 0.89, 95% CI, 0.77 to 1.01, $I^2 = 0\%$, p = 0.08) using a fixed-effects model. Note that Pentasa was on both sides of the comparison for this endpoint. For the failure to maintain global or clinical or endoscopic remission at 12 months, there was no difference between the 5-ASA formulations (balsalazide, Pentasa, and olsalazine) and the comparators (Asacol, mesalamine) in 5 studies (N = 457) (38% vs 37%, pooled RR 1.01, 95% CI, 0.80 to 1.28, $I^2 = 39\%$, p = 0.95). The incidences of adverse events between the various formulations were not significantly different. Risk of bias was low for most study factors; however, 1 study was single-blind, and 3 were open-label. There were numerous products in this systematic review which are not currently available in the U.S. *(Feagan et al 2013).*
  - A 2016 Cochrane review of 53 studies with 8548 patients with UC evaluated the oral 5-ASA preparations and sulfasalazine for the induction of active UC remission. The newer 5-ASA derivatives were “superior” to placebo with 71% of 5-ASA patients failing to enter clinical remission compared to 83% for placebo (11 studies; N = 2387; RR 0.86, 95% CI, 0.82 to 0.89). No statistically significant differences in efficacy between 5-ASA and sulfasalazine were observed, with 54% of 5-ASA-treated patients and 58% of sulfasalazine-treated patients failing to enter remission (8 studies; N = 526; RR 0.90, 95% CI, 0.77 to 1.04). Adherence did not appear to be enhanced by once daily dosing in the clinical trials; however, it is not known if once daily dosing would improve adherence in the community setting. Failure to enter clinical remission rates were 45% for once daily vs 48% for conventional dosing regimens (4 studies;

N = 944; RR 0.94, 95% CI, 0.83 to 1.07). No significant differences among the 5-ASA products for safety and efficacy were found *(Wang et al 2016[a]).*

- In a 2016 Cochrane review of 41 studies with 8928 patients, all 5-ASA formulations were "superior" to placebo for maintenance of clinical or endoscopic remission of UC. Relapse rates were 41% for 5-ASA-treated patients and 58% for placebo-treated patients (7 studies; N = 1298; RR 0.69; 95% CI, 0.62 to 0.77). Sulfasalazine was found to have a statistically significant benefit over 5-ASA in the maintenance of UC when looking at all trials at study endpoint (12 studies; N = 1655; RR 1.14, 95% CI, 1.03 to 1.27); however, when only trials of 12 months or longer were evaluated, there was no longer a difference between sulfasalazine and 5-ASA (8 studies; N = not reported; RR 1.10, 95% CI, 0.98 to1.23). No significant difference in efficacy was demonstrated between once daily and conventional dosing regimens; 29% of once daily-treated patients relapsed over 12 months vs 31% of conventionally dosed patients (8 studies; N = 3127; RR 0.91, 95% CI, 0.82 to 1.01). No significant difference in efficacy was found when comparing the various 5-ASA formulations. Relapse rate was 44% in the 5-ASA group vs 41% in the 5-ASA comparator group (6 studies; N = 707; RR 1.08, 95% CI, 0.91 to 1.28). No statistically significant differences were found for the incidence of adverse events between 5-ASA and placebo, 5-ASA and sulfasalazine, once daily and conventionally dosed 5-ASA, 5-ASA and comparator 5-ASA formulations, and 5-ASA dose ranging studies *(Wang et al 2016[b]).*
- A network meta-analysis evaluated the comparative efficacy and tolerability of agents used to treat mild to moderate UC. The analysis included 75 trials (12,215 patients) that evaluated either sulfasalazine, diazo-bonded 5-ASA, mesalamine, or budesonide, alone or in combination with rectal 5-ASA therapy. Agents were ranked using surface under the cumulative ranking curve (SUCRA) probabilities. For the induction of remission, combined oral and rectal 5-ASAs (SUCRA, 0.99) and high-dose mesalamine (> 3 g/day; SUCRA, 0.82) were the highest ranked therapies; both were also found to be superior to standard-dose mesalamine. For the maintenance of remission, all therapies were found to be superior to placebo, but high-dose mesalamine was not superior to standard-dose mesalamine (*Nguyen et al 2018*).
- Another systematic review evaluated once daily oral mesalamine compared to conventional dosing regimens of oral mesalamine for induction and maintenance of remission of UC in 11 studies with 4070 patients. Of the 11 studies, 5 studies were single-blind, and 1 study was performed in an open-label manner. Products assessed were Lialda, Asacol, Pentasa, and Salofalk (mesalazine - not available in the U.S.). Failure to induce global or clinical remission was not different between once daily and conventional dosing of mesalamine (3 studies, N = 738; pooled RR 0.95, 95% CI, 0.82 to 1.10; I^2 = 0%). No difference was observed between dosing regimens in failure to maintain global or clinical remission at 12 months (5 studies, N = 1394; pooled RR 0.92, 95% CI, 0.83 to 1.03, I^2 = 40.9%). Rates of medication adherence or adverse events between once daily and conventional dosing regimens of mesalamine were not significantly different. The authors noted that adherence rates in clinical trials may be higher than real world usage *(Feagan and MacDonald 2012).*
- A meta-analysis of 10 studies that evaluated mesalamine once daily vs multiple daily dosing regimens in 3410 patients with quiescent UC was conducted to determine the efficacy in preventing a relapse. The intention to treat analysis found that mesalamine once daily (26.3%) was as effective as multiple daily doses (26.5%) (8 studies, RR 1.00, 95% CI, 0.89 to 1.12, I^2 = 41%, p = 0.105). An analysis of the efficacy of once daily vs multiple daily dosing of mesalamine for inducing remission in active UC found that remission was not observed in 29.8% of patients on once daily mesalamine and 37.8% of patients receiving multiple daily doses. The risk of failure to achieve remission was higher with multiple daily doses (2 studies, RR 0.80; 95% CI, 0.64 to 0.99, I^2 = 21.6%, p = 0.259). When evaluating the same outcome on a per-protocol analysis, there was no significant difference between the 2 groups. No significant differences in adverse events were observed between the 2 groups *(Tong et al 2012).*
- In another 2012 meta-analysis, 9 of 10 studies included in the Tong et al analysis were evaluated by another group *(Zhu et al 2012).* There were no significant differences for once daily compared to more frequent dosing (twice or 3 times daily) of mesalamine for UC for the maintenance of clinical remission, endoscopic remission, maintenance of combined clinical and endoscopic remission, and the overall incidence of adverse events.

- A Cochrane review evaluated oral budesonide for induction of remission in UC. A total of 6 studies (N = 1808) were evaluated. Budesonide multi-matrix (MMX) (Uceris) 9 mg was superior to placebo for inducing remission at 8 weeks (15% vs 7%, respectively; 3 studies, N = 900; RR 2.25, 95% CI, 1.50 to 3.39; moderate quality of evidence). An analysis of 2 studies with budesonide MMX 6 mg showed that it was not superior to placebo for induction of remission (11% vs 6%, respectively; 2 studies, N = 440; RR 1.80, 95% CI, 0.94 to 3.42; low quality of evidence). Budesonide (Entocort EC) was significantly less likely to induce clinical remission than oral mesalamine after 8 weeks (1 study, N = 343; RR 0.72, 95% CI 0.57 to 0.91; moderate quality of evidence). However, another study found no difference in remission rates between budesonide MMX 9 mg and mesalamine (1 study; N = 247; RR 1.48, 95% CI, 0.81 to 2.71; low quality of evidence). In a comparison of the 2 budesonide formulations, there was no difference in remission rates between

budesonide MMX 9 mg and budesonide 9 mg (1 study, N = 212; RR 1.38, 95%CI, 0.72 to 2.65; low quality of evidence) *(Sherlock et al, 2015).*

- Two additional Cochrane reviews have evaluated oral budesonide for induction and maintenance of remission in CD.
  - For induction of remission, budesonide was found to be superior to placebo at 8 weeks (47% vs 22%, respectively; 3 studies, N = 379; RR 1.93, 95% CI, 1.37 to 2.73; moderate quality of evidence). Budesonide was found to be significantly less effective than conventional steroids (52% vs 61%, respectively; 8 studies, N = 750; RR 0.85, 95% CI, 0.75 to 0.97; moderate quality of evidence), but treatment with budesonide resulted in significantly fewer adverse events (RR 0.64, 95% CI, 0.54 to 0.76) (*Rezaie et al, 2015*).
  - For maintenance of remission, budesonide 6 mg daily was not found to be more effective than placebo at 3, 6, or 12 months. The authors concluded that budesonide is not effective for maintenance of remission in CD, particularly when used longer than 3 months following the induction of remission (*Kuenzig et al, 2014*).

Topical therapy

- According to a meta-analysis comparing rectal 5-ASA therapy to either placebo or other active agents for the treatment of distal disease, rectal 5-ASA was superior to placebo and rectal corticosteroids. Rectal 5-ASA was not superior to oral 5-ASA for symptomatic improvement *(Marshall et al 2010).* A 2012 smaller meta-analysis found that rectal 5-ASA therapy was superior to placebo and similar to oral 5-ASA on rates of symptomatic remission and endoscopic remission. No dose response relationship for 5-ASA enemas or other rectal dosage forms has been observed *(Marshall et al 2012).*
- A meta-analysis found greater efficacy with topical mesalamine than placebo for the prevention of relapse of disease activity in quiescent UC, with a number needed to treat (NNT) of 3. Time to relapse was longer with topical mesalamine in the 2 trials, and there was a trend toward a greater effect size with continuous topical therapy compared to intermittent therapy *(Ford et al 2012[b]).*
- Budesonide rectal foam was compared to placebo in 2 randomized, Phase 3 trials in patients with mild to moderate ulcerative proctitis or ulcerative proctosigmoiditis. Compared to placebo, a significantly greater proportion of patients receiving budesonide rectal foam experienced remission, resolution of rectal bleeding, and endoscopic improvement at week 6 ($p < 0.05$ for all comparisons in both trials) *(Sandborn et al 2015).* Additionally, in a randomized, Phase 3 trial in patients with mild to moderate UC with distal active inflammation, significantly more patients who received budesonide rectal foam experienced clinical remission and complete mucosal healing of distal lesions compared to placebo ($p = 0.0035$ and $p = 0.0003$, respectively) *(Naganuma et al 2017)*.

Oral vs. topical mesalamine

- A meta-analysis found combined oral and topical 5-ASA therapy to be superior to oral 5-ASA therapy for induction of remission in mild to moderately active UC. Additionally, intermittent topical 5-ASA therapy was reported to be superior to oral 5-ASA therapy for preventing relapse of quiescent UC *(Ford et al 2012[a]).*

CLINICAL GUIDELINES

- The 2010 Ulcerative Colitis Practice Guidelines in Adults from the American College of Gastroenterology (ACG) recommend oral mesalamine but do not differentiate between the different oral formulations available; a blanket recommendation for mesalamine is provided. All aminosalicylates are superior to placebo and equivalent to sulfasalazine in acute therapy of UC *(Kornbluth et al 2010).* A guideline update is underway *(ACG 2019).*
  - For the management of mild to moderate distal colitis, oral aminosalicylates, topical mesalamine, or topical corticosteroids are recommended (Evidence A [defined as High level of evidence; further research is very unlikely to change our confidence in the estimate of effect). Topical mesalamine agents are “superior” to topical steroids or oral aminosalicylates (Evidence A). The combination of oral and topical agents is “superior” to each agent used alone (Evidence A). Oral therapies effective for achieving and maintaining remission include balsalazide, mesalamine, olsalazine, and sulfasalazine. For the maintenance of remission in distal disease, mesalamine suppositories are effective for maintenance of remission in patients with proctitis, and mesalamine enemas are effective in patients with distal colitis (Evidence A). Balsalazide, mesalamine, and sulfasalazine are effective in maintaining remission; combination oral and topical mesalamine is more effective than oral mesalamine alone (Evidence A). Topical corticosteroids, including budesonide, have not been proven effective at maintaining remission (Evidence A).
  - For the management of active mild to moderate extensive colitis, oral sulfasalazine or oral aminosalicylates in doses up to 4.8 g per day of the active 5-ASA moiety are considered first-line (Evidence A). Oral steroids are generally reserved for patients who are refractory to oral aminosalicylates or patients who require rapid improvement (Evidence B [defined as Moderate level of evidence; further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.]). For patients refractory to oral corticosteroids, 6-MP or azathioprine can be used for patients who are acutely ill, requiring intravenous therapy (Evidence A). Infliximab is effective in patients who are steroid refractory or steroid-dependent despite the use of thiopurine at adequate doses or who are intolerant to these medications. For maintenance of remission for mild to moderate extensive colitis,

balsalazide, mesalamine, olsalazine, and sulfasalazine are effective in reducing the number of relapses (Evidence A). Azathioprine or 6-MP can be used for steroid sparing in steroid-dependent patients and have been shown to effectively maintain remission in patients not adequately sustained on aminosalicylates (Evidence A). Infliximab effectively maintains remission in patients who responded to the infliximab induction regimen (Evidence A).
  - For the management of severe colitis in a patient who is refractory to maximum oral treatment with aminosalicylates, oral prednisone, and topical medications, infliximab is a treatment option if urgent hospitalization is not required (Evidence A). Patients who show signs of toxicity should be hospitalized to receive intravenous steroids. Infliximab may also be used to avoid colectomy in patients failing intravenous steroids; however, long-term efficacy in this setting is unknown (Evidence A).
- The 2018 guidelines on management of Crohn's Disease in Adults from the ACG recommend controlled ileal release budesonide at a dose of 9 mg once daily for induction of symptomatic remission for patients with mild to moderate ileocecal CD (strong recommendation, low level of evidence). They do not recommend use of budesonide beyond 4 months (strong recommendation, moderate level of evidence). The guideline also recommends against the use of oral mesalamine to treat patients with active CD, since it has not consistently been shown effective for inducing remission and achieving mucosal healing when compared to placebo (strong recommendation, moderate level of evidence). Sulfasalazine is recommended for symptoms of mild to moderate colonic CD (conditional recommendation, low level of evidence) (*Lichtenstein et al 2018*).
- The World Gastroenterology Organization Global Guidelines state that 5-ASA products are useful for treating both colitis flare-ups and maintenance of remission. A combination of oral with topical 5-ASA products is more effective than oral agents alone for induction of remission of mild to moderate UC. Rectal 5-ASA products are more beneficial than rectal corticosteroids in UC. Limited evidence exists for 5-ASA products in CD; these products are mainly used in patients who cannot tolerate corticosteroids. Corticosteroids provide rapid relief of symptoms by suppressing inflammation and should be used to induce remission; they have no role in maintenance of remission and side effects limit duration of use. Budesonide may have fewer adverse events than other corticosteroid options *(Bernstein et al 2015).*
- The American Gastroenterological Association (AGA) guideline on the management of mild to moderate UC recommends standard-dose oral mesalamine (2 to 3 g/day) or diazo-bonded 5-ASA (balsalazide, olsalazine) as first-line options for most patients with mild to moderate disease, rather than low-dose mesalamine, sulfasalazine, or no treatment (strong recommendation, moderate evidence). The guideline also suggests using standard-dose oral mesalamine or diazo-bonded 5-ASA over budesonide preparations for induction of remission (conditional recommendation, low evidence) (*Ko et al 2019*).
  - For management of extensive or left-sided disease, rectal mesalamine can be added to oral 5-ASA (conditional recommendation, moderate evidence). For management of left-sided ulcerative proctosigmoiditis or proctitis, mesalamine enemas or suppositories are suggested over oral mesalamine (conditional recommendation, very low evidence). Further, in patients with ulcerative proctosigmoiditis, mesalamine enemas are suggested over rectal corticosteroids (conditional recommendation, moderate evidence).
  - For patients who have a suboptimal response to first-line treatment for mild to moderate UC, high-dose mesalamine (> 3 g/day) with rectal mesalamine is suggested (conditional recommendation, moderate evidence for induction, low evidence for maintenance).
- The ACG recently released a clinical guideline addressing preventive care in IBD. According to published data, patients with IBD do not receive preventive care services at the same rate as general medical patients. Increased coordination between gastroenterology and primary care providers is recommended, as well as proper age-appropriate immunization, cervical and skin cancer screenings, depression and anxiety screening, and smoking cessation counseling for patients with CD *(Farraye et al 2017).*
- The AGA pregnancy care pathway for inflammatory bowel disease recommends that aminosalicylates may be continued during pregnancy, delivery, and during the postpartum period. For maintenance therapy in pregnancy, monotherapy is preferred. The pathway notes that Azulfidine EN-tabs contains phthalates, which may be better to avoid in pregnancy, and all mesalamine preparations are phthalate-free. Both mesalamine and sulfasalazine are compatible with breastfeeding, though mesalamine is preferred (*Mahadevan et al 2019*).

SAFETY SUMMARY

- Contraindications include hypersensitivity to salicylates or any component for the drugs in this class. Sulfasalazine is contraindicated in patients with intestinal or urinary obstruction or in patients with porphyria, as sulfonamides may precipitate an acute attack.
- Warnings include mesalamine acute intolerance syndrome, exacerbations of colitis, and caution using drugs in this class in patients with hepatic or renal impairment. Mesalamine products (Lialda, Pentasa, and Canasa) and sulfasalazine

products (Azulfidine and Azulfidine EN-tabs) may interfere with laboratory tests for normetanephrine. Rectal mesalamine may cause oligospermia and pancolitis.

- Due to the potential for severe blood dyscrasias, complete blood counts, including differential white cell count, and liver function tests should be performed before starting sulfasalazine therapy (Azulfidine and Azulfidine EN-tabs) and every second week during the first 3 months of therapy; tests should be repeated once monthly for 3 months, then once every 3 months, and as clinically indicated.
- Budesonide may cause hypercorticism, adrenal axis suppression, and increased risk of infection.
- Concurrent use of NSAIDs with mesalamine products may increase the risk of nephrotoxicity; use with caution.
- Oral mesalamine and Canasa should not be used with 6-mercaptopurine and azathioprine due to decreased thiopurine metabolism; an increased risk of myelosuppression may result.
- In general, the inflammatory bowel agents are most commonly associated with gastrointestinal-related adverse events.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Balsalazide	Capsule (Colazal) 750 mg	Oral	Capsule (Colazal): 3 times daily	Capsule (Colazal): approved for use in children 5 to 17 years old
Budesonide	Delayed-release capsule (Entocort EC) 3 mg Extended-release tablet (Uceris) 9 mg Rectal foam (Uceris) 2 mg/actuation	Oral, Rectal	Delayed-release capsule: once daily Extended-release tablet: once daily Rectal foam: once to twice daily	Delayed-release capsule (Entocort EC) is used to treat active CD (children ≥ 8 years of age); Uceris is used to treat UC Patients with moderate to severe hepatic impairment should be monitored for signs and symptoms of hypercorticism
Mesalamine	Controlled-release capsule (Pentasa) 250 mg, 500 mg Delayed-release capsule (Delzicol) 400 mg Delayed-release tablet 800 mg (Asacol HD), 1.2 g (Lialda) Extended-release capsule (Apriso) 0.375 g Rectal suppository (Canasa) 1000 mg Rectal enema (Rowasa, sfRowasa) 4 g/60 mL	Oral, Rectal	Controlled-release capsule (Pentasa): 4 times daily Delayed-release capsule (Delzicol): twice to 4 times daily Delayed-release tablet (Asacol HD): 3 times daily Delayed-release tablet (Lialda): once daily Extended-release capsules (Apriso): once daily Rectal suppository (Canasa): once daily at bedtime Rectal enema (Rowasa; sfRowasa): once daily at bedtime	Delayed-release capsule (Delzicol): approved for use in children ≥ 5 years of age Complete blood counts should be periodically monitored in elderly patients. Renal function should be evaluated prior to initiation of most mesalamine products; use with caution in patients with a history of or known renal dysfunction. Two Delzicol 400 mg capsules have not been shown to be interchangeable or substitutable with one Asacol HD tablet.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Olsalazine (Dipentum)	Capsule 250 mg	Oral	Twice daily	
Sulfasalazine	Tablet (Azulfidine) 500 mg Delayed-release tablet (Azulfidine EN-tabs) 500 mg	Oral	Tablet and delayed-release tablet: twice to 4 times daily	Sulfasalazine products may cause an orange-yellow discoloration of the urine or skin. Safety and effectiveness for UC in patients < 2 years of age have not been established. FDA-approved for rheumatoid arthritis in adults and juvenile rheumatoid arthritis for children ≥ 6 years of age. (Azulfidine EN-tabs only)

See the current prescribing information for full details

CONCLUSION

- Treatment goals of IBD are to resolve acute inflammatory processes, resolve systemic complications, alleviate systemic manifestations, and maintain remission from acute inflammation.
- For induction of remission of UC, no differences in efficacy or safety among the oral 5-ASA formulations have been identified *(Wang et al 2016[a]).* Oral 5-ASA is similarly effective to sulfasalazine for induction of UC remission *(Kornbluth et al 2010)*.
- No overall differences in efficacy or safety among the oral 5-ASA formulations have been observed for the maintenance of UC remission *(Wang et al 2016[b]).* Once daily dosing and traditional dosing of oral 5-ASA regimens were similarly effective for maintenance of UC remission *(Feagan and MacDonald 2012, Feagan et al 2013).*
- Topical rectal therapies are the formulations of choice for distal disease and have been shown to be more effective than oral sulfasalazine therapy. In a meta-analysis, rectal 5-ASA therapy was shown to be superior to placebo and rectal corticosteroids; however, rectal 5-ASA therapy was not superior to oral 5-ASA for symptomatic improvement or remission rates *(Marshall et al 2010).* For maintenance of symptomatic and endoscopic remission of UC, rectal 5-ASA was not significantly different compared to oral 5-ASA. It has also been shown in clinical trials that topical mesalamine is more effective than placebo for the prevention of relapse of disease activity in quiescent UC *(Ford et al 2012[b]).* Similarly, trials showed budesonide rectal foam was more effective than placebo in inducing remission in patients with mild to moderate ulcerative proctitis and ulcerative proctosigmoiditis and patients with mild to moderate UC with distal active inflammation *(Sandborn et al 2015; Naganuma et al 2017).*
- According to the 2010 UC ACG guidelines, oral therapies effective for achieving and maintaining remission in distal disease include aminosalicylates, balsalazide, mesalamine, olsalazine, and sulfasalazine. Topical mesalamine agents are “superior” to topical steroids or oral aminosalicylates and the combination of oral and topical agents is “superior” to each agent used alone. In maintaining remission of disease, balsalazide, mesalamine, and sulfasalazine are effective, and combination oral and topical therapy is better than oral mesalamine alone *(Kornbluth et al 2010).*
- The ACG guidelines recognize sulfasalazine as a first-line agent in the management of mild to moderately active colitis, and note balsalazide, mesalamine, olsalazine, and sulfasalazine as effective therapies for reducing the number of relapses and the maintenance of mild to moderate disease remission *(Kornbluth et al 2010).*
- The 2019 AGA guideline on the management of mild to moderate UC recommends standard-dose oral mesalamine (2 to 3 g/day) or diazo-bonded 5-ASA (balsalazide, olsalazine) as first-line options for most patients. For management of left-sided ulcerative proctosigmoiditis or proctitis, mesalamine enemas or suppositories are suggested over oral mesalamine or rectal corticosteroids (*Ko et al 2019*).
- The 2018 ACG guideline on management of CD recommends controlled ileal release budesonide at a dose of 9 mg once daily for induction of symptomatic remission for patients with mild to moderate ileocecal CD, but does not recommend use of budesonide beyond 4 months (*Lichtenstein et al 2018*).

- The differences in drug therapies (ie, pH-dependent parameters) allow for the tailoring of treatment based upon an individual's disease location and severity.
- Overall, oral therapies are generally well tolerated; however, adverse events often limit the use of sulfasalazine in favor of the newer 5-ASA therapy options given their local mechanism of action compared to the systemic absorption of sulfasalazine.

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Therapeutic Class Overview
Erythropoiesis Stimulating Agents

INTRODUCTION

- Iron deficiency anemia is the most common form of anemia. Anemia is also associated with a variety of conditions including cancer, chronic kidney disease (CKD), rheumatoid arthritis, human immunodeficiency virus (HIV), chronic heart failure, and chronic obstructive pulmonary disease (*Schrier and Camaschella 2018, Schrier 2018*).
- Management of anemia of chronic disease is often more complex, and administration of erythropoiesis-stimulating agents (ESAs) or red blood cell (RBC) transfusions may be necessary for patients with severe, symptomatic anemia (eg, hemoglobin [Hb] <10 g/dL) (*Schrier and Camaschella 2018*).
- Although allogeneic RBC transfusions provide rapid correction of Hb stores, they are also accompanied by significant risks, which include transmission of communicable diseases, allergic and immune transfusion reactions, volume overload, hyperkalemia, and iron overload (*Carson and Kleinman 2019*).
- Erythropoietin is a naturally occurring glycoprotein hormone that stimulates the production and maturation of erythrocytes in the bone marrow. Erythrocytes, or RBCs, are responsible for transporting oxygen from the lungs to the peripheral tissues. Erythropoietin is primarily produced and released into the bloodstream by the kidneys. Renal production of erythropoietin is stimulated when the renal oxygen sensor is triggered by hypoxia or low tissue oxygen (*Hörl 2013*).
- The ESAs were first introduced in the early 1980's to provide a treatment option for anemia in patients with CKD, and later, in patients with malignancies who were unable to maintain their Hb within the acceptable ranges (*Schrier et al 2018*).
- Although ESAs may decrease the need for RBC transfusions, multiple meta-analyses of randomized controlled trials (RCTs) have demonstrated an increase in mortality, cardiovascular events, and cancer progression without significant improvements in morbidity or quality of life (QoL) for patients receiving therapy (*Collister et al 2016, Grant et al 2013, Palmer et al 2014a, Tonia et al 2012*).
- The ESAs approved by the Food and Drug Administration (FDA) in the United States include Epogen (epoetin alfa), Procrit (epoetin alfa), Aranesp (darbepoetin alfa), Retacrit (epoetin alfa-epbx), and Mircera (methoxy polyethylene glycol-epoetin beta). Retacrit is the first and only FDA-approved ESA biosimilar in the United States.
- Epoetin alfa and darbepoetin alfa products carry boxed warnings regarding shortened survival and increased risk of tumor progression or recurrence in patients with breast, non-small cell lung, head and neck, lymphoid, and cervical cancers. Furthermore, the warnings emphasize to use ESAs only for the treatment of anemia due to concomitant myelosuppressive chemotherapy and to discontinue ESAs following completion of a chemotherapy course. ESAs should not be initiated in cancer patients receiving myelosuppressive therapy when the anticipated outcome is cure.
- Medispan Therapeutic Class: Erythropoietins

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Biosimilar Availability
Aranesp (darbepoetin alfa)	Amgen	09/17/2001	-
Epogen, Procrit (epoetin alfa)	Amgen	06/01/1989	+
Retacrit (epoetin alfa-epbx)*	Hospira/Pfizer	05/15/2018	-
Mircera (methoxy polyethylene glycol-epoetin beta)	Galenica	11/14/2007	-

*Retacrit is an ESA biosimilar to Epogen/Procrit.

(*DRUGS@FDA 2019, Purple Book: lists of licensed biological products with reference product exclusivity and biosimilarity or interchangeability evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Aranesp (darbepoetin alfa)†	Epogen, Procrit, Retacrit (epoetin alfa; epoetin alfa-epbx)‡	Mircera (methoxy polyethylene-epoetin beta)§
Treatment of anemia associated with chronic kidney disease, including patients on dialysis and patients not on dialysis	✔ †	✔ *	✔
Treatment of anemia associated with chronic kidney disease in pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their Hb level was stabilized with an ESA			✔
Treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of 2 additional months of planned chemotherapy	✔	✔	
Treatment of anemia due to zidovudine administered at ≤ 4200 mg/week in human immunodeficiency virus (HIV)-infected patients with endogenous serum erythropoietin levels of ≤ 500 mUnits/mL		✔	
Reduce the need for allogeneic red blood cell transfusions among patients with perioperative Hb > 10 to ≤ 13 g/dL who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery		✔	

*To decrease the need for transfusions in these patients.

† The safety and effectiveness of Aranesp was studied in pediatric patients 1 month to 16 years old who have CKD and are receiving or not receiving dialysis; safety and efficacy of Aranesp in pediatric patients with cancer have not been established.

‡ Indicated in pediatric patients 1 month to 16 years of age for treatment of anemia in CKD requiring dialysis, and in patients 5 to 18 years of age for treatment of anemia due to concomitant myelosuppressive chemotherapy. Limited data are available on the use of epoetin in children with HIV receiving zidovudine.

§Mircera is indicated for the treatment of anemia due to CKD in patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their Hb level was stabilized with an ESA

- **Limitations of use:**
  - All ESAs have not been shown to improve QoL, fatigue, or patient well-being.
  - ESAs are not indicated as a substitute for RBC transfusions in patients who require immediate correction of anemia.
- Aranesp, Epogen, Procrit, and Retacrit are not indicated for use:
  - In patients with cancer receiving hormonal agents, biologic products, or radiotherapy, unless also receiving concomitant myelosuppressive chemotherapy.
  - In patients with cancer receiving myelosuppressive chemotherapy when the anticipated outcome is cure.
  - In patients with cancer receiving myelosuppressive chemotherapy in whom the anemia can be managed by transfusion.
- Epogen, Procrit, and Retacrit are not indicated for use:
  - In patients scheduled for surgery who are willing to donate autologous blood.
  - In patients undergoing cardiac or vascular surgery.
- Mircera is not indicated for use:

- In the treatment of anemia due to cancer chemotherapy.

(*Prescribing information: Aranesp 2019, Epogen 2018, Mircera 2018, Procrit 2018, Retacrit 2019*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Only a few clinical studies have compared the efficacy and safety of epoetin alfa to darbepoetin alfa for the treatment of anemia due to CKD or myelosuppressive chemotherapy. None of these agents have been shown to improve QoL, fatigue, or patient well-being. Since initial FDA-approval, the ESAs have been shown to increase the risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access, and tumor progression or recurrence. Earlier studies utilized ESA to maintain higher Hb targets than the targets recommended currently. Numerous observational, non-interventional, retrospective, and single-center studies have evaluated these agents in the correction of anemia due to CKD or myelosuppressive chemotherapy. However, these studies are not included in this review.
- Retacrit (epoetin alfa-epbx) was approved as a biosimilar to Epogen/Procrit (epoetin alfa) in May 2018 (*FDA News Release 2018*). The approval of Retacrit was based on a review of evidence including extensive structural and functional characterization, animal study data, human pharmacokinetic and pharmacodynamic data, clinical immunogenicity data, and other clinical safety and effectiveness data demonstrating its biosimilarity. Retacrit was approved as a biosimilar, not as an interchangeable product.

Anemia in CKD

- ESAs provided an attractive solution to decreasing the number of allogeneic blood transfusions; however, multiple meta-analyses of RCTs have demonstrated an increase in mortality, cardiovascular events, and cancer progression without improvement in morbidity or QoL for patients receiving therapy (*Collister et al 2016, Grant et al 2013, Palmer et al 2014a*).
- According to a Cochrane review, use of ESAs in predialysis patients corrected anemia and avoided blood transfusions compared to placebo or no treatment (*Cody et al 2016*). A total of 19 studies (N = 993) evaluated ESAs, with the majority of the studies being published prior to 2000. ESAs improved Hb (mean difference [MD] 1.90 g/dL, 95% CI, -2.34 to -1.47) and decreased the number of patients with blood transfusions (risk ratio [RR] 0.32, 95% confidence interval [CI], 0.12 to 0.83). No differences with the measure of kidney disease progression were observed. Endpoints of QoL and change in exercise capacity were not measured in a manner which was suitable for analysis.
- The harms of high Hb targets compared to lower Hb targets were evaluated. The Correction of Anemia with Epoetin Alfa in Chronic Kidney Disease (CHOIR) trial was a notable trial that found that patients with CKD with a higher target Hb had higher risk for the composite outcome of death, nonfatal myocardial infarction, stroke, and hospitalization for congestive heart failure (CHF) than patients with a lower Hb target (17.5 vs 13.5%; hazard ratio [HR], 1.34; 95% CI, 1.03 to 1.74; p = 0.03) (*Singh et al 2006*). Analysis of study data in the intent-to-treat (ITT) population and including all events from randomization until study termination or 30 days after the last dose showed a higher incidence of events in the high-Hb group (HR, 1.3; 95% CI, 1.01 to 1.62; p = 0.04). Even though the trial was halted early, evidence suggested that higher Hb levels led to an increased rate of adverse events. The prescribing information and warnings for all drugs of this class were updated to reflect these findings. Findings were similar to the Normal Hematocrit Study performed in patients with CKD on dialysis with CHF or ischemic heart disease (*Besarab et al 1998*).
- A systematic review evaluated 9 trials comparing epoetin alfa and darbepoetin alfa for all-cause mortality in patients with anemia in adults with CKD including those on dialysis (N = 2024). Duration of the trials was 20 to 52 weeks. No significant difference in mortality between epoetin and darbepoetin was detected (odds ratio [OR] 1.33; 95% CI, 0.88 to 2.01) (*Wilhelm-Leen et al 2015*).
- Numerous trials have evaluated extended dosing intervals of epoetin for patients with CKD. In general, larger doses given less frequently demonstrated similar outcomes with epoetin alfa and darbepoetin (*Benz et al 2007, Patel et al 2012, Pergola et al 2009, Pergola et al 2010, Provenzano et al 2004, Provenzano et al 2005, Spinowitz et al 2008a, Warady et al 2018*). A systematic review confirmed that various dosing frequencies of darbepoetin and epoetin result in similar mean final Hb values in patients receiving hemodialysis (*Hahn et al 2014*). Many of these dosing regimen studies

were completed in small patient populations and open-label design. The FDA-approved dosing regimen for epoetin alfa is 3 times weekly for patients with CKD.

- Patients with CKD on dialysis should receive intravenous (IV) darbepoetin and epoetin alfa. Cases of pure red cell aplasia and severe anemia have been reported more frequently with the subcutaneous (SC) administration of ESAs in patients with CKD. Comparisons of the method of administration (IV vs SC) have been completed with epoetin and darbepoetin. In an open-label, German study, switching patients on dialysis from SC darbepoetin to IV administration led to stable mean Hb levels and mean weekly darbepoetin doses (*Bommer et al 2008*). Another open-label study showed that switching patients on dialysis from SC epoetin to IV darbepoetin resulted in stable mean Hb levels at stable darbepoetin doses after 3 months (*Chazot et al 2009*). Mircera is indicated for IV or SC administration.
- In a double-blind, multicenter, placebo-controlled, randomized clinical trial, the safety of darbepoetin in patients with type 2 diabetes mellitus, CKD, and anemia were evaluated (*Pfeffer et al 2009*). The patients had a baseline Hb level of ≤11 g/dL. The primary endpoint of the TREAT study was the composite of death or a non-fatal cardiovascular event (nonfatal myocardial infarction, congestive heart failure, stroke or hospitalization for myocardial ischemia) and death or end-stage renal disease. The primary cardiovascular composite outcome of death or nonfatal cardiovascular event occurred in 632 patients (31.4%) of the darbepoetin group and 602 patients (29.7%) treated with placebo (HR for darbepoetin vs placebo, 1.05; 95% CI, 0.94 to 1.17; p = 0.41). For the individual endpoints contributing to the composite, there were no statistically significant differences between the groups for any parameter except for fatal and non-fatal stroke which occurred more frequently with darbepoetin (5% vs 2.6%; HR, 1.92; 95% CI, 1.38 to 2.68; p < 0.001). For the composite endpoint of death or end-stage renal disease, no significant difference was detected (darbepoetin 32.4% vs 30.5% placebo; HR, 1.06; 95% CI, 0.95 to 1.19; p = 0.29). The study was performed from 2004 to 2007, when the standard of care target Hb level was 13 g/dL. Additional notification was sent to investigators and participants of the adverse outcomes with higher Hb targets; however, the study protocol was not modified. A third party vendor assayed Hb levels and reported the dosage adjustment necessary for patients receiving darbepoetin. At baseline, the darbepoetin group had a lower proportion of patients with a history of CHF (31.5 vs 35.2%; unadjusted p = 0.01). In summary, darbepoetin in patients with anemia, diabetes and chronic renal disease did not increase the risk of the composite outcome of death or cardiovascular outcome and death or end-stage renal disease. It was noted that stroke, fatal or non-fatal, occurred more frequently in patients who received darbepoetin compared to placebo.
- A systematic review evaluated darbepoetin and the other ESAs in 21 studies in patients with CKD for the effect on blood transfusion (*Palmer et al 2014b*). Darbepoetin reduced the need for blood transfusions compared to placebo or no treatment; however, in 3 studies comparing darbepoetin to epoetin, darbepoetin had uncertain effects on RBC transfusions and all-cause mortality compared to epoetin. Darbepoetin and methoxy polyethylene glycol-epoetin beta were similar for risk of RBC transfusions.
- A Cochrane review compared the efficacy and safety of the ESAs (Mircera, epoetin alfa, epoetin beta, darbepoetin alfa, and biosimilar ESAs) in adults with CKD. A total of 56 studies (N = 15,596) were included in the analysis. In network analyses, there was moderate to low confidence that the ESAs prevented blood transfusions compared to placebo. The authors concluded that there was insufficient evidence to suggest superiority of any ESA formulation based on available safety and efficacy data (*Palmer et al 2014a*).
- A systematic review evaluated 17 studies (N = 10,049) with ESAs for effects on health-related quality of life (HRQoL) in CKD patients (*Collister et al 2016*). Higher Hb target levels (range: 10.2 to 13.6 g/dL) resulted in no statistically significant improvements in Short-Form 36 (SF-36) domains or for the Kidney Disease Questionnaire (KDQ) compared to patients on placebo or lower Hb target levels (range: 7.4 to 12 g/dL). For the KDQ, patients with higher Hb targets had an improvement of 0.5 (95% CI, -2.2 to 1.2) points in the physical symptom domain, 0.5 point improvement in the fatigue domain (95% CI, -1.6 to 0.5), and 0.2 point improvement in the depression domain (95% CI, -1.1 to 0.8). A clinically meaningful benefit is considered a minimum of 0.5 point improvement on the KDQ. The systematic review is consistent with the prescribing information and previously published reports.
- Very few randomized controlled studies comparing darbepoetin and epoetin alfa have been published. Two non-inferiority studies comparing epoetin alfa to darbepoetin alfa in the treatment of anemia of CKD demonstrated no difference in efficacy between the 2 agents. In a study of adult patients with CKD by *Nissenson et al*, the mean changes in Hb levels from baseline to the evaluation period were similar between the darbepoetin alfa (0.16 to 0.09 g/dL) and epoetin alfa (0 to 0.06 g/dL) groups (difference, 0.16 g/dL; 95% CI, -0.06 to 0.38; p value not reported). In a second study by *Vanrenterghem et al* (N = 522) of patients with CKD on dialysis, the mean change in Hb was 0.05 g/dL in the

darbepoetin alfa group compared to 0 g/dL in the epoetin alfa treatment (difference, 0.05 g/dL; 95% CI, -0.14 to 0.24; p values not reported). No statistically significant differences in the mean change in Hb levels from baseline, the primary endpoint were reported. In addition, in both studies there were no differences in safety profiles, and no antibodies detected to either treatment (*Nissenson et al 2002, Vanrenterghem et al 2002*). An open-label trial comparing darbepoetin SC 0.45 mcg/kg once weekly and epoetin SC 50 units/kg twice weekly found similar efficacy in achieving a Hb response and similar safety profile in 166 patients with CKD not on dialysis (*Locatelli et al 2001*).

- The safety and efficacy of Mircera were established in Phase 3, multicenter, open-label, active-controlled trials that randomized patients with CKD with anemia to treatment with either Mircera or a comparator ESA.
- Four of the clinical trials assessed Mircera in the maintenance of Hb levels among patients currently treated with other ESAs for anemia of CKD (*Canaud et al 2008, Levin et al 2007, Spinowitz et al 2008b, Sulowicz et al 2007*). Patients were randomized to receive Mircera administered either once every 2 weeks or once every 4 weeks, or to continue their current ESA schedule and dose. Throughout the trials, treatment with Mircera consistently maintained Hb concentrations within the targeted range (10 to 13.5 g/dL) and demonstrated non-inferiority compared to other ESAs.
- In addition, an extension trial was conducted that demonstrated the long-term safety and efficacy of Mircera administered every 4 weeks in maintaining stable Hb levels in patients with CKD not on dialysis following correction with Mircera administered every 2 weeks (*Kessler et al 2010*).
- Other direct-comparative trials have been conducted to evaluate the safety and efficacy of Mircera to other ESAs. In the trials, mean Hb concentrations remained constant within the recommended target range in all treatment groups and further confirmed the efficacy and safety of once monthly Mircera for correction and maintenance of Hb (*Al-Ali et al 2015, Carrera et al 2010, Roger et al 2011*).
  - The PATRONUS study evaluated Mircera IV every 4 weeks to IV darbepoetin alfa every 4 weeks in patients on hemodialysis (N = 490) (*Carrera et al 2010*). For the primary endpoint, Hb response rate (average Hb ≥ 10.5 g/dL with a decrease from baseline of ≤ 1 g/dL) was significantly higher in patients on Mircera (64.1%) in comparison to those given IV darbepoetin alfa (40.4%) ($p < 0.0001$).
- A systematic review compared the efficacy and tolerability of Mircera with darbepoetin alfa for the treatment of anemia in non-dialysis dependent patients (N = 1155) with CKD (*Alsalimy et al 2014*), Based on the analysis, changes in Hb level from baseline demonstrated that Mircera was clinically non-inferior to darbepoetin alfa.
- Two studies evaluated Mircera in the correction of Hb levels in anemic patients with CKD who were not treated with an ESA at baseline.
  - In the ARCTOS study, patients (N = 324) not currently receiving dialysis were randomized to Mircera administered every 2 weeks or darbepoetin alfa administered once a week for 28 weeks. Hb response rate, defined as an increase ≥1 g/dL vs baseline and a concentration ≥11 g/dL, was achieved in 97.5% of patients treated with Mircera and 96.3% of patients treated with darbepoetin alfa (*Macdougall et al 2008*).
  - In the second study, patients who were receiving either peritoneal dialysis or hemodialysis were randomized to Mircera IV every 2 weeks or epoetin alfa or beta IV administered 3 times weekly for 24 weeks. Hb response rate was achieved in 93.3% of patients treated with Mircera and 91.3% of patients treated with epoetin (*Klinger et al 2007*). Peak Hb levels were 12.28 g/dL for Mircera and 12.19 g/dL for epoetin.
- A Cochrane systematic review and meta-analysis evaluated the effect of treatment with continuous erythropoiesis receptor activator (Mircera) on health outcomes from 27 RCTs in 5410 adults with anemia and CKD, vs a different ESA (darbepoetin alfa or epoetin alfa or beta) or placebo (*Saglimbene et al 2017*).
  - The analysis demonstrated that overall, there was low certainty evidence that Mircera had little or no effects on patient-centered outcomes, including little or no effects on mortality (RR 1.07, 95% CI 0.73 to 1.57; RR 1.11, 95% CI 0.75 to 1.65), major adverse cardiovascular events (RR 5.09, 95% CI 0.25 to 105.23; RR 5.56, 95% CI 0.99 to 31.30), need for blood transfusion (RR 1.02, 95% CI 0.72 to 1.46; RR 0.94, 95% CI 0.55 to 1.61), or additional iron therapy (RR 1.03, 95% CI 0.91 to 1.15; RR 0.99, 95% CI 0.95 to 1.03) vs epoetin alfa/beta or darbepoetin alfa respectively.
  - There was insufficient evidence to compare the effect of Mircera to placebo on clinical outcomes.
  - No studies reported comparative treatment effects of different ESAs on HRQoL.
- A systematic review and meta-analysis of 30 randomized controlled trials in adults with CKD did not find statistically significant differences for efficacy and safety between ESA biosimilars and their originators. When comparing epoetin alfa and darbepoetin alfa, darbepoetin alfa had more favorable results for blood transfusions (RR 2.18, 95% CI 1.31 to 3.62) (*Amato et al 2018*).

Anemia associated with chemotherapy

- In patients with anemia due to chemotherapy, ESAs should be avoided when the anticipated outcome of chemotherapy is cure. The use of ESAs for anemia from myelosuppressive chemotherapy should be at the lowest dose to avoid RBC transfusions and should be discontinued upon the completion of chemotherapy.
- The Agency for Healthcare Research and Quality (AHRQ) performed an updated meta-analysis of 59 randomized controlled studies, 5 of which directly compared epoetin alfa to darbepoetin alfa in patients diagnosed with malignant disease that were anemic or at risk for anemia from chemotherapy and/or radiotherapy or the underlying malignant disease. Of the endpoints evaluated, AHRQ found that the evidence did not show any clinically significant differences between epoetin alfa and darbepoetin alfa with regard to transfusion risk (pooled relative risk [RR], 1.14; 95% CI, 0.82 to 1.59; I^2=43%; 5 trials; N = 2005), on-study mortality (pooled HR, 0.9; 95% CI, 0.67 to 1.2; I^2 = 72%; 2 trials; N = 1567) and thromboembolic events (pooled RR, 0.86; 95% CI, 0.61 to 1.21; I^2 = 0%; 3 trials; N = 1873). ESA therapy was associated with higher thromboembolic event rates (pooled RR, 1.51; 95% CI, 1.3 to 1.74; I^2 = 0%; 37 trials; N = 12,570) and rates of on-study mortality (pooled HR, 1.17; 95% CI, 1.04 to 1.31; I^2 = 0%; 37 trials; N = 11,266) compared to controls. Of the other endpoints evaluated, it was determined that the evidence was not sufficient for conclusions on effects of either epoetin alfa or darbepoetin alfa compared to control on HRQoL, tumor response and progression, overall survival or adverse outcomes (*Grant et al 2013*).
- In another systematic review, ESAs were associated with a hematological response (defined as ≥2 g/dL increase in Hb or ≥6% increase in hematocrit) compared to control (risk ratio, 3.39; 95% CI, 3.1 to 3.71; 31 trials; N = 6413). However, there was significant heterogeneity between trials (I^2 = 53%). It was noted that all trials indicated a beneficial effect of ESAs on hematological response (*Tonia et al 2012*). Other meta-analyses have reported similar findings (*Bohlius et al 2009*).
- In a patient-level meta-analysis, the effectiveness of darbepoetin in improving Hb levels and blood transfusions was evaluated in patients with chemotherapy-induced anemia with an initial Hb of ≤10 g/dL (*Pirker et al 2016*). Patient level data were obtained from 4, Phase 3, randomized, double-blind, placebo-controlled trials of darbepoetin of 12 to 18 weeks in duration; for this analysis, data were extracted for patients with baseline Hb ≤10 g/dL (n = 261 for darbepoetin; n = 273 for placebo). This represented only 33% of the enrolled population. A second analysis evaluated darbepoetin only and identified 15 studies (n = 3768) without front loading and 6 studies with front loading (n = 901). For the endpoint of Hb increase of ≥1 g/dL or ≥2 g/dL vs placebo, darbepoetin improved Hb levels (HR 2.07, 95% CI, 1.62 to 2.63) and (HR 2.91, 95% CI, 2.09 to 4.06), respectively. Mean time to ≥1 g/dL increase in Hb was 43 days (95% CI, 37 to 50 days) for darbepoetin and not evaluable for placebo. Median time to a ≥2 g/dL increase was 78 days (95% CI, 71–not evaluable days) for darbepoetin and not evaluable for placebo. Transfusions were more commonly required between the start of week 5 and end of week 12 in patients who received placebo than in patients who received darbepoetin. Note that only Amgen sponsored studies were included in this analysis, and Amgen supported the meta-analysis.
- In an open-label, multicenter, randomized noninferiority trial, the impact on epoetin 40,000 units weekly on tumor outcomes was compared with the best supportive care for the treatment of anemia in 2098 patients receiving chemotherapy for metastatic breast cancer (*Leyland-Jones et al 2016*). The median progression-free survival (PFS) (based on investigator-determined disease progression) was 7.4 months in both groups (HR 1.089, 95% CI, 0.988 to 1.200) with the upper bound exceeding the prespecified noninferiority margin of 1.15. There was a reduction in the number of RBC transfusions in the epoetin-treated patients vs best supportive care (5.8 vs 11.4%; p < 0.001), while the rate of thrombotic vascular events was higher (2.8 vs 1.4%, respectively; p = 0.038). Overall, the noninferiority of treatment with epoetin was not established, and RBC transfusion was shown to be the best approach to manage anemia in patients with metastatic breast cancer receiving chemotherapy.
- Extended dosing intervals have been investigated. These extended dosing intervals of epoetin such as once every 3 weeks are not FDA-approved (*Glaspy et al 2009*).

Anemia associated with zidovudine in patients with HIV

- Early trials with epoetin in HIV were performed when zidovudine was one of only a few antiretrovirals available for treatment of HIV. Since the late 1980's and 1990's, numerous antiretroviral treatment options have become available and resulted in limited use of zidovudine. A meta-analysis of 4, small, double-blind, randomized trials evaluated the efficacy and safety of epoetin compared to placebo in improving hematocrit values in patients with HIV or Acquired Immunodeficiency Syndrome (AIDS) (*Henry et al 1992*). In the 12-week trials, epoetin significantly increased hematocrit

from baseline compared to placebo in patients with an endogenous erythropoietin level of ≤500 IU/L (mean change, 4.6 vs 0.5, respectively; p = 0.0002; mean difference, 3.9; 95% CI, 1.8 to 6).

- A meta-analysis of 6 randomized, clinical trials with 537 subjects evaluated the risk of death associated with epoetin or placebo in patients with HIV or AIDS and anemia (*Martí-Carvajal et al 2011*). None of the studies included evaluated death as a primary outcome. The risk of death was not statistically significant for epoetin versus placebo or when comparing epoetin once weekly vs 3 times weekly. Studies had significant attrition bias.

Reduced need for transfusions associated with surgery

- Clinical trials have evaluated the use of epoetin in reducing the need for blood transfusions in adults undergoing elective surgeries (*de Andrade et al 1996, Faris et al 1996, Goldberg et al 1996, Zhao et al 2016*). Epoetin is associated with an increased risk of deep venous thrombosis; therefore, appropriate preventative measures should be utilized.
- In a double-blind, multicenter, placebo-controlled trial, the efficacy and safety of epoetin 300 units/kg and 100 units/kg were compared to placebo in 316 adult patients scheduled for elective orthopedic surgery. The primary outcome was the rate of transfusion which was significantly lower in patients receiving epoetin 300 units/kg with a pretreatment Hb of >10 to ≤13 g/dL (epoetin 300 units/kg,16%; epoetin 100 units/kg, 23%; placebo, 45%; p = 0.024) (*de Andrade et al 1996*).
- Epoetin has been shown to reduce the need for blood transfusions in 200 patients undergoing elective orthopedic surgeries compared to placebo (*Faris et al 1996*). Epoetin 100 units/kg/day (17%) and epoetin 300 units/kg/day (25%) led to a reduction in the percentage of patients who required a blood transfusion following a major elective orthopedic surgery compared to control (54%; p ≤ 0.001 for both epoetin groups vs placebo). There was no significant difference between the 2 epoetin groups (p value not reported). The mean number of units transfused for each patient was significantly lower in the epoetin groups compared to the placebo group (epoetin 100 units/kg/day, 0.37±0.96; epoetin 300 units/kg/day, 0.58±1.15; placebo, 1.42±1.67; p < 0.01 for both epoetin groups compared to placebo). There was no significant difference between the epoetin groups (p > 0.05).
- A meta-analysis evaluated 7 studies (N = 2439) to evaluate efficacy and safety of treatment with erythropoietin compared with controls (placebo or no intervention) in patients undergoing total hip or knee arthroplasty (*Voorn et al 2016*). Erythropoietin was shown to reduce exposure to RBC transfusion in both hip (RR 0.45, 95% CI, 0.33 to 0.61) and knee (RR 0.38, 95% CI 0.27 to 0.53) arthroplasty, without differences between indications (p = 0.44), and the mean number of transfused RBC units was decreased in erythropoietin-treated patients (mean difference -0.57, 95% CI -0.86 to -0.29) for both indications. There were no differences detected in thromboembolic and vascular adverse events (RR 1.14, 95% CI 0.71 to 1.84), nor other adverse events (RR 1.01, 95% CI 0.94 to 1.01) between erythropoietin compared with controls.
- A systematic review and meta-analysis evaluated 15 RCTs (N = 2155) to evaluate the hematopoiesis-promoting effect and potential complications, preoperative use of erythropoietin in patients scheduled for total hip or knee arthroplasty (*Zhao et al 2016*). Preoperative use of erythropoietin was associated with lower exposure to allogeneic blood transfusion (OR = 0.41) and higher hemoglobin concentration after surgery (standardized mean difference 0.86; p < 0.001). Complications were not generally reported, but there was no significant difference between the group with and without erythropoietin based on given data.

CLINICAL GUIDELINES

CKD

- The Kidney Disease Improving Global Outcomes (KDIGO) guidelines suggest that ESAs not be used to maintain Hb concentration above 11.5 g/dL in adults with CKD. In all adult patients, ESAs should not be used to increase Hb concentrations above 13 g/dL (*KDIGO 2012*). Current practice guidelines for anemia of CKD do not specify a preferred agent. The guidelines recommend that 'copy' versions of ESAs should only be those which have been designated true biosimilars (*KDIGO 2012*).
- Based on the recommendations from the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NHF – KDOQI) Clinical Practice Guidelines and Clinical Practice Recommendations for Anemia in CKD, the Hb level at which ESA therapy should be initiated as well as the Hb target during therapy should be based on the individual patient, potential benefits (including improvement in QoL and avoidance of transfusion) and potential harms of therapy (including the risk of life-threatening adverse events). Generally speaking, the guidelines recommend that patients with CKD, both dialysis and nondialysis, receiving ESA therapy have a Hb target range of 11 to 12 g/dL, and the Hb levels should not exceed 13 g/dL. This recommendation is based on clinical studies demonstrating that patients with a Hb ≥13 g/dL do not

have improvements in survival, hospitalization or left ventricular hypertrophy and may in fact be more prone to excessive adverse cardiovascular events compared to individuals with lower Hb targets (*KDOQI 2006, KDOQI 2007*).
  - In June 2011, the FDA released more conservative recommendations for using the ESAs in patients with anemia of CKD resulting from data showing that using ESAs to target a Hb level of >11 g/dL increased the risk of cardiovascular events, without providing any additional benefit to patients (*FDA Drug Safety Communication 2011*). For patients with anemia of CKD who are not on dialysis, ESA treatment can be considered when the Hb level is <10 g/dL, and the dose should be reduced or interrupted when Hb exceeds 10 g/dL. For patients with anemia of CKD currently on dialysis, ESA treatment should be initiated when the Hb level is <10 g/dL and the dose should be reduced or interrupted when Hb approaches or exceeds 11 g/dL.
  - The KDOQI US Commentary on the 2012 KDIGO guidelines state KDOQI continues to endorse the FDA-recommended upper cutoff of 11 g/dL (*Kliger et al 2013*).
- The European Renal Best Practice guidelines state Hb target range in patients with CKD should be 11 to 12 g/dL, ESAs should not be used to maintain Hb above 11.5 g/dL, and Hb should not exceed 13 g/dL (*Locatelli et al 2009, Locatelli et al 2010, Locatelli et al 2013*). Continuous erythropoiesis receptor activator (Mircera), a modified recombinant human erythropoietin, has a considerably longer half-life than other ESAs and should be dosed once every 2 weeks for anemic correction and once every 4 weeks for maintenance of Hb levels. The safety and tolerability of continuous erythropoiesis receptor activator are similar to that of other ESAs. Biosimilars of epoetin alfa can only be administered intravenously and should not be used in exchange of the original ESA or other ESAs without physician's approval. A lower Hb target range of 10 to 12 g/dL is reasonable in nondialysis patients with type 2 diabetes. In initiating and maintaining ESA therapy, the potential benefits of reducing blood transfusions and anemia-related symptoms should be balanced against the risks of harm in individual patients (eg, stroke, vascular access loss, or hypertension). ESAs should be used with great caution, if at all, in CKD patients with active malignancy, in particular when cure is the anticipated outcome, or with a history of stroke or malignancy. The lowest possible ESA dose should be used to reach the Hb target.

Chemotherapy Associated Anemia

- Based on the recommendations from the clinical guidelines, ESAs should be considered equivalent with respect to effectiveness and safety for the management of chemotherapy-induced anemia in patients with cancer (*Rizzo et al 2010*).

Perioperative Use of ESA

- Literature supports the use of ESAs with or without iron, as ESAs are effective in reducing the number of patients requiring allogeneic blood transfusions and reducing the volume of allogenic blood transfused (*American Society of Anesthesiologists Task Force 2015*) (Category A1-B evidence – supported by a sufficient number of randomized clinical trials to conduct a meta-analysis and supported by membership opinion).
  - Insufficient evidence exists to evaluate the efficacy of ESA with iron compared to ESA without iron.
  - ESAs with or without iron may be given, when possible, to reduce the need for allogeneic blood transfusions in selected patient populations such as renal insufficiency, anemia of chronic disease, or cases of refusal of transfusion.

SAFETY SUMMARY

- Contraindications:
  - Epoetin alfa from multiple-dose vials contains benzyl alcohol and is contraindicated for use in neonates, infants, pregnant women, and lactating women.
    - Benzyl alcohol has been associated with serious adverse events and death, particularly in pediatric patients.
    - When therapy is needed in neonates and infants, or pregnant or nursing mothers, use single-dose vials.
  - ESAs should not be used in patients with uncontrolled hypertension.
  - ESAs are contraindicated if pure red blood cell aplasia (PRCA) begins after treatment with erythropoietin agents.
- Boxed Warnings:
  - ESAs increase the risk of death, myocardial infarction (MI), stroke, venous thromboembolism, thrombosis of vascular access, and tumor progression or recurrence.
  - In controlled trials, patients with CKD experienced greater risks for death, serious adverse cardiovascular reactions, and stroke when administered ESAs to a target Hb level of > 11 g/dL. No trial has identified a Hb target level, ESA dose, or dosing strategy that does not increase these risks. Use the lowest dose of ESA sufficient to reduce the need for RBC transfusions.

- In patients with cancer, ESAs shortened overall survival and/or increased the risk of tumor progression or recurrence in patients with breast, non-small cell lung, head and neck, lymphoid and cervical cancers. The warnings emphasize to only administer darbepoetin, epoetin, or epoetin alfa-epbx for the treatment of anemia due to concomitant myelosuppressive chemotherapy and to discontinue ESAs following completion of a chemotherapy course. ESAs should not be initiated in cancer patients receiving myelosuppressive therapy when the anticipated outcome is cure.
- Mircera is not indicated and is not recommended for the treatment of anemia due to cancer chemotherapy. A dose-ranging study of Mircera was terminated early because of more deaths among patients receiving Mircera than another ESA.
- Perisurgery: Deep venous thrombosis prophylaxis is recommended when epoetin alfa is used preoperatively.

- Key Warnings/Precautions:
  - ESAs increase the risk of seizures in patients with CKD.
  - Epoetin alfa contains albumin, a derivative of human blood. There is an extremely remote risk for transmission of viral diseases.
  - Severe cutaneous reactions, including erythema multiforme and Stevens-Johnson Syndrome/toxic epidermal necrolysis, have been reported in patients treated with ESAs.
  - There is a risk of serious adverse reactions due to benzyl alcohol preservative in multiple-dose vials of epoetin alfa. Do not mix epoetin alfa with bacteriostatic saline (which also contains benzyl alcohol) when administering to neonates, infants, pregnant women, and lactating women.
    - Serious and fatal reactions including “gasping syndrome” may occur in neonates and infants treated with benzyl alcohol-preserved drugs. The “gasping syndrome” is characterized by central nervous system depression, metabolic acidosis, and gasping respirations.
    - There is a potential for similar risks to fetuses and infants exposed to benzyl alcohol in utero or in breast-fed milk, respectively.
    - The minimum amount of benzyl alcohol at which serious adverse reactions may occur is not known
  - There is a risk of PRCA with darbepoetin alfa, epoetin alfa, epoetin alfa-epbx, and methoxy polyethylene glycol-epoetin beta therapy.
  - ESAs may decrease progression-free survival and overall survival in patients with breast cancer, lymphoid malignancy, cervical cancer, advanced head and neck cancer, non-small cell lung cancer or other malignancies.
- Risk Evaluation and Mitigation Strategy (REMS):
  - On April 13, 2017, the FDA removed the REMS from Aranesp, Epogen, and Procrit (*FDA REMS program 2019, Information for Epogen/Procrit 2017*). The decision was based on a survey showing that prescribers were already educated on the potential contribution of these products to the decreased survival or increased risk of tumor progression or recurrence when used for anemia due to myelosuppressive chemotherapy. Moreover, most data showed that ESAs were prescribed for FDA-approved indications. Due to removal of the REMS, health care providers and hospitals are no longer required to enroll and become certified to prescribe and dispense these agents.
- Adverse events
  - The most commonly reported adverse events with ESAs include hypertension, arthralgia, muscle spasm, and fever.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Aranesp (darbepoetin alfa)	Single-dose vials, single-dose prefilled syringe	IV or SC injection	Anemia associated with CKD for patients on dialysis when Hb < 10 g/dL: Initial, once weekly or once every 2 weeks; maintenance, dose should be individualized to maintain Hb levels that do not exceed 11 g/dL Anemia associated with CKD for patients not on dialysis when Hb is < 10 g/dL, and the rate of decline indicates a blood transfusion is likely	• Safety and efficacy of Aranesp in adults and pediatric patients were similar for the initial treatment of anemia in patients with CKD or in transition from another

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			and reducing RBC transfusion-related risks is a goal: Initial, once every 4 weeks; maintenance, dose should be individualized to maintain Hb levels that do not exceed 10 g/dL. Pediatrics with CKD: Initiate when Hb is < 10 g/dL. Anemia associated with concomitant chemotherapy in patients with non-myeloid malignancies when Hb < 10 g/dL and 2 or more additional months of chemotherapy are planned: Initial, once weekly or once every 3 weeks until completion of a chemotherapy course; maintenance, dose should be individualized to maintain desired response.	erythropoietin.
Epogen, Procrit, Retacrit (epoetin alfa; epoetin alfa-epbx)	Multiple-dose vials (preserved solution)*, single-dose vials (preservative-free solution)	IV or SC injection	Anemia associated with CKD, including patients on dialysis and patients not on dialysis: Initial, 3 times weekly; maintenance, dose should be individualized to maintain Hb levels that do not exceed 11 g/dL (dialysis) or 10 g/dL (non-dialysis). For pediatric patients, 3 times weekly (dialysis). Anemia associated with concomitant chemotherapy in patients with non-myeloid malignancies when Hb < 10 g/dL and 2 or more additional months of chemotherapy are planned: Initial, 3 times weekly or once weekly until completion of a chemotherapy course; maintenance, dose should be individualized to maintain the lowest Hb level sufficient to avoid red blood cell transfusion. Pediatric patients (5 to 18 years of age): weekly until completion of chemotherapy course. Anemia associated with therapy of zidovudine in HIV-infected patients with endogenous serum erythropoietin levels < 500 mUnits/mL: Initial, 3 times weekly for 8 weeks; maintenance, dose should be individualized to maintain desired response. Withhold epoetin if Hb >12 g/dL. Treatment of anemic patients (Hb > 10 to < 13 g/dL) at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery to reduce the need for allogeneic blood transfusions: daily dose for 10 days	• Benzyl alcohol, found in multiple-dose preserved formulations, has been reported to be associated with an increased incidence of neurological and other complications, which are sometimes fatal, in premature infants. Benzyl alcohol has also been associated with serious adverse events and death, particularly in pediatric patients. • Single-dose preservative-free vials should be used in neonates and infants, as well as pregnant and nursing women.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			before surgery, on the day of surgery and for 4 days after surgery; alternative dosing schedule is once weekly, at 21, 14 and 7 days before surgery, with a fourth dose on the day of surgery.	
Mircera (methoxy poly-ethylene glycol-epoetin beta)	Prefilled syringes	IV or SC injection	Anemia associated with CKD, including adult patients on dialysis and patients not on dialysis: Initial, once every 2 weeks; dose should be individualized to maintain Hb levels that do not exceed 11 g/dL (dialysis) or 10 g/dL (non-dialysis). Once the Hb has been stabilized, may be administered once monthly. Treatment of anemia associated with CKD in pediatric patients 5 to 17 years of age on hemodialysis who are converting from another ESA after their Hb level was stabilized with an ESA: once every 4 weeks at a dose based on the total weekly ESA dose at the time of conversion	• Should be injected in the abdomen, arm or thigh with SC administration. • Pregnancy Category C†

*Retacrit is only available as single-dose vials.
†Pregnancy Category C = risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

See the current prescribing information for full details.

- The iron status in all patients should be evaluated in all patients before and during treatment, and iron repletion maintained. Other causes of anemia should be corrected or excluded before initiating ESA.
- IV administration of ESAs is recommended for patients receiving hemodialysis.
- For all ESAs, the dosing should be individualized and the lowest dose sufficient to reduce the need for RBC transfusions should be used.

CONCLUSION

- The FDA-approved erythropoiesis-stimulating agents (ESAs) in the United States are Aranesp (darbepoetin alfa), Epogen (epoetin alfa), Procrit (epoetin alfa), Retacrit (epoetin alfa-epbx), and Mircera (methoxy polyethylene-glycol epoetin beta). Retacrit (epoetin alfa-epbx) was approved as a biosimilar to Epogen/Procrit (epoetin alfa) in May 2018 (*FDA News Release 2018*). All agents are indicated for the treatment of anemia associated with CKD.
  - Aranesp, Epogen, Procrit, and Retacrit are also indicated for the treatment of anemia due to the effect of concomitantly administered chemotherapy in patients with non-myeloid malignancies.
  - Epogen, Procrit, and Retacrit are also indicated for treatment of anemia related to therapy with zidovudine in HIV-infected patients as well as the treatment of anemic patients who are at high risk for perioperative blood loss from elective, noncardiac, nonvascular surgery.
- Clinical trials and meta-analyses comparing the efficacy of epoetin alfa and darbepoetin alfa for the treatment of anemia associated with CKD as well as anemia due to concomitant chemotherapy have demonstrated no differences between the agents (*Bohlius et al 2009, Collister et al 2016, Grant et al 2013, Nissenson et al 2002, Palmer et al 2014a, Palmer et al 2014b, Vanrenterghem et al 2002, Tonia et al 2012, Wilhelm-Leen et al 2015*).

- A systematic review and meta-analysis did not find statistically significant differences for efficacy and safety between ESA biosimilars and their originators. When comparing epoetin alfa and darbepoetin alfa, darbepoetin alfa had more favorable results for blood transfusions (*Amato et al 2018*).

- Numerous RCTs provide supportive evidence demonstrating the effectiveness of Mircera for the correction and maintenance of Hb in patients with anemia of CKD. Throughout the trials, treatment with Mircera corrected and maintained Hb concentrations within the targeted Hb range and demonstrated non-inferiority compared to other ESAs (*Al-Ali et al 2015, Carrera et al 2010, Canaud et al 2008, Levin et al 2007, Spinowitz et al 2008b, Sulowicz et al 2007, Roger et al 2011*). A meta-analysis demonstrated a low certainty of evidence that Mircera had little or no effects on patient-centered outcomes, including little or no effects on mortality, major adverse cardiovascular events, or need for blood transfusion vs epoetin alfa/beta or darbepoetin alfa (*Saglimbene et al 2017*).
- The ESAs are commonly used for the treatment of anemia associated with CKD to reduce the need for transfusions. The KDIGO guidelines suggest that ESAs not be used to maintain Hb concentration above 11.5 g/dL in adults with CKD. In adult patients, ESAs should not be used to increase Hb concentrations above 13 g/dL (*KDIGO 2012*). Current practice guidelines for anemia of CKD do not specify a preferred agent. The KDOQI guidelines state that each of the agents is effective at achieving and maintaining target Hb levels, and endorse the FDA-recommended upper cutoff of 11 g/dL (*KDIGO 2012, KDOQI 2006, KDOQI 2007, Kliger et al 2013*).
  - Based on the recommendations from the clinical guidelines, ESAs should be considered equivalent with respect to effectiveness and safety for the management of chemotherapy-induced anemia in patients with cancer (*Rizzo et al 2010*).
- All ESAs carry a boxed warning of increased mortality, serious cardiovascular and thromboembolic events, stroke and increased risk of tumor progression.
  - Multiple-dose vials of Epogen (epoetin alfa) and Procrit (epoetin alfa) contain benzoyl alcohol.
- Aranesp (darbepoetin alfa) is administered weekly or every 2 weeks, Epogen (epoetin alfa), Procrit (epoetin alfa), and Retacrit (epoetin alfa-epbx) are administered 1 to 3 times weekly and Mircera (methoxy polyethylene-glycol epoetin beta) is administered every 2 to 4 weeks.

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Therapeutic Class Overview
Biguanides

INTRODUCTION

- Diabetes mellitus affects more than 30 million people in the United States. More than 84 million American adults have prediabetes, with 90% of this population unaware that they have the condition (*Centers for Disease Control and Prevention [CDC] 2018).*
- Type 2 diabetes mellitus (T2DM) is the most common form of diabetes, and is characterized by elevated fasting and postprandial glucose concentrations. It is a chronic illness that requires continuing medical care and ongoing patient self-management education and support to prevent acute complications and to reduce the risk of long-term complications (*American Diabetes Association [ADA] 2019, CDC 2018*).
- Complications of T2DM include heart disease, stroke, vision loss, kidney disease, and lower-limb amputations. It is the leading cause of kidney failure, lower-limb amputations, and adult-onset blindness and the seventh leading cause of death in the United States (*CDC 2018*).
- Medical costs for patients with diabetes are double the costs for patients without diabetes (*CDC 2018*).
- Classes of oral medications for the management of blood glucose levels in patients with T2DM may exert their effects through various mechanisms, including decreasing hepatic glucose production, increasing insulin secretion, increasing insulin sensitivity, decreasing the rate of carbohydrate absorption, decreasing glucagon secretion, and blocking glucose reabsorption by the kidney (*Davies et al 2018*).
- Key pharmacologic options for T2DM include sulfonylureas, biguanides, thiazolidinediones (TZDs), meglitinides (or glinides), alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and insulin (*Davies et al 2018*). Many patients with T2DM will require combination therapy (*Garber et al 2018*).
- Metformin, the sole available biguanide, is thought to have several mechanisms of action. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. With metformin therapy, insulin secretion remains unchanged.
- In addition to diabetes, metformin is used off-label for management of women with polycystic ovarian syndrome (PCOS), a condition that affects approximately 6% to 10% of women (*Azziz 2017, Legro et al 2013*).
- Although metformin is the sole biguanide in the class, it is available in various dosage forms including tablets, several forms of extended-release tablets, and an oral solution. This review includes the single-ingredient metformin products. Metformin is also available in combination products with several other classes of antihyperglycemic drugs; however, the combination products are not included in this review.
- Medispan class: Biguanides

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Glucophage (metformin tablets)	✔
Glucophage XR (metformin tablets, extended release)	✔
Fortamet (metformin tablets, extended release)	✔
Glumetza (metformin tablets, extended release)	✔
Riomet (metformin oral solution)	✔ *

*Authorized generic

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Glucophage	Glucophage XR	Fortamet	Glumetza	Riomet
Adjunct to diet and exercise to improve glycemic control in adults and pediatric patients 10 years of age and older with T2DM	✔				✔
Adjunct to diet and exercise to improve glycemic control in adults with T2DM		✔	✔	✔	

(*Prescribing Information: Fortamet 2018, Glucophage/Glucophage XR 2018, Glumetza 2018, Riomet 2018*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The effectiveness of metformin in T2DM as monotherapy and in combination with other oral antidiabetic agents and/or insulin has been demonstrated through many clinical trials. Most trials evaluated a number of glycemic outcomes such as hemoglobin A1c (HbA1c) and fasting plasma glucose (FPG). Other metabolic outcomes often reported were body weight, body mass index (BMI), effects on insulin secretion, and effects on lipid parameters. However, results from recent cardiovascular outcomes trials of patients with T2DM are moving away from a glucocentric approach, since drugs that lower HbA1c to similar levels may have different effects on patient outcomes. Furthermore, the diabetes field is moving away from its historical reliance on surrogate markers and toward studies that assess outcomes such as heart disease and mortality to identify drugs that achieve the goals of diabetes care (*Lipska and Krumholz 2017*).
- A number of trials have demonstrated the effectiveness of metformin compared to placebo (*Douek et al 2005, Jones et al 2002, Kooy et al 2009, Wulffele et al 2002*). More often, metformin has been studied in comparison to an alternative antihyperglycemic drug, either as monotherapy or in various combination regimens (*Aschner et al 2010, Bailey et al 2010, Bosi et al 2009, Cryer et al 2005, Defronzo et al 1995, Derosa et al 2010, Fonseca et al 2012, Gottschalk et al 2007, Henry et al 2012, Jadzinsky et al 2009, Kahn et al 2006, Lewin et al 2007, Lund et al 2009, Neutel et al 2013, Pavo et al 2003, Russell-Jones et al 2012, Stewart et al 2006, United Kingdom Prospective Diabetes Study [UKPDS] Group 1998, Weissman et al 2005*).
- A large meta-analysis estimated the effect of metformin on HbA1c to be approximately 1.1% in monotherapy trials, 0.95% in trials adding metformin to other oral therapies, and 0.6% in trials adding metformin to insulin (*Hirst et al 2012*).
- A number of trials and analyses have evaluated cardiovascular and other diabetes outcomes (*Boussageon et al 2012, Hemmingsen et al 2012, Johnson et al 2005, Kooy et al 2009, Lamanna et al, 2011*). Trial results have not always been in agreement for these outcomes. A landmark study often cited in the literature is UKPDS 34, which compared metformin therapy to conventional treatment (primarily diet alone) on diabetes-related cardiovascular and other clinical outcomes, diabetes-related death, and all-cause mortality in overweight patients with T2DM. The study demonstrated a significantly reduced risk of these 3 outcomes in the group treated with metformin. However, the investigators also evaluated the use of metformin when added to sulfonylurea compared to sulfonylurea alone, and found contrary results: patients treated with metformin had an increased risk of diabetes-related death and all-cause mortality (*UKPDS Group 1998*).
- Since UKPDS 34 was published, several other studies and meta-analyses have sought to gather more information on cardiovascular and other patient-relevant outcomes. Overall, the evidence supporting a potential cardiovascular benefit for metformin is not robust (*Fitchett et al 2017*). A retrospective trial compared metformin to sulfonylureas and their combination for a composite endpoint of fatal or nonfatal cardiovascular-related events, and the trial demonstrated that patients in the metformin monotherapy group had a lower risk of the composite cardiovascular endpoint compared to sulfonylurea monotherapy (*Johnson et al 2005*). A Cochrane meta-analysis and systematic review evaluated metformin compared to non-pharmacologic and other pharmacologic interventions for T2DM, and it was concluded that metformin

showed a significant benefit compared to chlorpropamide, glyburide, or insulin for all-cause mortality and for any diabetes-related outcome (a composite measure evaluating a large number of outcomes such as sudden death, myocardial infarction, heart failure, stroke, amputation, retinopathy, and blindness) (*Saenz et al 2005*); this review has since been withdrawn from publication due to multiple changes like new publications, methods and standards since its publication. In contrast, a prospective study with a 4.3-year follow-up that compared insulin plus metformin to insulin plus placebo failed to demonstrate a significant benefit for metformin for a composite macrovascular and microvascular endpoint. In this trial, a small benefit was seen for metformin on an aggregate macrovascular endpoint, but this failed to reach statistical significance after adjusting for changes in body weight (*Kooy et al 2009*). Several meta-analyses have failed to conclusively demonstrate a cardiovascular benefit with metformin (*Boussageon et al 2012, Hemmingsen et al 2012, Lamanna et al 2011*). Some investigators noted that significant differences were found for some outcomes, but these differences did not persist when data from UKPDS 34 was excluded (*Boussageon et al 2012, Lamanna et al 2011*).

- In addition to these outcomes, a number of studies evaluated the use of different dosage forms of metformin. Metformin is available in several different formulations, which include metformin immediate-release tablets and solution, as well as 3 sustained-release formulations. Metformin solution was found to have an equivalent rate and extent of absorption as metformin immediate-release tablets. Clinical studies reported comparable changes in HbA1c between the immediate-release formulations and sustained-release formulations (*Fujioka et al 2003, Schwartz et al 2006*).

CLINICAL GUIDELINES

- Current guidelines recommend that metformin, along with lifestyle intervention, should be the initial pharmacologic therapy for T2DM in the absence of specific contraindications.
  - According to the ADA and a joint consensus report by the ADA and the European Association for the Study of Diabetes (EASD), dual therapy or triple therapy can be considered in patients not achieving their HbA1c goal on metformin monotherapy (*ADA 2019, Davies et al 2018*). Choice of add-on therapy should be determined based on 1) whether the patient has established atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CKD); and 2) whether there is a compelling need to minimize hypoglycemia or a compelling need to minimize weight gain or promote weight loss in patients without established ASCVD or CKD.
    - If ASCVD predominates, a GLP-1 receptor agonist with proven cardiovascular disease (CVD) benefit or an SGLT2 inhibitor with proven CVD benefit (if estimated glomerular filtration rate [eGFR] is adequate) is recommended.
    - If heart failure or CKD predominates, an SGLT2 inhibitor with evidence of reducing heart failure and/or CKD progression is preferred if the eGFR is adequate. If the SGLT2 inhibitor is not tolerated or contraindicated, or if the eGFR is less than adequate, a GLP-1 receptor agonist with proven CVD benefit is recommended.
    - In patients without established ASCVD or CKD:
      - If there is a compelling need to minimize hypoglycemia, recommendations include a DPP-4 inhibitor, a GLP-1 receptor agonist, an SGLT2 inhibitor, or a TZD.
      - If there is a compelling need to minimize weight gain or promote weight loss, a GLP-1 receptor agonist with good efficacy for weight loss or an SGLT2 inhibitor is recommended.
    - The early introduction of insulin should be considered if there is evidence of ongoing catabolism (eg, weight loss), if symptoms of hyperglycemia are present, or when HbA1c levels or blood glucose levels are very high (> 10% or ≥ 300 mg/dL, respectively).
    - In most patients who need the greater glucose-lowering effect of an injectable medication (ie, HbA1c is above target despite dual/triple therapy), GLP-1 receptor agonists are preferred to insulin. Insulin should be considered as the first injectable if the HbA1c is very high (> 11%), in the presence of symptoms or evidence of catabolism, or if type 1 diabetes is a possibility.
  - According to the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE), the choice of diabetes therapies must be individualized based on attributes specific to the patient and the medication (*Garber et al 2018*). Metformin is recommended as the preferred initial agent for monotherapy in patients with an entry HbA1c < 7.5%; however, monotherapy with other agents may be considered. Combination therapies including metformin plus 1 or 2 additional agents are recommended for patients with an entry HbA1c ≥ 7.5%. Several options for dual- and triple-therapy are presented in a hierarchy, with GLP-1 receptor agonists and SGLT2 inhibitors listed as the top 2 options to be added. In patients with an entry HbA1c > 9%, dual- or triple therapy should be considered if patients are asymptomatic, and insulin considered if patients are symptomatic.

- Metformin is also utilized to treat women with PCOS. The Endocrine Society guideline recommends using metformin in women with PCOS and T2DM or impaired glucose tolerance and as a second-line therapy in women with PCOS and menstrual irregularity who cannot tolerate hormonal contraceptives. Metformin has no benefit in improving hirsutism, acne, or infertility (*Legro et al 2013*).
- See the individual guidelines for additional details on subsequent therapy and patient-specific considerations.

SAFETY SUMMARY

- Metformin has a strong safety record when used according to guidelines. A main safety concern is lactic acidosis. However, a 2010 Cochrane Review including 347 studies failed to identify any cases of fatal or non-fatal lactic acidosis caused by metformin (*Salpeter et al 2010*).
- Contraindications:
  - Severe renal impairment (eGFR < 30 mL/min/1.73 m^2)
  - Known hypersensitivity to metformin hydrochloride
  - Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma
- Boxed warnings:
  - Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias.
    - Risk factors include renal impairment, concomitant use of certain drugs, age ≥ 65 years, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment.
    - Symptoms include malaise, myalgias, respiratory distress, somnolence, and abdominal pain.
    - If lactic acidosis is suspected, metformin should be discontinued and general supportive measures should be instituted in a hospital setting. Prompt hemodialysis is recommended.
- Warnings:
  - Vitamin B_{12} levels: Low vitamin B_{12} levels have been observed in some patients on metformin, possibly due to reduced B_{12} absorption. Monitoring of hematologic parameters annually, and vitamin B_{12} levels at 2 to 3 year intervals, is advised.
  - Hypoglycemia: May occur with insufficient caloric intake, strenuous exercise or with other drugs that lower glucose. A lower dose of insulin or insulin secretagogue may be required to minimize the risk of hypoglycemia when used in combination with metformin.
  - There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with metformin.
- Adverse drug events:
  - The most common are gastrointestinal in nature: diarrhea, flatulence, nausea and vomiting.
- Drug Interactions:
  - Carbonic anhydrase inhibitors (eg, topiramate, zonisamide, acetazolamide or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs with metformin may increase the risk for lactic acidosis. More frequent monitoring should be considered.
  - Drugs that reduce metformin clearance: Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (eg, ranolazine, vandetanib, dolutegravir, and cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis. Benefits and risks of concomitant use should be considered.
  - Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients should be warned against excessive alcohol intake.
  - Medications affecting glycemic control (eg, thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid): The co-administered drug may lead to loss of glycemic control; thus the patient should be closely observed.
- Special populations:
  - Renal insufficiency: In April 2016, the FDA issued a Drug Safety Communication requiring a change to metformin labeling in order to convey that metformin may be safely used in patients with mild to moderate renal impairment. The FDA also recommended that a better estimate of renal function (ie, eGFR) be used in place of blood creatinine as a measure of renal function. These recommendations have resulted in updates to the product labeling (*FDA 2017*).

- Metformin is contraindicated in patients with an eGFR < 30 mL/minute/1.73 m^2. Initiation is not recommended in patients with eGFR between 30 and 45 mL/minute/1.73 m^2. In patients taking metformin whose eGFR falls below 45 mL/min/1.73 m^2, the benefit and risk of continuing therapy should be assessed.

- Hepatic impairment: Use of metformin in patients with hepatic impairment has been associated with some cases of lactic acidosis. Metformin is not recommended in patients with hepatic impairment.
- Pregnancy: Limited data with metformin in pregnant women are not sufficient to determine a drug-associated risk for major birth defects or miscarriage. Published studies with metformin use during pregnancy have not reported a clear association with metformin and major birth defect or miscarriage risk. There are risks to the mother and fetus associated with poorly controlled diabetes mellitus in pregnancy.
- Lactation: Limited published studies report that metformin is present in human milk. There is insufficient information to determine the effects of metformin on the breastfed infant and no available information on the effects of metformin on milk production.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Glucophage	Tablets	Oral	Twice daily	With meals. May be used in children 10 to 16 years of age in addition to adults.
Glucophage XR	Extended-release tablets	Oral	Once daily	With evening meal. Safety and effectiveness in pediatric patients have not been established. Should not be crushed or chewed.
Fortamet	Extended-release tablets	Oral	Once daily	With evening meal. Safety and effectiveness in pediatric patients have not been established. Should not be cut, crushed, or chewed.
Glumetza	Extended-release tablets	Oral	Once daily	With evening meal. Safety and effectiveness in pediatric patients have not been established. Should not be split, crushed, or chewed.
Riomet	Oral solution	Oral	Twice daily	With meals. May be used in children 10 to 16 years of age in addition to adults.

See the current prescribing information for full details.

CONCLUSION

- Metformin is a well-established medication for the treatment of T2DM. Treatment guidelines are consistent in their recommendation that metformin be considered a first-line treatment for T2DM in the absence of contraindications.
- Metformin has been shown to be effective as monotherapy, in combination with other oral antidiabetic agents, and in combination with insulin.

- Consistent benefits are seen with metformin for HbA1c and FPG. A large meta-analysis estimated the effect of metformin on HbA1c to be approximately 1.1% in monotherapy trials, 0.95% in trials adding metformin to other oral therapies, and 0.6% in trials adding metformin to insulin (*Hirst et al 2012*).
- Despite strong efficacy on metabolic outcomes in T2DM, data on cardiovascular outcomes and mortality have not consistently demonstrated a benefit with metformin.
- Metformin is used off-label as a second-line agent in women with PCOS and menstrual irregularities if they do not tolerate hormonal contraceptives (*Legro et al 2013*).
- Metformin has a strong safety record when used according to guidelines. A main safety concern is lactic acidosis. However, a 2010 Cochrane Review including 347 studies failed to identify any cases of fatal or non-fatal lactic acidosis caused by metformin (*Salpeter et al 2010*).
- The most common adverse effects associated with metformin are gastrointestinal.
- Metformin is available in several dosage forms for dose individualization and patient convenience. Several products (Glucophage, Glucophage XR, Glumetza, and Fortamet) are available generically. Riomet is available as a brand and an authorized generic.

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OPTUMRx

Therapeutic Class Overview
Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

INTRODUCTION

- In the United States (US), diabetes mellitus affects more than 30 million people and is the 7th leading cause of death (*Centers for Disease Control and Prevention [CDC] 2018*).
- Type 2 diabetes mellitus (T2DM) is the most common form of diabetes and is characterized by elevated fasting and postprandial glucose concentrations *(American Diabetes Association [ADA] 2019[a])*. It is a chronic illness that requires continuing medical care and ongoing patient self-management education and support to prevent acute complications and to reduce the risk of long-term complications *(ADA 2019[b])*.
  - Complications of T2DM include hypertension, heart disease, stroke, vision loss, nephropathy, and neuropathy *(ADA 2019[a])*.
- In addition to dietary and lifestyle management, T2DM can be treated with insulin, one or more oral medications, or a combination of both. Many patients with T2DM will require combination therapy *(Garber et al 2019)*.
- Classes of oral medications for the management of blood glucose levels in patients with T2DM focus on increasing insulin secretion, increasing insulin responsiveness, or both, decreasing the rate of carbohydrate absorption, decreasing the rate of hepatic glucose production, decreasing the rate of glucagon secretion, and blocking glucose reabsorption by the kidney *(Garber et al 2019)*.
- Pharmacologic options for T2DM include sulfonylureas (SFUs), biguanides, thiazolidinediones (TZDs), meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogs, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, combination products, and insulin *(Garber et al 2019)*.
- The DPP-4 inhibitors or gliptins (alogliptin, linagliptin, saxagliptin, sitagliptin) are indicated as adjuncts to diet and exercise to improve glycemic control in adults with T2DM. All of the DPP-4 inhibitors are available as combination products with metformin hydrochloride (HCl) and/or extended-release metformin HCl *(Drugs@FDA 2019)*.
  - Alogliptin is also approved as a combination product with pioglitazone (a thiazolidinedione [TZD]).
  - Linagliptin is also approved as a combination product with empagliflozin (an SGLT2 inhibitor).
  - Saxagliptin is also approved as a combination product with dapagliflozin (an SGLT2 inhibitor).
  - Sitagliptin is also approved as a combination product with ertugliflozin (an SGLT2 inhibitor).
- The activity of the DPP-4 inhibitors is based on inhibition of the DPP-4 enzyme that mediates physiological degradation of the incretin hormones, glucagon-like peptide 1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP) *(Davis 2014)*. GLP-1 and GIP are secreted by specialized mucosal intestinal cells in response to a meal, promoting insulin biosynthesis and release, as well as other aspects of pancreatic beta cell function in a glucose-dependent manner which circumvents hypoglycemia *(Davis 2014)*. GLP-1 inhibits inappropriate glucagon secretion, delays gastric emptying and, at higher concentrations, suppresses appetite *(Davis 2014)*.
- DPP-4 inhibitors have modest glycated hemoglobin (HbA1c)-lowering properties, are weight neutral, and are associated with a low risk of hypoglycemia *(American Diabetes Association [ADA] 2018, Garber et al 2018)*. DPP-4 inhibitors are not considered as initial therapy for the majority of patients with T2DM *(ADA 2018)*. Indicated as adjuncts to diet and exercise, DPP-4 inhibitors are generally considered after patients have tried/failed metformin (ie, glycemic targets have not been achieved after 3 months at maximum tolerated doses and thus, a DPP-4 can be considered as add-on therapy) or when patients are otherwise intolerant or unable to take metformin, in which case, a DPP-4 inhibitor may be considered as monotherapy *(ADA 2018, Deacon et al 2016, Garber et al 2018, Dungan 2017)*.
- The choice of antidiabetic therapy should be individualized based upon patient specific factors such as comorbidities, the risk of hypoglycemia, and potential adverse effects *(ADA 2018)*.
- Medispan Class: Antidiabetics, Dipeptidyl -4 (DPP-4) inhibitors

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Alogliptin-containing products*	
Nesina (alogliptin)	✔
Kazano (alogliptin/metformin HCl)	✔

Drug	Generic Availability
Oseni (alogliptin/pioglitazone)	✔
Linagliptin-containing products	
Tradjenta (linagliptin)	-
Glyxambi (linagliptin/empagliflozin)	-
Jentadueto (linagliptin/metformin HCl)	-
Jentadueto XR (linagliptin/metformin HCl extended-release)	-
Saxagliptin-containing products	
Onglyza (saxagliptin)	-
Kombiglyze XR (saxagliptin/metformin HCl extended-release)	-
Qtern (saxagliptin/dapagliflozin)	-
Sitagliptin-containing products	
Januvia (sitagliptin)	-
Janumet (sitagliptin/metformin HCl)	-
Janumet XR (sitagliptin/metformin HCl extended-release)	-
Steglujan (sitagliptin/ertugliflozin)	-

*Alogliptin-containing products have been made available by two different manufacturers. Takeda Pharmaceuticals makes brand Nesina, Kazano, and Oseni. Perrigo Pharmaceuticals markets the authorized generics alogliptin, alogliptin/metformin, and alogliptin/pioglitazone *(Perrigo Pharmaceuticals Web site)*.

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration (FDA) Approved Indications: Alogliptin-containing products

Indication	Nesina (alogliptin)*	Kazano (alogliptin/metformin HCl)*	Oseni (alogliptin/pioglitazone)*
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	✔		
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM in multiple clinical settings when treatment with both alogliptin and metformin is appropriate		✔	
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM in multiple clinical settings when treatment with both alogliptin and pioglitazone is appropriate			✔

* Limitation of use: Should not be used for the treatment of type 1 diabetes or diabetic ketoacidosis, as it would not be effective in those settings.

(Prescribing information: Kazano 2017, Nesina 2016, Oseni 2017)

Table 3. Food and Drug Administration Approved Indications: Linagliptin-containing products

Indication	Tradjenta (linagliptin)*†	Glyxambi (linagliptin/ empagliflozin)*†	Jentadueto (linagliptin/ metformin HCl)*†	Jentadueto XR (linagliptin/ metformin HCl extended-release)*†
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	✔			
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both linagliptin and empagliflozin is		✔		

Indication	Tradjenta (linagliptin)*†	Glyxambi (linagliptin/ empagliflozin)*†	Jentadueto (linagliptin/ metformin HCl)*†	Jentadueto XR (linagliptin/ metformin HCl extended-release)*†
appropriate Empagliflozin is indicated to reduce the risk of cardiovascular (CV) death in adults with T2DM and established CV disease; however, the effectiveness of Glyxambi on reducing the risk of CV death in adults with T2DM and CV disease has not been established				
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both linagliptin and metformin is appropriate			✔	✔

* Limitation of use: Should not be used for the treatment of type 1 diabetes or diabetic ketoacidosis, as it would not be effective in those settings.

† Limitation of use: Has not been studied in patients with a history of pancreatitis.

(Prescribing information: Glyxambi 2018, Jentadueto 2017, Jentadueto XR 2017, Tradjenta 2017)

Table 4. Food and Drug Administration Approved Indications: Saxagliptin-containing products

Indication	Onglyza (saxagliptin)*	Kombiglyze XR (saxagliptin/ metformin HCl extended-release)*	Qtern (saxagliptin/dapagliflozin)*†
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	✔		
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both saxagliptin and metformin is appropriate		✔	
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM who have inadequate control with dapagliflozin or who are already treated with dapagliflozin and saxagliptin			✔

***** Limitation of use: Should not be used for the treatment of type 1 diabetes or diabetic ketoacidosis, as it would not be effective in those settings.

† Limitation of use: Should only be used in patients who can tolerate 10 mg dapagliflozin.

(Prescribing information: Kombiglyze XR 2017, Onglyza 2017, Qtern 2018)

Table 5. Food and Drug Administration Approved Indications: Sitagliptin-containing products

Indication	Januvia (sitagliptin)*†	Janumet (sitagliptin/ metformin HCl)*†	Janumet XR (sitagliptin/ metformin HCl extended-release)*†	Steglujan (sitagliptin/ ertugliflozin)*†
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	✔			
As an adjunct to diet and exercise to improve glycemic control in adults with		✔		

Indication	Januvia (sitagliptin)*†	Janumet (sitagliptin/ metformin HCl)*†	Janumet XR (sitagliptin/ metformin HCl extended-release)*†	Steglujan (sitagliptin/ ertugliflozin)*†
T2DM when treatment with both sitagliptin and metformin is appropriate				
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both sitagliptin and metformin extended-release is appropriate			✔	
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both sitagliptin and ertugliflozin is appropriate				✔

***** Limitation of use: Should not be used for the treatment of type 1 diabetes or diabetic ketoacidosis, as it would not be effective in those settings.

† Limitation of use: Has not been studied in patients with a history of pancreatitis.

(Prescribing information: Janumet 2018, Janumet XR 2018, Januvia 2018, Steglujan 2018)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Alogliptin-containing products

- In the following 10 pivotal trials described in the Nesina prescribing information (2016) and published as cited, alogliptin has been shown to have activity for improving glucose control when:
  - used as monotherapy vs placebo *(DeFronzo et al 2008)*
  - used as initial combination therapy with metformin vs placebo or alogliptin or metformin monotherapy *(Pratley et al 2014)*
  - used as add-on therapy to metformin vs placebo + metformin *(Nauck et al 2009)*
  - used as combination add-on therapy with pioglitazone to metformin vs placebo or alogliptin or pioglitazone monotherapy *(DeFronzo et al 2012)*
  - used as add-on therapy to pioglitazone vs placebo + pioglitazone *(Pratley et al 2009[a])*
  - used as add-on therapy to pioglitazone vs alogliptin or pioglitazone monotherapy *(Rosenstock et al 2010)*
  - used as add-on combination therapy with pioglitazone and metformin vs placebo + pioglitazone and metformin *(Bosi et al 2011)*
  - used as add-on therapy to glyburide (an SFU) vs placebo + glyburide *(Pratley et al 2009[b])*
  - used as add-on therapy to insulin +/- metformin vs placebo + insulin +/- metformin *(Rosenstock et al 2009[a])*
  - used as monotherapy vs glipizide *(Rosenstock et al 2013[b])*
- There have been no clinical efficacy studies conducted with Kazano, the alogliptin/metformin combination product. However, bioequivalence of Kazano with co-administered alogliptin and metformin tablets was demonstrated, and the efficacy of the combination of alogliptin and metformin has been demonstrated in three Phase 3 efficacy studies *(Bosi et al 2011, Nauck et al 2009, Pratley et al 2014)*.
- There have been no clinical efficacy studies conducted with Oseni, the alogliptin/pioglitazone combination product. However, bioequivalence of Oseni with co-administered alogliptin and pioglitazone tablets was demonstrated and the efficacy of the combination of alogliptin and pioglitazone has been demonstrated in four Phase 3 efficacy studies *(Bosi et al 2011, DeFronzo et al 2012, Pratley et al 2009[a], Rosenstock et al 2010)*.

- **CV outcomes** *(White et al 2011, White et al 2013, Zannad et al 2015)*
  - Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care (EXAMINE) was a Phase 3, double-blind (DB), placebo-controlled (PC), multi-center (MC), randomized controlled trial (RCT) [N = 5380] conducted to determine whether alogliptin was noninferior to placebo with respect to major CV events in patients with T2DM who

were at very high CV risk. The primary endpoint was a composite of death from CV causes, nonfatal myocardial infarction (MI), or nonfatal stroke.
  - A primary endpoint event occurred in 305 patients assigned to alogliptin (11.3%) and in 316 patients assigned to placebo (11.8%) (hazard ratio [HR] = 0.96, upper boundary of the one-sided repeated confidence interval [CI]: 1.16; p < 0.001 for noninferiority).
  - Based on the intent-to-treat (ITT) population, more patients in the alogliptin group (106/2701 [rate of 2.6 per 100 patient-years]) than in the placebo group (89/2679 [rate of 2.2 per 100 patient-years]) were hospitalized for heart failure (HF) (3.9% vs 3.3%, HR = 1.19; 95% CI, 0.90 to 1.58; p = 0.220); however, this result was not statistically significant, and the association between alogliptin and hospitalization for HF remains inconclusive *(FDA Drug Safety Communication 2016, FDA Endocrinologic and Metabolic Drugs Advisory Committee 2015, Zannad et al 2015)*.

Linagliptin-containing products

- In the following 10 pivotal trials described in the Tradjenta prescribing information (2017) and published as cited, linagliptin has been shown to have activity for improving glucose control when:
  - used as monotherapy vs placebo *(Barnett et al 2012[b], Del Prato et al 2011)*
  - used as add-on therapy to metformin vs placebo + metformin *(Taskinen et al 2011)*
  - used as initial combination therapy with metformin vs placebo or linagliptin or metformin monotherapy *(Haak et al 2012)*
  - used with metformin vs glimepiride + metformin *(Gallwitz et al 2012)*
  - used as add-on combination therapy with pioglitazone vs placebo + pioglitazone *(Gomis et al 2011)*
  - used as add-on combination therapy with an SFU vs placebo + an SFU *(Lewin et al 2012)*
  - used as add-on combination therapy with metformin and an SFU vs placebo + metformin + an SFU *(Owens et al 2011)*
  - used as add-on combination therapy with insulin vs placebo + insulin *(Yki-Järvinen et al 2013)*
  - used in patients with severe renal impairment vs placebo *(McGill et al 2014)*
- There have been no clinical efficacy studies conducted with Jentadueto, the linagliptin/metformin combination product; bioequivalence of Jentadueto to linagliptin and metformin co-administered as individual tablets was demonstrated in healthy subjects. The labeling of Jentadueto includes the results of some of the aforementioned studies *(Gallwitz et al 2012, Haak et al 2012, McGill et al 2014, Owens et al 2011, Ross et al 2015, Taskinen et al 2011, Yki-Järvinen et al 2013)*, as well as confirmatory results from a 24-week, DB, RCT designed to assess the efficacy of linagliptin in combination with metformin vs linagliptin monotherapy + placebo *(Ross et al 2015)*.
- The safety and efficacy of Jentadueto XR, the linagliptin/metformin ER combination product, have been established on the basis of the aforementioned adequate and well-controlled studies of linagliptin and metformin co-administered in patients with T2DM inadequately controlled on diet and exercise and in combination with an SFU *(Gallwitz et al 2012, Haak et al 2012, Owens et al 2011, Ross et al 2015, Taskinen et al 2011)*. No new studies were conducted with Jentadueto XR.
- Glyxambi, the linagliptin/empagliflozin combination product, was shown to have activity in improving glucose control when used as add-on combination therapy with metformin *(DeFronzo et al 2015, Lewin et al 2015)*.
- **CV outcomes** *(Rosenstock et al 2015[a])*
  - A pooled safety analysis of all DB, RCTs ≥ 12 weeks' duration (19 trials; N = 9459 subjects) found that linagliptin was not associated with an increase in CV risk, compared with a pooled comparator group of placebo, glimepiride, or voglibose (not available in the United States), in patients with T2DM, irrespective of background therapy.
    - Overall, 420 patients with adverse events (AEs) were identified from the pre-specified list of trigger events. A total of 60 (1.0%) primary components of 4-point major adverse cardiac events (4P-MACE) (ie, CV death, stroke, MI, and hospitalization for unstable angina) were reported in the linagliptin group and 62 (1.7%) in the comparator group. The incidence rate of 4P-MACE was 13.4 events per 1000 patient-years for linagliptin-treated patients compared with 18.9 in the active comparator group with a Cox regression HR indicating no significant difference between the 2 treatment groups (HR = 0.78; 95% CI, 0.55 to 1.12).
    - In the placebo cohort of the overall group (ie, 18 of the 19 trials; n = 7746), 4P-MACE incidence rates were 14.9 per 1000 patient-years for linagliptin (43 events) and 16.4 for total comparators (29 events), yielding an overall HR = 1.09 (95% CI: 0.68 to 1.75).
    - In the placebo cohort, there was no signal for an increased risk of either all-cause or CV mortality with linagliptin therapy. All-cause mortality for linagliptin (2538 patient-years exposure) vs placebo (1608 patient-years exposure)

was reported for 13 vs 11 patients, respectively (HR = 0.81; 95% CI, 0.36 to 1.81). For CV mortality with linagliptin (2538 patient-years exposure) vs placebo (1608 patient-years exposure), 8 vs 6 deaths were reported, respectively (HR = 0.88; 95% CI, 0.30 to 2.55).
    - For hospitalization for congestive heart failure (CHF), a small number of patients reported events (n = 21), and the overall risk estimate was similar for linagliptin (12 events; 2039 patients) and the total comparator group (9 events, 1275 patients), with an HR = 1.04 (95% CI: 0.43 to 2.47).
  - CAROLINA, the CARdiovascular Outcome trial of LINAgliptin vs glimepiride in T2DM, is an ongoing, randomized trial in subjects with early T2DM and increased CV risk or established complications that will determine the long-term CV impact of linagliptin vs the SFU glimepiride *(Marx et al 2015, Rosenstock et al 2013[a])*. Started in 2010 with 6041 randomized patients, CAROLINA is the first head-to-head CV outcome trial of a DPP-4 inhibitor vs an active comparator that is sufficiently powered to demonstrate potential differences in CV events between treatment groups *(Rosenstock et al 2015[a])*. The estimated study completion date is September 2018 *(Rosenstock et al 2015[a])*.
  - CARdiovascular Safety & Clinical outcoME with LINAgliptin (CARMELINA) was a DB, PC, MC, RCT (N = 6979) that evaluated CV and renal outcomes with linagliptin in patients with T2DM and high CV and renal risk over a median follow-up of 2.2 years. For the primary outcome of 3-point MACE (composite of CV death, nonfatal MI, or nonfatal stroke), linagliptin demonstrated noninferiority to placebo (12.4% vs 12.1%, respectively; HR, 1.02; 95% CI, 0.89 to 1.17; p < 0.001 for noninferiority; p = 0.74 for superiority). The risk of a secondary outcome event (composite of death due to renal failure, end-stage renal disease [ESRD], or ≥ 40% decrease in estimated glomerular filtration rate [eGFR] from baseline) did not differ significantly in the linagliptin and placebo groups (9.4% vs 8.8%, respectively; HR, 1.04; 95% CI, 0.89 to 1.22; p = 0.62) *(Rosenstock et al 2019)*.

Saxagliptin-containing products

- In the following 10 pivotal trials described in the Onglyza prescribing information (2017) and published as cited, saxagliptin has been shown to have activity for improving glucose control when:
  - used as monotherapy vs placebo *(Frederich et al 2012, Rosenstock et al 2009[b])*
  - used as add-on combination therapy with metformin vs placebo + metformin *(DeFronzo et al 2009)*
  - co-administered with metformin in treatment-naïve patients vs placebo + metformin *(Jadzinsky et al 2009)*
  - used as add-on combination therapy with a TZD vs placebo + a TZD *(Hollander et al 2009)*
  - used as add-on combination therapy with glyburide (an SFU) vs placebo + glyburide *(Chacra et al 2009)*
  - used as add-on combination therapy with metformin vs glipizide add-on combination therapy with metformin *(Goke et al 2013)*
  - used as add-on combination therapy with insulin (+/- metformin) vs placebo + insulin (+/- metformin) *(Barnett et al 2012[a])*
  - used as add-on combination therapy with metformin + an SFU vs placebo + metformin + an SFU *(Moses et al 2014)*
  - used as monotherapy vs placebo in patients with renal impairment *(Nowicki et al 2011)*
- There have been no clinical efficacy or safety studies conducted with Kombiglyze XR to characterize its effect on HbA1c reduction; however, the bioequivalence of Kombiglyze XR to saxagliptin and extended-release metformin tablets co-administered as individual tablets has been demonstrated.
- The bioequivalence of saxagliptin/dapagliflozin fixed-dose combination tablets to the co-administration of the individual tablets in healthy subjects has been demonstrated *(Vakkalagadda et al 2016)*. Efficacy and safety were observed as add-on therapy with saxagliptin in patients on dapagliflozin plus metformin at 24 weeks *(Matthaei et al 2015)* and at 52 weeks *(Matthaei et al 2016)*; with dapagliflozin added to saxagliptin plus metformin at 24 weeks *(Mathieu et al 2015[a])* and 52 weeks *(Mathieu et al 2016)*; and with saxagliptin plus dapagliflozin addition vs the single addition of saxagliptin or dapagliflozin to metformin at 24 weeks *(Rosenstock et al 2015[b])*.
- **CV outcomes** *(Scirica et al 2013, Scirica et al 2014)*
  - The Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus (SAVOR-TIMI 53) was a Phase 4, DB, PC, MC, RCT (N = 16,492) evaluating the safety and efficacy of saxagliptin vs placebo with respect to CV outcomes in patients with T2DM who were at risk for CV events. The primary endpoint was a composite of CV death, MI, or ischemic stroke.
    - A primary endpoint event occurred in 613 patients in the saxagliptin group and in 609 patients in the placebo group (7.3% and 7.2%, respectively, according to 2-year Kaplan–Meier estimates; HR with saxagliptin = 1.00; 95% CI: 0.89 to 1.12; p = 0.99 for superiority; p < 0.001 for noninferiority [pre-specified noninferiority margin of 1.3 for the HR]).

- The major secondary endpoint of a composite of CV death, MI, stroke, hospitalization for unstable angina, coronary revascularization, or HF occurred in 1059 patients in the saxagliptin group and in 1034 patients in the placebo group (12.8% and 12.4%, respectively, according to 2-year Kaplan–Meier estimates; HR = 1.02; 95% CI: 0.94 to 1.11; p = 0.66).
- More patients in the saxagliptin group than in the placebo group were hospitalized for HF (3.5% vs 2.8%, HR = 1.27; 95% CI, 1.07 to 1.51; p = 0.007).
- More patients in the saxagliptin group than the placebo group experienced death from any cause, although the difference was not statistically significant (n = 420/8280 [5.1%] vs 378/8212 [4.6%], HR = 1.11; 95% CI, 0.96 to 1.27; p = 0.15).

Sitagliptin-containing products

- In the following 11 pivotal trials described in the Januvia prescribing information (2017) and published as cited, sitagliptin has been shown to have activity for improving glucose control when:
  - used as monotherapy vs placebo *(Aschner et al 2006, Raz et al 2006)*
  - used as monotherapy vs placebo in patients with chronic renal insufficiency *(Chan et al 2008)*
  - used as add-on combination therapy with metformin vs placebo + metformin *(Charbonnel et al 2006)*
  - used as initial combination therapy with metformin vs placebo or sitagliptin or metformin monotherapy *(Goldstein et al 2007)*
  - used in combination with metformin vs glipizide + metformin *(Nauck et al 2007)*
  - used as add-on combination therapy with pioglitazone vs placebo + pioglitazone *(Rosenstock et al 2006)*
  - used as initial combination therapy with pioglitazone vs pioglitazone monotherapy *(Yoon et al 2011)*
  - used as add-on combination therapy with metformin and rosiglitazone vs placebo + metformin + rosiglitazone *(Scott et al 2008)*
  - used as add-on combination therapy with glimepiride +/- metformin vs placebo + glimepiride +/- metformin *(Hermansen et al 2007)*
  - used as add-on combination therapy with insulin +/- metformin vs placebo + insulin +/- metformin *(Mathieu et al 2015[b])*
- While the co-administration of sitagliptin and metformin has been studied in patients with T2DM inadequately controlled on diet and exercise and in combination with other antihyperglycemic agents, there have been no clinical efficacy studies conducted with Janumet, the sitagliptin/metformin combination product; bioequivalence of Janumet with co-administered sitagliptin and metformin hydrochloride tablets was demonstrated (*Drugs@FDA 2018*).
- There have been no clinical efficacy or safety studies conducted with Janumet XR to characterize its effect on HbA1c reduction, however, bioequivalence of Janumet XR tablets with co-administered sitagliptin and extended-release metformin tablets has been demonstrated for all tablet strengths (*Drugs@FDA 2018*).
- Steglujan, the combination product of sitagliptin and ertugliflozin, showed significant improvements in HbA1c over 26 weeks compared with individual agents in patients uncontrolled on metformin alone, compared with placebo in patients uncontrolled on diet and exercise alone, and when ertugliflozin was added vs placebo in patients uncontrolled on metformin and sitagliptin *(Dagogo-Jack et al 2018, Miller et al 2018, Pratley et al 2017).*
- **CV outcomes** *(Green et al 2015)*
  - The Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) was a Phase 3, DB, PC, MC, RCT (N = 14,671 ITT population) evaluating CV outcomes after treatment with sitagliptin in patients with T2DM, inadequate glycemic control, and established CV disease. The primary CV outcome was a composite of CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina.
    - Overall, the primary outcome occurred in 839 patients in the sitagliptin group (11.4%; 4.06 per 100 person-years) and 851 patients in the placebo group (11.6%; 4.17 per 100 person-years). Sitagliptin was noninferior to placebo for the primary composite CV outcome (HR = 0.98; 95% CI, 0.88 to 1.09; p < 0.001). Rates of hospitalization for HF did not differ between the 2 groups (HR = 1.00; 95% CI, 0.83 to 1.20; p = 0.98).

Comparative studies

- Many clinical trials are available comparing DPP-4 inhibitors to placebo and to alternative antihyperglycemic agents, both as monotherapy and in combination regimens. Consistent with treatment guidelines, most trials have evaluated DPP-4 inhibitors not as initial therapy, but as add-on therapy to provide additional glucose control to patients who are not at their goal HbA1c on 1 or more existing therapies. Most trials evaluated HbA1c as a primary outcome measure,

with or without also measuring fasting plasma glucose (FPG), postprandial glucose (PPG), and other metabolic outcomes. Some studies have evaluated longer-term diabetes outcomes, such as CV outcomes or overall mortality.

- Although comparative trials between different DPP-4 inhibitors are uncommon, 1 trial comparing saxagliptin 5 mg daily to sitagliptin 100 mg daily demonstrated that saxagliptin was noninferior to sitagliptin for HbA1c reduction (-0.52% in the saxagliptin group vs -0.62% in the sitagliptin group, adjusted mean decrease in HbA1c = 0.09%; 95% CI, -0.01 to 0.2; p-value not reported). Sitagliptin decreased FPG to a greater extent than saxagliptin (-16.2 vs -10.8 mg/dL, respectively; mean difference = 5.42 mg/dL; 95% CI: 1.37 to 9.47 mg/dL; p-value not reported) *(Scheen et al 2010)*.
- A meta-analysis (MA) of 80 RCTs of incretin-based therapies (DPP-4 inhibitors and GLP-1 agonists) in patients with T2DM (N = 41,807) demonstrated that the highest maintenance doses of the DPP-4 inhibitors resulted in mean HbA1c changes from baseline of -0.6 to -1.1%. Each DPP-4 inhibitor demonstrated similar mean reductions from baseline in HbA1c when adjusted for baseline differences: alogliptin -0.70% (95% CI: -0.90 to -0.50%), linagliptin -0.60% (95% CI: -0.80 to -0.40%), saxagliptin -0.71% (95% CI: -0.89 to -0.54%), and sitagliptin -0.70% (95% CI: -0.78 to -0.63%) *(Aroda et al 2012).*
- A systematic review (SR) and MA of 27 reports of 19 studies in patients with T2DM (N = 13,881) demonstrated that in comparison with metformin, DPP-4 inhibitors were associated with a smaller decline in HbA1c [weighted mean difference = 0.2; 95% CI, 0.08 to 0.32; I^2 = 60%] and a lower chance of attainment of the HbA1c goal of < 7% (risk ratio in favor of metformin = 1.18; 95% CI, 1.07 to 1.29; I^2 = 34%). As second-line treatment, DPP-4 inhibitors less effectively reduced HbA1c vs SFUs (weighted mean difference = 0.07; 95% CI, 0.02 to 0.13) and GLP-1 agonists (weighted mean difference = 0.49; 95% CI, 0.31 to 0.67), but were equally effective as pioglitazone (weighted mean difference = 0.09; 95% CI, -0.07 to 0.24) *(Karagiannis et al 2012)*.
- An SR and MA of randomized and observational studies that examined HF and hospitalization for HF identified 43 RCTs (N = 68,775 patients) and 12 observational studies (9 cohort studies + 3 nested case-control studies in N = 1,777,358 total patients); the length of follow-up ranged from 12 to 206 weeks. Thirty-eight (38) trials reported 75 HF events occurring in 28,292 patients who were treated with at least 1 drug (raw event rate 0.27% vs 0.26% for controls [odds ratio (OR) = 0.97, 95% CI: 0.61 to 1.56, I^2 = 0%]). Overall, 1174 events of admission for HF occurred in 37,028 patients (raw event rate 3.4% for DPP-4 inhibitors vs 3.0% for controls). Pooling across trials showed a borderline increase in the risk of hospital admission for HF in patients with T2DM using DPP-4 inhibitors vs control (OR = 1.13, 95% CI: 1.00 to 1.26; I^2 = 0%) *(Li et al 2016)*.
- An SR and MA by Verma et al (2017) attempted to examine the totality of RCT evidence concerning the association between DPP-4 inhibitors and HF. A total of 100 RCTs (N = 79,867) were identified, including the 3 large, CV outcomes studies, EXAMINE, SAVOR-TIMI 53, and TECOS. A total of 96% (1192/1244) of HF events were pre-specified, blindly adjudicated, and required hospital admission. Pooled results suggested a 13% increase in HF (relative risk [RR] = 1.13; 95% CI, 1.01 to 1.26, I^2 = 0%; 32 RCTs, N = 54,640 and 1244 events). When including only the 3 large RCTs, the increase was similar, but not significant (RR = 1.14; 95% CI, 0.97 to 1.32; 3 RCTs, N = 36,543 and 1169 adjudicated events; number needed to harm = 246) owing to heterogeneity (I^2 = 42%), which lead to wider CIs, because SAVOR-TIMI 53 showed increased HF, while TECOS showed no effect.
- A network MA indirectly evaluated comparative risks for HF among DPP-4 inhibitors *(Guo 2017)*. Analysis of 50 RCTs demonstrated that compared with placebo, no increased risk of HF events was seen for sitagliptin (RR = 0.86; 95% CI, 0.43 to 1.57) or saxagliptin (RR = 0.84; 95% CI, 0.33 to 1.61), but alogliptin was associated with a higher risk of events (RR = 2.13; 95% CI, 1.06 to 6.26). Among agents available in the United States, indirect comparisons favored sitagliptin over alogliptin (RR = 0.40; 95% CI, 0.11 to 0.96), sitagliptin over linagliptin (RR = 0.31; 95% CI, 0.09 to 0.95), and saxagliptin over linagliptin (RR = 0.30; 95% CI, 0.07 to 0.97). The product with the highest probability to be the safest with regard to HF risk was saxagliptin (26.56%), followed by sitagliptin (20.76%), linagliptin (0.25%), and alogliptin (0.12%).
- An SR of literature concerning the overall CV and long-term safety of DPP-4 inhibitors in patients with T2DM identified 36 DB, PC, RCTs (N = 54,664). Overall, there were no significant differences in all-cause mortality (RR = 1.03; 95% CI, 0.95 to 1.12), CV mortality (RR = 1.02; 95% CI, 0.92 to 1.12), MI (RR = 0.98; 95% CI, 0.89 to 1.08), stroke (RR = 1.02; 95% CI, 0.88 to 1.17), renal failure (RR = 1.06; 95% CI, 0.88 to 1.27), severe hypoglycemia (RR = 1.14; 95% CI, 0.95 to 1.36), and pancreatic cancer (RR = 0.54; 95% CI, 0.28 to 1.04) with the use of DPP-4 inhibitors. However, the DDP-4 inhibitors were associated with an increased risk of HF (RR = 1.13; 95% CI, 1.01 to 1.26) and acute pancreatitis (RR = 1.57; 95% CI, 1.03 to 2.39) *(Rehman et al 2017)*. A subsequent MA evaluating acute pancreatitis across 5 RCTs found significant increases in risk (RR = 1.67; 95% CI, 1.08 to 2.59), but similar results were not observed in a pooled analysis of 3 cohort studies (HR = 1.06; 95% CI, 0.89 to 1.26) *(Chen et al 2017).*

- An SR to evaluate the association between DPP-4 inhibitors/GLP-1 receptor agonists and MACE in patients with T2DM identified 36 articles that included a total of 11 pooled analyses, 17 MAs, and 8 RCTs (including secondary analyses). Over the short-term (up to 4 years), those exposed to a DPP-4 inhibitor or a GLP-1 receptor agonist were not at increased risk for MACE or its component endpoints vs comparators. Two MAs showed a significant reduction in the incidence of MACE associated with overall DPP-4 inhibitor therapy, but the beneficial effect was not observed in other MAs that included larger CV outcomes studies (ie, EXAMINE, SAVOR-TIMI 53, TECOS). An increased rate of HF hospitalizations was associated with saxagliptin *(Manucci et al 2017)*.
- A network MA evaluated the CV effects of empagliflozin compared to DPP-4 inhibitors in patients with T2DM with established CV disease or at high risk for CV outcomes. The analysis pooled 4 studies and found that empagliflozin was superior to saxagliptin (HR, 0.60; 95% credible interval [CrI], 0.46 to 0.80) and sitagliptin (HR, 0.60; 95% CrI, 0.46 to 0.79) in reducing the risk of CV mortality. Similar results were found for all-cause mortality (empagliflozin vs saxagliptin: HR, 0.61; 95% CrI, 0.49 to 0.76; and vs sitagliptin: HR, 0.67; 95% CrI, 0.54 to 0.83) *(Balijepalli et al 2018)*.
- In a network MA of 236 trials (N = 176,310) comparing DPP-4 inhibitors, SGLT2 inhibitors, and GLP-1 agonists, DPP-4 inhibitors were not associated with significantly lower all-cause mortality compared to placebo or no treatment (absolute risk difference [RD], 0.1%; HR, 1.02; 95% CrI, 0.94 to 1.11). SGLT2 inhibitors (absolute RD, -0.9%; HR, 0.78; 95% CrI, 0.68 to 0.90) and GLP-1 agonists (absolute RD, -0.5%; HR, 0.86; 95% CrI, 0.77 to 0.96) were associated with significantly lower mortality compared to DPP-4 inhibitors *(Zheng et al 2018).*

CLINICAL GUIDELINES

Overview

- Professional society guidelines are consistent in recommending metformin as the optimal first-line pharmacologic therapy for treatment-naïve patients with T2DM, unless the patient has contraindications or intolerance. DPP-4 inhibitors are among the second-line options for subsequent therapy. All guidelines emphasize individualized therapy based upon patient-specific factors such as comorbidities, weight, risk of hypoglycemia, and duration of diabetes *(ADA 2019, Copeland et al 2013, Davies et al 2018, Garber et al 2019)*.
- A 2018 American College of Cardiology expert consensus decision pathway on CV risk reduction in patients with T2DM and atherosclerotic CV disease (ASCVD) suggests adding an SGLT2 inhibitor or GLP-1 receptor agonist that has demonstrated beneficial CV outcomes to other guideline-directed therapy for diabetes (specifically, metformin). Among the SGLT2 inhibitors with CV outcome data at the time that the pathway was written (canagliflozin and empagliflozin), empagliflozin was the preferred SGLT2 inhibitor based on the available evidence and overall risk to benefit ratio *(Das et al 2018)*.

- **ADA/European Association for the Study of Diabetes (EASD): Management of Hyperglycemia in Type 2 Diabetes, 2018** *(Davies et al 2018)*
  - The goals of T2DM therapy are to prevent or delay complications and maintain quality of life, which requires glycemic control, CV risk factor management, regular follow-up, and a patient-centered approach to enhance patient engagement in self-care activities. Careful consideration of patient-specific factors and preferences must inform the process of individualizing treatment goals and strategies.
  - Due to new evidence of benefit with specific agents in the reduction of mortality, HF, and progression of renal disease, the overall approach to glucose-lowering medication in T2DM for the ADA/EASD consensus report was updated in 2018. A history of CVD, chronic kidney disease (CKD), and HF should be taken into consideration early in the process of treatment selection. Additionally, the guideline recommends early consideration of weight, hypoglycemic risk, treatment cost, and other patient-related factors that may influence the choice of drug therapy.
    - Among patients with T2DM who have established ASCVD, SGLT2 inhibitors or GLP-1 receptor agonists with proven CV benefit are recommended as part of glycemic management.
    - For patients with ASCVD with concomitant HF, SGLT2 inhibitors are recommended.
    - For patients with T2DM and CKD (with or without ASCVD), an SGLT2 inhibitor shown to reduce CKD progression should be considered. If SGLT2 inhibitors are contraindicated or not preferred, a GLP-1 receptor agonist shown to reduce CKD progression should be considered.
  - Initial monotherapy: Metformin remains the preferred drug for initial monotherapy based on its efficacy, safety, tolerability, low cost, and extensive clinical experience.

- Add-on to metformin: The selection of a second agent added to metformin is based on patient preference and clinical characteristics. Important clinical characteristics include the presence of established ASCVD and other comorbidities such as HF or CKD; the risk for specific AEs, particularly hypoglycemia and weight gain; as well as safety, tolerability, and cost.
- Intensification beyond 2 medications: Intensification of treatment beyond dual therapy to maintain glycemic targets requires consideration of the impact of medication side effects on comorbidities, as well as the burden of treatment and cost.
- Addition of injectable medications: For patients who require the greater glucose-lowering effect of an injectable medication, GLP-1 receptor agonists are preferred over insulin. For patients with extreme and symptomatic hyperglycemia, insulin is recommended.
- Beyond basal insulin: Patients who are unable to maintain glycemic targets on basal insulin in combination with oral medications can have treatment intensified with GLP-1 receptor agonists, SGLT2 inhibitors, or prandial insulin.

- **ADA: Standards of Medical Care in Diabetes – 2019** *(ADA 2019)*
  - Pharmacological therapy for T2DM:
    - Metformin (if not contraindicated and if tolerated) is the preferred initial pharmacological agent for T2DM (level A).
    - Metformin should be continued when used in combination with other agents, including insulin, if not contraindicated and if tolerated (level A).
    - Dual therapy should be considered in patients with newly diagnosed T2DM who have HbA1c ≥ 1.5% above their glycemic target (level E).
    - Early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when HbA1c levels (> 10%) or blood glucose levels (> 300 mg/dL) are very high (level E).
    - A patient-centered approach should be used to guide the choice of pharmacologic therapy. Considerations include comorbidities (ASCVD, HF, CKD), hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences (level E).
    - In patients with T2DM and established ASCVD, SGLT2 inhibitors or GLP-1 receptor agonists with demonstrated CVD benefit are recommended as part of the antihyperglycemic regimen (level A).
    - In patients with T2DM and established ASCVD with a high risk of or existing HF, SGLT2 inhibitors are preferred (level C).
    - In patients with T2DM and CKD, use of SGLT2 inhibitors or GLP-1 receptor agonists shown to reduce the risk of CKD progression, CV events, or both should be considered (level C).
    - In most patients who require the greater glucose-lowering effect of an injectable medication, GLP-1 receptor agonists are preferred over insulin (level B).
    - The medication regimen should be reevaluated at regular intervals (every 3 to 6 months) and adjusted as needed to incorporate new patient factors (level E).
  - Initial therapy
    - Metformin should be initiated at the time T2DM is diagnosed if there are no contraindications.
    - For patients with contraindications or intolerance to metformin, initial therapy with an SGLT2 inhibitor, GLP-1 receptor agonist, DPP-4 inhibitor, TZD, SFU (2nd generation), or insulin should be considered based on patient factors.
  - Combination therapy
    - Dual therapy is recommended for patients who do not achieve their HbA1c goal after 3 months of monotherapy.
    - For patients without ASCVD or CKD, an agent from any of the 6 preferred classes (SFU, TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or basal insulin) can be added to metformin, with the choice of agent based on drug-specific effects (ie, avoidance of adverse effects such as hypoglycemia and weight gain) and patient factors (ie, cost and personal preference).
    - For patients with ASCVD, HF, or CKD, the best choice for add-on therapy is a GLP-1 receptor agonist or SGLT2 inhibitor with demonstrated benefit.
    - Similar considerations are applied in patients who require a third agent to achieve glycemic goals.

Table 6. ADA Factors to Consider for Antihyperglycemic Therapies in T2DM

Class*	Efficacy	Hypoglycemia	Weight	ASCVD	CHF	Route	DKD	Additional

								considerations
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Oral	Neutral	GI AEs common B12 deficiency
SGLT2i	Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, empagliflozin	Oral	Benefit: canagliflozin, empagliflozin	Boxed warning for amputation: canagliflozin Genitourinary infections
GLP-1ra	High	No	Loss	Neutral: lixisenatide Benefit: liraglutide > semaglutide > exenatide ER	Neutral	SQ	Benefit: liraglutide	Boxed warning for thyroid C-cell tumors (liraglutide, albiglutide, dulaglutide, exenatide ER)
DPP-4i	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin, alogliptin	Oral	Neutral	Potential risk of acute pancreatitis Joint pain
TZD	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Oral	Neutral	Boxed warning for CHF (pioglitazone, rosiglitazone)
SFU (2nd generation)	High	Yes	Gain	Neutral	Neutral	Oral	Neutral	FDA special warning on increased risk of CV mortality based on studies of an older SFU (tolbutamide)
Insulin	Highest	Yes	Gain	Neutral	Neutral	SQ	Neutral	Injection site reactions

Abbreviations: AE = adverse event; ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; CV = cardiovascular; DKD = diabetic kidney disease; DPP-4i = dipeptidyl peptidase 4 inhibitor; ER = extended-release; GI = gastrointestinal; GLP-1ra = glucagon-like peptide-1 receptor agonist; SFU = sulfonylurea; SGLT2i = sodium-glucose cotransporter-2 inhibitor; SQ = subcutaneous; T2DM = type 2 diabetes mellitus; TZD = thiazolidinediones

* Other antidiabetic drugs not shown in above table (eg, inhaled insulin, alpha-glucosidase inhibitors (AGIs), colesevelam, bromocriptine, and pramlintide) may be tried in specific situations; however, considerations include modest efficacy in T2DM, frequency of administration, potential for drug interactions, cost, and/or side effects.

- **American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) - Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm** *(Garber et al 2019)*
  - Founding principles of the Comprehensive Type 2 Diabetes Management Algorithm:
    - Lifestyle optimization is essential for all patients with diabetes.
    - Minimizing the risk of both severe and non-severe hypoglycemia is a priority. Minimizing risk of weight gain is also a priority.
    - The HbA1c target should be individualized based on numerous factors, such as age, life expectancy, comorbid conditions, duration of diabetes, risk of hypoglycemia or adverse consequences from hypoglycemia, patient motivation, and adherence. A target HbA1c ≤ 6.5% is considered optimal if it can be achieved in a safe and affordable manner, but higher targets may be appropriate for certain individuals and may change for a given individual over time.
    - Glycemic control targets include fasting and post-prandial glucose as determined by self-monitoring of blood glucose.
    - The choice of diabetes therapies must be individualized based on attributes specific to both patients and the medications themselves. Medication attributes include antihyperglycemic efficacy, mechanism of action, risk of inducing hypoglycemia, risk of weight gain, other AEs, tolerability, ease of use, likely adherence, cost, and safety or risk reduction in heart, kidney, or liver disease. Patient-specific considerations include initial A1C, duration of T2D, and obesity status.
      - The choice of therapy depends on the individual patient's cardiac, cerebrovascular, and renal status. Combination therapy is usually required and should involve agents with complementary mechanisms of action.
    - Therapy must be evaluated frequently (eg, every 3 months) until the patient is stable, using multiple criteria (eg, HbA1c, self-monitoring of blood glucose records, lipid and blood pressure levels, hypoglycemia events, AEs).
  - Glycemic control algorithm for T2DM:

- In patients with recent-onset T2DM or mild hyperglycemia (HbA1c < 7.5%), lifestyle therapy plus antihyperglycemic monotherapy (preferably with metformin) is recommended. For patients with ASCVD or CKD, GLP-1 receptor agonists and SGLT2 inhibitors with proven benefits may be preferred.
  - Other acceptable alternatives to metformin include DPP-4 inhibitors and TZDs; AGIs, SFUs, and meglitinides may also be appropriate as monotherapy for select patients.
- In patients who do not achieve their HbA1c goal after 3 months of monotherapy or patients who present with HbA1c ≥ 7.5%, dual therapy should be started by adding 1 of the following agents to metformin (in order of preference): GLP-1 receptor agonist, SGLT2 inhibitor, DPP-4 inhibitor, TZD, basal insulin, colesevelam, bromocriptine quick release (QR), AGI, SFU, or meglitinide.
- If dual therapy does not achieve the HbA1c goal in 3 months, triple therapy should be started by adding 1 of the following agents to metformin plus a second-line agent (in order of preference): GLP-1 receptor agonist, SGLT2 inhibitor, TZD, basal insulin, DPP-4 inhibitor, colesevelam, bromocriptine QR, AGI, SFU, or meglitinide.
- If triple therapy fails to achieve the HbA1c goal in 3 months, then the patient should proceed to or intensify insulin therapy.
- In patients with entry HbA1c > 9.0%, dual therapy or triple therapy is recommended if the patient is asymptomatic. If the patient is symptomatic, insulin therapy alone or in combination with other agents is recommended.

○ DPP-4 inhibitor-specific information:

- DPP-4 inhibitors have modest A1C-lowering properties, are weight-neutral, have low risk of hypoglycemia, and neutral with respect to CV outcomes.
- DPP-4 inhibitors should be used with caution in patients with a history of pancreatitis (and stopped if pancreatitis occurs), although a causative association has not been established.
- A possible slight increased risk of HF with saxagliptin and alogliptin was found in the respective CV outcome trials.

Table 7. AACE/ACE Profiles of Antidiabetic Medications

	Hypoglycemia	Weight	Renal/GU	GI	Cardiac	Bone	Ketoacidosis
Metformin	Neutral	Slight loss	eGFR < 30: contraindicated	Moderate	Neutral	Neutral	Neutral
GLP-1ra	Neutral	Loss	Possible benefit: liraglutide Exenatide not indicated CrCl < 30	Moderate	Liraglutide FDA approved for prevention of MACE	Neutral	Neutral
SGLT2i	Neutral	Loss	Genital mycotic infections Not indicated eGFR < 45 Possible CKD benefit	Neutral	Empagliflozin FDA approved to reduce CV mortality Canagliflozin FDA approved to reduce MACE	Neutral	DKA can occur
DPP-4i	Neutral	Neutral	Dose adjustment necessary (except linagliptin) Albuminuria reduction	Neutral	Alogliptin, saxagliptin: Possible increased HHF	Neutral	Neutral
AGI	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral
TZD	Neutral	Gain	Neutral	Neutral	Moderate CHF risk May reduce stroke risk	Moderate fracture risk	Neutral
SFU	Moderate/severe	Gain	More hypoglycemia risk	Neutral	Possible ASCVD risk	Neutral	Neutral
Meglitinide	Mild	Gain	More hypoglycemia risk	Neutral	Possible ASCVD risk	Neutral	Neutral
Colesevelam	Neutral	Neutral	Neutral	Mild	ASCVD benefit	Neutral	Neutral
Bromocriptine QR	Neutral	Neutral	Neutral	Moderate	Safe	Neutral	Neutral
Insulin	Moderate to severe	Gain	More hypoglycemia risk	Neutral	CHF risk	Neutral	Neutral
Pramlintide	Neutral	Loss	Neutral	Moderate	Neutral	Neutral	Neutral

Abbreviations: AGI = alpha-glucosidase inhibitor; ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; CrCl = creatinine clearance; CV = cardiovascular; DKA = diabetic ketoacidosis; DPP-4i = dipeptidyl peptidase 4 inhibitor; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; GI = gastrointestinal; GLP-1ra = glucagon-like peptide-1 receptor agonist; GU = genitourinary; HHF = hospitalization for heart

failure; MACE = major adverse cardiovascular events; QR = quick release; SFU = sulfonylurea; SGLT2i = sodium-glucose cotransporter-2 inhibitor; TZD = thiazolidinedione

SAFETY SUMMARY

- All of the metformin combination products contain a boxed warning for lactic acidosis and are contraindicated in patients with renal impairment and in patients with acute or chronic metabolic acidosis, including diabetic ketoacidosis. Alogliptin/pioglitazone contains a boxed warning for CHF and is contraindicated for initiation in patients with established New York Heart Association (NYHA) Class III or IV HF. Linagliptin/empagliflozin and sitagliptin/ertugliflozin are contraindicated in patients with severe renal impairment, ESRD, or in those receiving dialysis. Saxagliptin/dapagliflozin is contraindicated in patients with moderate to severe renal impairment (eGFR < 45 mL/min/1.73 m^2), ESRD, or patients on dialysis.
- Warnings and precautions common to all of the DPP-4 and DPP-4-combination products concern the risks of acute pancreatitis, HF, hypersensitivity reactions, arthralgia, postmarketing reports of bullous pemphigoid requiring hospitalization, and the increased risk of hypoglycemia when added to an insulin secretagogue or insulin therapy.
  - Warnings/precautions common to all of the metformin-containing products concern hepatic impairment, potentiation of metformin effects by alcohol, vitamin B12 deficiency, radiologic studies/surgical procedures necessitating temporary medication discontinuation, hypoxic states, changes in clinical status, loss of blood glucose control, and interactions with concomitant medications. There is the potential for unintended pregnancy with premenopausal women as therapy with metformin may result in ovulation in some premenopausal anovulatory women. Drug interactions include:
    - Concomitant use of topiramate and other carbonic anhydrase inhibitors with metformin may increase the risk of lactic acidosis; frequent monitoring of patients should be considered.
    - Concomitant use of drugs that interfere with common renal tubular transport systems involved in the renal elimination of metformin (eg, ranolazine, vandetanib, dolutegravir, cimetidine) could increase systemic exposure to metformin and may increase the risk for lactic acidosis; benefits and risks of concomitant use should be weighed.
    - Alcohol is known to potentiate the effect of metformin on lactate metabolism; patients should be warned against excessive alcohol intake while on metformin-containing products.
    - Co-administration with an insulin secretagogue (eg, SFU) or insulin may require lower doses of the insulin secretagogue or insulin to reduce the risk of hypoglycemia.
    - Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control; they include thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving metformin-containing products, the patient should be closely observed to maintain adequate glycemic control.
  - Warnings/precautions specific to the SGLT2 inhibitors (ie, dapagliflozin contained in Qtern, empagliflozin contained in Glyxambi, and ertugliflozin contained in Steglujan) concern the risks of genital mycotic infections, hypotension, increased low density lipoprotein cholesterol, ketoacidosis, urosepsis and pyelonephritis, necrotizing fasciitis of the perineum, and the need for renal function monitoring. Drug interactions include:
    - Co-administration of empagliflozin with diuretics resulted in increased urine volume and frequency of voids, which might enhance the potential for volume depletion.
    - Co-administration of empagliflozin with insulin or insulin secretagogues increases the risk for hypoglycemia.
    - Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Alternative methods for monitoring glycemic control should be used.
    - Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5-AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors; alternative methods for monitoring glycemic control should be used.
  - Warnings/precautions specific to pioglitazone (contained in Oseni) concern the risks of edema, fractures, urinary bladder tumors, macular edema, and changes in ovulation. Drug interactions include:
    - The maximum recommended dose of pioglitazone is 15 mg daily if used in combination with gemfibrozil or other strong CYP2C8 inhibitors due to increased exposure and half-life of pioglitazone.
    - Inducers of CYP2C8 may significantly decrease the exposure of pioglitazone. If an inducer of CYP2C8 is started or stopped during treatment with Oseni, changes in antidiabetic therapy may be needed on the basis of clinical response, but should not exceed the maximum recommended daily dose of 45 mg for pioglitazone.

- Post-marketing reports of hepatic failure, both fatal and non-fatal, have been seen with alogliptin; the warning also appears in the labeling of alogliptin/metformin and alogliptin/pioglitazone.
- Worsening renal function, including acute renal failure sometimes requiring dialysis, has been reported in patients treated with sitagliptin with or without metformin.

- The DPP-4 inhibitors were well tolerated in short-term studies; there are no effects on body weight or risk of hypoglycemia (in the absence of concomitant treatment with insulin or SFUs). Furthermore, an SR and MA demonstrated that DPP-4 inhibitors are well tolerated with an incidence of AEs similar to placebo *(Gooβen et al 2012)*.
  - Commonly reported AEs include headache, nasopharyngitis, and upper respiratory tract infection.
  - Despite the growing body of evidence gleaned from CV outcomes trials, the long-term safety with DPP-4 inhibitors has not been established *(Dungan 2017)* and there have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with DPP-4 inhibitors.

DPP-4 inhibitors and HF

- Following an in-depth review of results from the SAVOR-TIMI 53 and EXAMINE CV outcomes studies by the FDA, a warning concerning the increased risk of HF was added to all products containing alogliptin (ie, Nesina, Kazano, Oseni) and saxagliptin (ie, Onglyza, Kombiglyze XR, Qtern) in April 2016.
  - The risks and benefits of these products should be considered prior to their initiation in patients at risk for HF, such as those with a prior history of HF and a history of renal impairment. Patients should be observed for signs and symptoms of HF during therapy.
  - Patients should be advised of the characteristic symptoms of HF and should be instructed to immediately report such symptoms.
  - If HF develops, patients should be evaluated and managed according to the current standards of care; discontinuation of these products should also be considered.
- On August 10, 2017, the labeling of all linagliptin- (ie, Glyxambi, Tradjenta, Jentadueto, Jentadueto XR) and sitagliptin-containing (ie, Januvia, Janumet, Janumet XR) products was updated with a similar HF warning that the FDA believed was warranted based on the association between DPP-4 inhibitor treatment and HF that was observed in CV outcomes trials [ie, SAVOR-TIMI 53 and EXAMINE] for the other 2 members of the DPP-4 inhibitor class [ie, saxagliptin and alogliptin]. The risks and benefits of these products should be considered in patients with known risk factors for HF; patients should be monitored for signs and symptoms of HF while on treatment.

DOSING AND ADMINISTRATION

Table 8. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Alogliptin-containing products				
Nesina (alogliptin)	Tablets	Oral	Daily	Taken with or without food Must be dose-adjusted in cases of moderate and severe renal impairment
Kazano (alogliptin/ metformin HCl)	Tablets	Oral	Two times daily	Individualize starting dose based on patient's current regimen; taken with food with gradual dose escalation to minimize GI AEs due to metformin; tablets must not be split before swallowing Not recommended in patients with an eGFR between 30 and 60 mL/min/1.73 m^2; contraindicated in patients with

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				an eGFR < 30 mL/min/1.73 m^2 Not recommended in patients with hepatic impairment
Oseni (alogliptin/ pioglitazone)	Tablets	Oral	Daily	Individualize dosing based on current regimen and medical condition; taken with or without food; tablets must not be split before swallowing Must be dose-adjusted in cases of moderate renal impairment; not recommended in severe renal impairment
Linagliptin-containing products				
Tradjenta (linagliptin)	Tablets	Oral	Daily	Taken with or without food
Glyxambi (linagliptin/ empagliflozin)	Tablets	Oral	Daily	Taken with or without food Should not be initiated in patients with an eGFR < 45 mL/min/1.73 m^2; should be discontinued in patients whose eGFR falls below 45 mL/min/1.73 m^2
Jentadueto (linagliptin/ metformin HCl)	Tablets	Oral	Two times daily	Individualize starting dose based on the patient's current regimen; taken with food with gradual dose escalation to minimize GI AEs due to metformin Not recommended in patients with an eGFR between 30 and 45 mL/min/1.73 m^2; contraindicated in patients with an eGFR < 30 mL/min/1.73 m^2 Not recommended in patients with hepatic impairment
Jentadueto XR (linagliptin/ metformin HCl extended release)	Tablets	Oral	Daily	Individualized based on patient's current regimen, effectiveness, and tolerability; taken with food; tablets must be swallowed whole and never split, crushed, dissolved, or chewed Not recommended in patients with an eGFR between 30 and 45 mL/min/1.73 m^2; contraindicated in patients with an eGFR < 30 mL/min/1.73 m^2

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Not recommended in patients with hepatic impairment
Saxagliptin-containing products				
Onglyza (saxagliptin)	Tablets	Oral	Daily	Taken with or without food; tablets must not be split or cut Must be dose-adjusted in cases of eGFR < 45mL/min/1.73 m^2
Kombiglyze XR (saxagliptin/ metformin HCl extended release)	Tablets	Oral	Daily	Individualized based on patient's current regimen, effectiveness, and tolerability; taken with an evening meal with gradual dose titration to reduce the GI side effects associated with metformin; tablets must be swallowed whole and never crushed, cut, or chewed Not recommended in patients with an eGFR between 30 and 45 mL/min/1.73 m^2; contraindicated in patients with an eGFR < 30 mL/min/1.73 m^2 Not recommended in patients with hepatic impairment
Qtern (saxagliptin/ dapagliflozin)	Tablets	Oral	Daily	Taken with or without food; tablets must not be split or cut Should not be initiated in patients with an eGFR < 60 mL/min/1.73 m^2; should be discontinued in patients whose eGFR falls below 60 mL/min/1.73 m^2; contraindicated in patients with an eGFR < 45 mL/min/1.73 m^2
Sitagliptin-containing products				
Januvia (sitagliptin)	Tablets	Oral	Daily	With or without food Must be dose-adjusted in patients with eGFR < 45 mL/min/1.73 m^2
Janumet (sitagliptin/ metformin HCl)	Tablets	Oral	Two times daily	Individualized based on the patient's current regimen, effectiveness, and tolerability; taken with meals with gradual dose escalation, to reduce the GI side effects due to metformin;

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				tablets must not be split or divided before swallowing Not recommended in patients with an eGFR between 30 and < 45 mL/min/1.73 m^2; contraindicated in patients with an eGFR < 30 mL/min/1.73 m^2 Not recommended in patients with hepatic impairment
Janumet XR (sitagliptin/ metformin HCl extended release)	Tablets	Oral	Daily	Individualized based on the patient's current regimen, effectiveness, and tolerability; taken with a meal preferably in the evening; tablets should be swallowed whole and not split, crushed, or chewed before swallowing Not recommended in patients with an eGFR between 30 and < 45 mL/min/1.73 m^2; contraindicated in patients with an eGFR < 30 mL/min/1.73 m^2 Not recommended in patients with hepatic impairment
Steglujan (sitagliptin/ ertugliflozin)	Tablets	Oral	Daily	Taken in the morning with or without food Volume depletion should be corrected prior to initiation Initiation not recommended if eGFR is between 30 and 60 mL/min/1.73 m^2 Not recommended in patients with an eGFR persistently between 30 and < 60 mL/min/1.73 m^2 Discontinue therapy if eGFR falls below 30 mL/min/1.73 m^2 Not recommended in cases of severe hepatic impairment

See the current prescribing information for full details

CONCLUSION

- The DPP-4 inhibitors or gliptins (alogliptin, linagliptin, saxagliptin, and sitagliptin) are indicated as adjuncts to diet and exercise to improve glycemic control in adults with T2DM. All of the DPP-4 inhibitors are available as combination products with metformin hydrochloride (HCl) and/or extended-release metformin HCl. Alogliptin is also approved as a combination product with the TZD, pioglitazone. Linagliptin, saxagliptin, and sitagliptin are approved as combination products with the SGLT2 inhibitors, empagliflozin, dapagliflozin, and ertugliflozin, respectively.
- The activity of the DPP-4 inhibitors is based on inhibition of the DPP-4 enzyme that mediates physiological degradation of the incretin hormones, glucagon-like peptide 1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP) *(Davis 2014)*.
- Many clinical trials are available comparing DPP-4 inhibitors to placebo and to alternative antihyperglycemic agents, both as monotherapy and in combination regimens. Consistent with treatment guidelines, most trials have evaluated DPP-4 inhibitors not as initial therapy, but as add-on therapy to provide additional glucose control to patients who are not at their goal HbA1c on 1 or more existing therapies *(ADA 2018, Garber et al 2018)*. Most trials evaluated HbA1c as a primary outcome measure, with or without also measuring FPG, PPG, and other metabolic outcomes *(ADA 2018)*.
- DPP-4 inhibitors have modest HbA1c-lowering properties, are weight neutral, and are associated with a low risk of hypoglycemia when not used with insulin secretagogues *(ADA 2018, Garber et al 2018)*. The 4 commercially available DPP-4 inhibitors appear to have similar glycemic efficacy and are well tolerated *(Dungan 2017)*.
- The DPP-4 inhibitors have demonstrated CV safety with respect to MACE in 4 large, DB, PC, randomized CV outcome trials with alogliptin (EXAMINE), saxagliptin (SAVOR-TIMI 53), sitagliptin (TECOS), and linagliptin (CARMELINA). An increased risk of HF with alogliptin and saxagliptin in their respective outcome trials prompted the FDA to add warnings on all of the alogliptin- and saxagliptin-containing products in April 2016 *(Dungan 2017)*. In August 2017, the FDA required similar HF warnings to be added to the labels of the remaining DPP-4 inhibitor-containing products *(Drugs@FDA 2018)*.
- According to current clinical guidelines for the management of T2DM, metformin is the preferred initial pharmacological agent for T2DM. The DPP-4 inhibitors are among the recommended second- or third-line treatment options for patients who are not candidates for metformin or who failed to achieve glycemic goals on metformin therapy. SGLT2 inhibitors and GLP-1 receptor agonists with proven benefit are preferred over DPP-4 inhibitors for patients with T2DM and ASCVD, CKD, or HF *(ADA 2019, Garber et al 2019)*.

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Therapeutic Class Overview
Incretin Mimetics & Amylinomimetics

INTRODUCTION

- Diabetes mellitus affects more than 30 million people in the United States (U.S.) (*Centers for Disease Control and Prevention [CDC] 2017*).
- Diabetes mellitus is defined as a group of metabolic disorders characterized by hyperglycemia that result from defects in the secretion and action of insulin (*American Diabetes Association [ADA] Diabetes Basics 2019*).
- The classification of diabetes includes 4 clinical classes: 1) type 1 diabetes mellitus (T1DM) which results from beta-cell (β-cell) destruction, usually leading to absolute insulin deficiency, 2) type 2 diabetes mellitus (T2DM) which results from a progressive insulin secretory defect on the background of insulin resistance, 3) other specific types of diabetes due to other causes, eg, genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced (such as in the treatment of human immunodeficiency virus/acquired immunodeficiency syndrome or after organ transplantation), and 4) gestational diabetes mellitus (GDM) (diabetes diagnosed during pregnancy that is not clearly overt diabetes) (*ADA 2019*).
- Insulin is the standard treatment for T1DM. Pharmacologic options for T2DM include sulfonylureas (SFUs), biguanides, thiazolidinediones (TZDs), meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, combination products, and insulin.
- The GLP-1 receptor agonists (albiglutide, dulaglutide, exenatide, exenatide extended-release [ER], liraglutide, lixisenatide, and semaglutide) were developed to mimic the effects of endogenous GLP-1 and are Food and Drug Administration (FDA)-approved as adjunctive therapy to diet and exercise to improve glycemic control in adults with T2DM. As of 2018, albiglutide was discontinued by the manufacturer due to limited prescribing of the drug and not because of safety concerns (*Tanzeum Discontinuation FAQ 2017*).
- Pramlintide is the only amylin analog, or amylinomimetic, in the class, and is FDA-approved as an adjunctive treatment with insulin in patients with T1DM or T2DM who have failed to achieve desired glucose control despite optimal insulin therapy. It is a synthetic analog of human amylin, a naturally occurring neuroendocrine hormone synthesized by pancreatic β-cells that contributes to glucose control during the post-prandial period.
- This review will focus on the GLP-1 receptor agonists and pramlintide and their respective FDA-approved indications for treatment of diabetes. Liraglutide (Saxenda) is also indicated as adjunctive therapy for chronic weight management; however, the use of liraglutide for this indication will not be included in this review.
- Medispan class: Endocrine and Metabolic Drugs; Incretin Mimetic Agents (GLP-1 Receptor Agonists) and Amylin Analogs

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Adlyxin (lixisenatide)	-
Bydureon (exenatide ER)	-
Bydureon BCise (exenatide ER)	-
Byetta (exenatide)	-
Ozempic (semaglutide)	-
Symlin (pramlintide)	-
Trulicity (dulaglutide)	-
Victoza (liraglutide)	-

(*DRUGS@FDA 2019*, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. FDA Approved Indications

Indication	Adlyxin (lixisenatide)	Byetta (exenatide)	Bydureon (exenatide ER)	Bydureon BCise (exenatide ER)	Ozempic (semaglutide)	Symlin (pramlintide)	Trulicity (dulaglutide)	Victoza (liraglutide)
T1DM, as an adjunctive treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.						✔		
T2DM, as an adjunctive treatment in patients who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.						✔		
Adjunct to diet and exercise to improve glycemic control in adults with T2DM.	✔	✔	✔	✔	✔		✔	✔
Reduce the risk of major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction [MI], or non-fatal stroke) in adults with T2DM and established cardiovascular disease								✔
Limitations of Use								
Not recommended as first-line therapy for patients inadequately controlled on diet and exercise because of the uncertain relevance of the rodent C-cell tumor findings to humans. Prescribe only to patients for whom the potential benefits are considered to outweigh the potential risk.			✔	✔	✔		✔	
Has not been studied in patients with a history of pancreatitis. Consider other antidiabetic therapies in these patients.	✔	✔	✔	✔	✔		✔	
Not indicated in treatment of patients with T1DM or for treatment of patients with diabetic ketoacidosis. Not a substitute for insulin in these patients.	✔	✔	✔	✔	✔		✔	✔
Has not been studied in patients with severe gastrointestinal (GI) disease, including severe gastroparesis. Not recommended in patients with pre-existing severe GI disease.							✔	

Indication	Adlyxin (lixisenatide)	Byetta (exenatide)	Bydureon (exenatide ER)	Bydureon BCise (exenatide ER)	Ozempic (semaglutide)	Symlin (pramlintide)	Trulicity (dulaglutide)	Victoza (liraglutide)
Has not been studied in patients with gastroparesis. Not recommended in patients with gastroparesis.	✔							
Not studied in combination with prandial/short-acting insulin.	✔	✔	✔					✔
Use with insulin has not been studied and is not recommended.				✔				

(Prescribing information: *Adlyxin 2019, Bydureon 2018, Bydureon BCise 2017, Byetta 2018, Ozempic 2017, Symlin 2016, Trulicity 2019, Victoza 2018*)

NOTE: Information on indications, mechanism of action, pharmacokinetics, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Dulaglutide

- The approval of dulaglutide was based on 6 pivotal trials enrolling over 3,000 patients as a part of the AWARD phase 3 program. Trials evaluated the use of dulaglutide 0.75 mg and 1.5 mg strengths. The primary outcome in each trial was the change in HbA1c from baseline to 26 through 52 weeks.
  - AWARD-1 demonstrated that once weekly dulaglutide resulted in significantly larger improvements in HbA1c at 26 weeks compared to placebo and exenatide in patients taking maximally tolerated doses of metformin and pioglitazone (*Wysham et al 2014*).
  - AWARD-2 was an OL study that demonstrated superiority of dulaglutide 1.5 mg once weekly and noninferiority of dulaglutide 0.75 mg once weekly compared to daily insulin glargine in terms of HbA1c reduction from baseline to week 52 (*Giorgino et al 2015*).
  - AWARD-3 was a DB study that demonstrated superiority of dulaglutide 0.75 mg and 1.5 mg once weekly to metformin in patients inadequately treated with diet and exercise with or without submaximal dosing of at least 1 oral antidiabetic drug (OAD). At 26 weeks, changes from baseline HbA1c were 0.78%, 0.71%, and 0.56% for dulaglutide 1.5 mg, dulaglutide 0.75 mg, and metformin, respectively (*Umpierrez et al 2014*).
  - AWARD-4 was an OL, 52-week, noninferiority study which found that dulaglutide once-weekly (both 1.5 mg and 0.75 mg strengths) in combination with insulin lispro resulted in significantly greater improvement in glycemic control than insulin glargine in combination with insulin lispro ($p = 0.005$ and $p = 0.015$ for dulaglutide 1.5 mg and 0.75 mg, respectively) (*Blonde et al 2015*).
  - AWARD-5 was a DB trial that compared placebo, once-weekly dulaglutide (0.75 mg and 1.5 mg), and sitagliptin 100 mg once daily in uncontrolled metformin-treated patients. At weeks 52 and 104, both dulaglutide strengths were superior to sitagliptin in terms of HbA1c reduction from baseline ($p < 0.001$ for all comparisons) (*Nauck et al 2014, Weinstock et al 2015*).
  - AWARD-6 was an OL trial which demonstrated that, in patients taking concurrent metformin, dulaglutide 1.5 mg once weekly was noninferior to liraglutide once daily in HbA1c reduction from baseline to week 26 (*Dungan et al 2014*).
  - The AWARD-7 trial was an OL, non-inferiority study that enrolled patients with T2DM and moderate-to-severe chronic kidney disease (CKD) who were currently on insulin therapy. Patients were randomized to once-weekly dulaglutide (0.75 mg or 1.5 mg) or daily insulin glargine, all in combination with insulin lispro. At week 26, the change in HbA1c with dulaglutide 1.5 mg and 0.75 mg was non-inferior to insulin glargine ($p \leq 0.0001$ for both comparisons) (*Tuttle et al 2018*).

Exenatide

- The efficacy of exenatide as add-on therapy to metformin alone, an SFU alone, or metformin in combination with an SFU was evaluated in 3 PC, 30-week, randomized controlled trials (RCTs). In all trials, there were significant decreases in HbA1c with exenatide compared to placebo ($p < 0.001$, $p < 0.002$, and $p < 0.0001$, respectively) (*Buse et al 2004, DeFronzo et al 2005, Kendall et al 2005*). Extensions of these 30-week trials demonstrated that the benefits of exenatide are sustained (*Blonde et al 2006, Buse et al 2007, Klonoff et al 2008, Ratner et al 2006, Riddle et al 2006*).
- A trial evaluating exenatide as add-on therapy in patients currently taking a TZD found that at week 16, exenatide significantly decreased HbA1c ($p < 0.001$), fasting plasma glucose (FPG) ($p < 0.001$), and body weight ($p < 0.001$) compared to placebo (*Zinman et al 2007*).
- When exenatide was compared to glyburide as add-on therapy to metformin, exenatide significantly decreased body weight and body mass index (BMI) ($p < 0.001$ for both), whereas the SFU caused significant increases in both ($p < 0.05$ for both). Both treatments significantly decreased HbA1c, FPG, and postprandial plasma glucose (PPG) (exenatide; $p < 0.001$ for all; glyburide; $p < 0.001$ for all). Only exenatide significantly improved insulin resistance ($p < 0.01$) and β-cell function ($p < 0.05$) (*Derosa et al 2010*).
- The EUREXA study compared the efficacy of exenatide and glimepiride as add-on therapy to metformin. Patients receiving exenatide exhibited greater reductions in HbA1c from baseline (-0.36%), compared to those receiving glimepiride (-0.21%; $p = 0.002$) (*Gallwitz et al 2012*).
- Several trials have compared exenatide to insulin therapy as add-on therapy to metformin and/or an SFU (*Bunck et al 2009, Bunck et al 2010, Davies et al 2009, Heine et al 2005, Nauck et al 2007, Secnik et al 2006*). Similar improvements in HbA1c between treatments were observed in 3 of the trials while mixed results were observed for decreases in FPG. Specifically, in 2 trials, insulin therapy was "superior" in decreasing FPG (p value not reported and $p < 0.0001$), while in another trial there was no difference between the 2 treatments ($p = 0.689$). Insulin therapy was associated with an increase in body weight compared to a decrease with exenatide (*Bunck et al 2009, Heine et al 2005, Nauck et al 2007*). Patient-reported health outcome measures demonstrated no differences between exenatide or insulin therapy; both achieved significant improvements from baseline. However, neither treatment improved Diabetes Treatment Flexibility Scores ($p = 0.93$ for both) (*Secnik et al 2006*).
- Exenatide once weekly was also compared to daily insulin glargine in diabetic patients inadequately controlled with OADs. Following 26 weeks of therapy, exenatide was found to be statistically noninferior to insulin glargine for the change in HbA1c from baseline to endpoint (*Inagaki et al 2012*).

Exenatide ER

- Approval of exenatide ER in the management of T2DM was based on the clinical evidence for safety and efficacy derived from the DURATION trials (1 through 5). Exenatide ER was added to existing antidiabetic regimens in 4 of the 5 trials (1, 2, 3, and 5). In contrast, DURATION-4 compared exenatide ER, metformin, pioglitazone, and sitagliptin all as monotherapy (*Bergenstal et al 2010, Blevins et al 2011, Diamant et al 2010, Drucker et al 2008, Russell-Jones et al 2012*).
  - Overall, exenatide ER as add-on therapy to existing antidiabetic regimens significantly decreased HbA1c compared to exenatide ($p < 0.005$), sitagliptin ($p < 0.0001$), pioglitazone ($p = 0.0165$), and insulin therapy ($p = 0.017$), with no increased risk of hypoglycemia. In terms of decreases in body weight, exenatide ER was superior compared to sitagliptin ($p = 0.0002$) and pioglitazone ($p < 0.0001$), and similar compared to exenatide ($p = 0.89$) (*Bergenstal et al 2010, Blevins et al 2011, Drucker et al 2008*).
  - As expected, GI-related adverse events (AEs) were reported more commonly with the incretin-based therapies. When compared to exenatide, exenatide ER was associated with lower incidences of nausea (14.0% vs 35.0%) and vomiting (4.7% vs 8.9%), and higher incidences of diarrhea (9.3% vs 4.1%) and injection site-related AEs (13% vs 10%) (*Blevins et al 2011*).
  - In the DURATION-4 trial, the decrease in HbA1c achieved with exenatide ER monotherapy was superior compared to sitagliptin ($p < 0.001$) and similar compared to metformin ($p = 0.62$) and pioglitazone ($p = 0.328$). Exenatide ER and metformin were similar in terms of associated decreases in body weight, with exenatide ER achieving superiority compared to sitagliptin and pioglitazone. Overall, exenatide ER was associated with more GI-related AEs, with the exception of diarrhea which occurred at the highest frequency in patients receiving metformin (*Diamant et al 2010*).
  - An OL extension of the DURATION-1 trial demonstrated that treatment with exenatide ER was associated with sustained improvements in glycemic control over a 7-year period with no unexpected safety findings (*Philis-Tsimikas et al 2018*).
- In a post-hoc analysis of 4 clinical trials, patients were treated with weekly exenatide for 52 weeks. Patients had significant lowering of HbA1c, blood pressure and low density lipoprotein (LDL) levels without an increase in weight or hypoglycemia (*Bergenstal et al 2013*).

- The DURATION-6 trial compared HbA1c reductions between liraglutide once daily and exenatide once weekly in patients with T2DM previously treated with lifestyle modifications and oral agents. Both therapies resulted in improvements in glycemic control; however, greater reductions were noted with liraglutide (*Buse et al 2013*).
- Bydureon BCise is a new formulation of Bydureon that is administered via an autoinjector device. It was approved based on the results of two 28-week, OL, AC trials. In the DURATION-NEO-1 trial, Bydureon BCise 2 mg once weekly achieved a statistically significant HbA1c reduction vs Byetta 10 mcg twice daily ($p < 0.05$) in patients with T2DM inadequately controlled with diet and exercise alone or with a stable regimen of metformin, an SFU, a TZD, or a combination of any 2 of these agents. In the DURATION-NEO-2 trial, Bydureon BCise 2 mg once weekly achieved a statistically significant HbA1c reduction vs placebo ($p < 0.05$) in patients with T2DM on metformin. The difference vs sitagliptin was -0.28% (95% CI, -0.62% to -0.02%) (*Bydureon BCise Prescribing Information 2017, Gadde et al 2017, Wysham et al 2017*).

Liraglutide

- Approval of liraglutide in the management of T2DM was based on the clinical evidence for safety and efficacy derived from the LEAD trials (1 through 6). The LEAD trials evaluated liraglutide monotherapy (LEAD-3); add-on therapy to an SFU (LEAD-1), metformin (LEAD-2), metformin plus a TZD (LEAD-4), metformin plus an SFU (LEAD-5); and monotherapy head-to-head with exenatide (LEAD-6).
  - In LEAD-1, liraglutide was compared to placebo or rosiglitazone as add-on therapy to an SFU. After 26 weeks, liraglutide (0.6, 1.2, and 1.8 mg per day) significantly decreased HbA1c compared to placebo ($p < 0.0001$ for all), with only higher doses achieving superiority compared to rosiglitazone ($p < 0.001$ for both) (*Marre et al 2009*).
  - In LEAD-2, liraglutide was compared to placebo and an SFU as add-on therapy to metformin. Liraglutide significantly decreased HbA1c compared to placebo; however, similar decreases were observed with liraglutide compared to the SFU. Liraglutide was associated with significant decreases in body weight compared to placebo ($p < 0.01$) and the SFU ($p < 0.001$) (*Nauck et al 2009*). Results of an 18-month OL extension trial were consistent with the DB study (*Nauck et al 2013*).
  - In LEAD-3, liraglutide was compared to an SFU as monotherapy, and liraglutide was superior in decreasing HbA1c ($p = 0.0014$ and $p < 0.0001$ for liraglutide 1.2 mg and 1.8 mg, respectively). In addition, increases in body weight were reported with the SFU, while liraglutide significantly decreased body weight ($p = 0.027$) (*Garber et al 2009*). In a 1-year extension trial, patients continuing liraglutide for a total of 2 years maintained significant improvements in HbA1c compared to the SFU (*Garber et al 2011*).
  - In LEAD-4 and LEAD-5, liraglutide was compared to placebo as add-on therapy to metformin plus an SFU and to a TZD. LEAD-5 also had an OL arm of insulin therapy. Results achieved with liraglutide in terms of decreases in HbA1c, body weight, and FPG compared to placebo were similar to those observed in the other LEAD trials (*Russell-Jones et al 2009; Zinman et al 2009*). When compared to insulin therapy, decreases in HbA1c ($p = 0.0015$) and body weight ($p < 0.001$) and improvements in β-cell function ($p = 0.0019$) were significantly greater with liraglutide. It was noted that decreases in PPG were not different between the 2 treatments, and the likelihood of patients achieving FPG goals were also similar (*Russell-Jones et al 2009*).
  - LEAD-6 was a head-to-head trial comparing liraglutide to exenatide as add-on therapy to existing antidiabetic treatment regimens. Liraglutide significantly decreased HbA1c compared to exenatide (1.12% vs 0.79%; $p < 0.0001$), and a significantly greater proportion of patients receiving liraglutide achieved HbA1c goals of < 7%. Significant decreases in FPG were also achieved with liraglutide ($p < 0.0001$); however, exenatide significantly decreased PPG after breakfast and dinner ($p < 0.0001$ and $p = 0.0005$) (*Buse et al 2009*). A 14-week, extension trial revealed that patients who were switched from exenatide to liraglutide achieved additional glycemic control and cardiometabolic benefits (*Buse et al 2010*).

Lixisenatide

- The approval of lixisenatide was based on several phase 3 trials as part of the GetGoal clinical trial program. Lixisenatide 20 mcg once daily was evaluated as monotherapy, in combination with OADs, and in combination with basal insulin (with or without OADs). Its efficacy was compared with placebo, exenatide, and insulin glulisine. The primary endpoint, the difference in change in HbA1c from baseline to trial end between the lixisenatide and comparator groups, was assessed at varying time points ranging between 12 and 26 weeks.
  - GetGoal-Mono found that lixisenatide 20 mcg once daily as monotherapy resulted in significantly larger improvements in HbA1c at 12 weeks compared to placebo in patients with T2DM inadequately controlled on diet and exercise ($p < 0.0001$) (*Fonseca et al 2012*).

- GetGoal-F1 was a DB study which found that lixisenatide 20 mcg once daily as add-on therapy to metformin was superior vs placebo in terms of HbA1c reduction from baseline to week 24. The least squares mean change from baseline was -0.26% for the placebo group vs -0.72% for the lixisenatide group. The difference vs placebo was -0.46% ($p < 0.0001$) (*Adlyxin Prescribing Information 2016, Bolli et al 2014*).
- GetGoal-M-Asia demonstrated superiority of lixisenatide 20 mcg once daily as add-on therapy to metformin with or without an SFU compared to placebo in terms of HbA1c reduction from baseline to week 24 (*Yu et al 2014*).
- GetGoal-S was a 24-week, DB study which found that lixisenatide 20 mcg once daily in combination with an SFU with or without metformin resulted in significantly greater improvement in glycemic control than placebo; the difference from placebo in change in HbA1c was -0.58% ($p < 0.0001$) (*Adlyxin Prescribing Information 2016, Rosenstock et al 2014*).
- GetGoal-P was a 24-week, DB study which found that lixisenatide 20 mcg once daily in combination with pioglitazone or without metformin resulted in significantly greater improvement in glycemic control than placebo; the difference from placebo in change in HbA1c was -0.48% ($p < 0.0001$) (*Adlyxin Prescribing Information 2016, Pinget al 2013*).
- In GetGoal-Duo 1, lixisenatide was compared to placebo as add-on therapy to basal insulin and metformin with or without a TZD. Treatment with lixisenatide resulted in a significant reduction in HbA1c at week 24 vs placebo (*Riddle et al 2013a*).
- In GetGoal-L, lixisenatide was compared to placebo as add-on therapy to basal insulin with or without metformin while in Get-Goal-L-Asia, lixisenatide was compared to placebo as add-on therapy to basal insulin with or without an SFU. Both studies found that lixisenatide was superior to placebo in terms of HbA1c reduction from baseline to week 24 (*Riddle et al 2013b, Seino et al 2012*).
- GetGoal-Duo 2 was a 26-week, OL trial that compared lixisenatide to insulin glulisine once daily or 3 times daily for intensification of optimized insulin glargine ± metformin in patients with T2DM uncontrolled on basal insulin ± OADs (ie, an SFU and/or a DPP-4 inhibitor, and/or a glinide). Lixisenatide was found to be noninferior to both insulin glulisine regimens in terms of HbA1c reduction from baseline to week 26. However, lixisenatide provided less HbA1c reduction than insulin glulisine 3 times daily and the difference was statistically significant; the least squares mean difference of lixisenatide vs insulin glulisine 3 times daily was 0.23 ($p = 0.0002$) (*Adlyxin Prescribing Information 2016, Rosenstock et al 2016*).
- GetGoal-X was a 24-week, OL trial that evaluated lixisenatide vs exenatide twice daily as add-on therapy to metformin. Lixisenatide met the pre-specified noninferiority margin vs exenatide twice daily for the difference in HbA1c reduction from baseline to week 24. However, lixisenatide provided less HbA1c reduction than exenatide and the difference was statistically significant; the least squares mean difference vs exenatide was 0.17% ($p = 0.0175$) (*Adlyxin Prescribing Information 2016, Rosenstock et al 2013*).
- A meta-analysis (MA) of 76-week data from 5 trials in the GetGoal clinical trial program (GetGoal-M, GetGoal-F1, GetGoal-S, GetGoal-P, and GetGoal-L) supported the sustained efficacy and tolerability of lixisenatide (*Broglio et al 2017*).

Semaglutide

- The approval of semaglutide was based on several phase 3 trials as part of the SUSTAIN clinical trial program. Semaglutide was evaluated as monotherapy, in combination with OADs, and in combination with basal insulin. Its efficacy was compared with placebo, sitagliptin, exenatide ER, insulin glargine, and dulaglutide. The primary endpoint, the difference in change in HbA1c from baseline to trial end between the semaglutide and comparator groups, was assessed at varying time points ranging between 30 and 56 weeks.
  - SUSTAIN 1 was a 30-week, PC trial which found that semaglutide 0.5 mg and 1 mg weekly significantly improved HbA1c vs placebo ($p < 0.0001$) (*Sorli et al 2017*).
  - SUSTAIN 2 was a 56-week, OL trial that compared semaglutide 0.5 mg and 1 mg weekly to sitagliptin 100 mg daily in patients on metformin and/or TZDs. Compared with sitagliptin, treatment with semaglutide resulted in statistically significant reductions in HbA1c from baseline to week 56. The mean change from baseline was -1.3% for semaglutide 0.5 mg, -1.5% for semaglutide 1 mg, and -0.7% for sitagliptin. The difference vs sitagliptin was -0.6% ($p < 0.0001$) for semaglutide 0.5 mg and -0.8% ($p < 0.0001$) for semaglutide 1 mg (*Ahrén et al 2017, Ozempic Prescribing Information 2017*).
  - SUSTAIN 3 was a 56-week, OL trial that compared semaglutide 1 mg to exenatide ER 2 mg once weekly. At week 56, mean change from baseline in HbA1c was -1.4% in the semaglutide group vs -0.9% in the exenatide ER group (difference: -0.5%, $p < 0.0001$) (*Ahmann et al 2018, Ozempic Prescribing Information 2017*).
  - SUSTAIN 4 was a 30-week OL, AC trial in patients on metformin with or without an SFU that compared semaglutide 0.5 mg and 1 mg to insulin glargine initiated at 10 units once daily. Compared with insulin glargine, treatment with

semaglutide resulted in statistically significant reductions in HbA1c from baseline to week 30. The mean change from baseline was -1.2% for semaglutide 0.5 mg, -1.5% for semaglutide 1 mg, and -0.9% for insulin glargine. The difference vs insulin glargine was -0.3% ($p < 0.0001$) for semaglutide 0.5 mg and -0.6% ($p < 0.0001$) for semaglutide 1 mg (*Aroda et al 2017*, *Ozempic Prescribing Information 2017*).
  - SUSTAIN 5 was a 30-week, DB, PC trial in patients inadequately controlled with basal insulin, with or without metformin, which found that semaglutide 0.5 mg and 1 mg significantly reduced HbA1c vs placebo ($p < 0.0001$) (*Rodbard et al 2018).*
  - SUSTAIN 7 was a 40-week, OL trial that compared semaglutide to dulaglutide once weekly in patients on metformin monotherapy. From a mean baseline HbA1c of 8.2%, semaglutide 0.5 mg achieved a statistically significant reduction of 1.5% vs a reduction of 1.1% with dulaglutide 0.75 mg at week 40, while semaglutide 1.0 mg achieved a statistically significant reduction of 1.8% vs a reduction of 1.4% with dulaglutide 1.5 mg (both $p < 0.0001$ for noninferiority and superiority) *(Pratley et al 2018).*

Cardiovascular (CV) outcomes

- Full results from the REWIND trial that evaluated the long-term effects of dulaglutide vs placebo in patients with T2DM with and without baseline CV disease are still forthcoming. Initial results reported by the trial sponsor indicate that dulaglutide significantly reduced the primary composite outcome (CV death, non-fatal MI, or non-fatal stroke) compared to placebo (*ClinicalTrials.gov [NCT01394952] 2018, Lilly press release 2018*).
- A MC, DB, PC, RCT (EXSCEL trial; N = 14,752) was conducted to evaluate the long-term effects of exenatide ER vs placebo, as added to usual care, on CV outcomes in patients with T2DM with or without previous CV disease. A total of 73.1% of patients had previous CV disease, and the median follow-up was 3.2 years. A primary composite outcome event (CV death, non-fatal MI, or non-fatal stroke) occurred in 11.4% of patients in the exenatide ER group vs 12.2% in the placebo group (hazard ratio [HR], 0.91; 95% confidence interval [CI], 0.83 to 1.00). Thus, exenatide ER was found to be noninferior to placebo with respect to safety ($p < 0.001$), but not superior to placebo with respect to efficacy ($p = 0.06$). The risk of death from any cause was 6.9% vs 7.9% in the exenatide ER and placebo groups, respectively (HR, 0.86; 95% CI, 0.77 to 0.97); the difference was not statistically significant on the basis of the hierarchical testing plan. The rates of death from CV causes, nonfatal MI, nonfatal stroke, and hospitalization for heart failure did not differ significantly between groups (*Holman et al 2017*).
- A MC, DB, PC, RCT (LEADER trial; N = 9340) was conducted to evaluate the long-term effects of liraglutide vs placebo on CV outcomes in patients with T2DM and high CV risk. The median follow-up was 3.8 years. It was found that the primary composite outcome (CV death, non-fatal MI, or non-fatal stroke) occurred in fewer patients in the liraglutide group (13.0%) vs the placebo group (14.9%) (HR, 0.87; 95% CI, 0.78 to 0.97; $p < 0.001$ for noninferiority; $p = 0.01$ for superiority). Fewer patients died from CV causes in the liraglutide group (4.7%) vs the placebo group (6.0%) (HR, 0.78; 95% CI, 0.66 to 0.93; $p = 0.007$). The rate of death from any cause was lower in the liraglutide group (8.2%) vs the placebo group (9.6%) (HR, 0.85; 95% CI, 0.74 to 0.97; $p = 0.02$). The rates of nonfatal MI, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group (*Marso et al 2016a*).
  - A prespecified secondary analysis found that the composite renal outcome (new-onset persistent macroalbumineria, persistent doubling of serum creatinine level, end-stage renal disease, and death due to renal disease) occurred in fewer patients in the liraglutide group vs the placebo group (5.7% vs 7.2%; HR, 0.78; 95% CI, 0.67 to 0.92; $p = 0.003$) (*Mann et al 2017*).
  - Post-hoc analyses of the LEADER trial have reported that the risk reduction in the primary outcome was consistent in patients with CKD (HR, 0.69; 95% CI, 0.57 to 0.85), a history of a MI or stroke (HR, 0.85; 95% CI, 0.73 to 0.99), and established atherosclerotic cardiovascular disease (ASCVD) (without a MI/stroke) (HR, 0.76; 95% CI, 0.62 to 0.94) (*Mann et al 2018, Verma et al 2018*).
- A MC, DB, PC, RCT (ELIXA trial; N = 6068) evaluated the long-term effects of lixisenatide vs placebo on CV outcomes in patients with T2DM who had a recent acute coronary syndrome (ACS) event within 180 days of screening. The median follow-up was 25 months. It was found that the primary endpoint event (a composite of the first occurrence of any of the following: death from CV causes, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina) occurred in 13.4% of patients in the lixisenatide group and 13.2% in the placebo group (HR, 1.02; 95% CI, 0.89 to 1.17), which demonstrated noninferiority of lixisenatide to placebo ($p < 0.001$), but did not demonstrate superiority ($p = 0.81$). The rates of the individual CV components of the primary endpoint were similar between the lixisenatide and placebo groups (*Pfeffer et al 2015*).
- *Marso et al 2016b* conducted a MC, DB, PC, RCT (SUSTAIN 6 trial; N = 3297) to assess the noninferiority of semaglutide as compared to placebo in terms of CV safety in patients with T2DM, 83.0% of whom had CV disease.

Patients were randomized to semaglutide 0.5 mg or 1.0 mg once weekly or placebo. The median observation time was 2.1 years. The primary composite outcome was the first occurrence of CV death, nonfatal MI, or nonfatal stroke. The noninferiority margin was 1.8 for the upper boundary of the 95% CI of the HR.
  - The primary composite outcome occurred in 6.6% of the semaglutide group vs 8.9% of the placebo group (HR: 0.74 [95%CI, 0.58 to 0.95]; p < 0.001 for noninferiority). Although a p value of 0.02 for superiority was calculated; testing for superiority was not prespecified. Nonfatal stroke occurred in 1.6% in the semaglutide group vs 2.7% in the placebo group (HR: 0.61 [95% CI, 0.38 to 0.99]; p = 0.04). Rates of nonfatal MI, CV death, and all-cause death were not statistically significantly different between groups.
  - Rates of new or worsening nephropathy were lower in the semaglutide group, but rates of retinopathy complications were significantly higher (3.0% for semaglutide vs 1.8% for placebo, HR: 1.76 [95% CI, 1.11 to 2.78]; p = 0.02).
  - A larger study (PIONEER 6) is ongoing to further assess the CV safety of semaglutide in patients with T2DM at high risk for CV events (*Bain et al 2019*).
- A MC, DB, PC, RCT (Harmony Outcomes trial; N=9463) evaluated the long-term effects of the previously available GLP-1 receptor agonist, albiglutide, vs placebo on CV outcomes in patients with T2DM and established CV disease. The median follow-up was 1.6 years. The primary endpoint (a composite of the first occurrence of any of the following: death from CV causes, MI, or stroke) occurred in 7% of patients in the albiglutide group and 9% in the placebo group (HR, 0.78; 95% CI, 0.68 to 0.90), which demonstrated noninferiority and superiority of albiglutide to placebo (p < 0.0001 for noninferiority; p = 0.0006 for superiority). The rate of fatal or non-fatal stroke was significantly improved in the albiglutide group, but other individual CV components of the primary endpoint were nonsignificantly lower in the albiglutide group than in the placebo group (*Hernandez et al 2018*).

Meta-analyses

- Meta-analyses and Cochrane Reviews evaluating GLP-1 receptor agonists have found that they lead to decreases in HbA1c of ~1%, with greater decreases in body weight and systolic blood pressure compared to placebo and other antidiabetic agents (*Wang et al 2013, Shyangdan et al 2011, Sun et al 2015*).
- A systematic review and mixed-treatment comparison analysis of GLP-1 receptor agonists found that there were no differences in efficacy within the short-acting (exenatide or lixisenatide) or long-acting (albiglutide, dulaglutide, exenatide ER, liraglutide) groups. However, dulaglutide, liraglutide, and exenatide ER were superior to exenatide and lixisenatide at lowering HbA1c and FPG. There were no clinically meaningful differences between agents in weight loss or hypoglycemia. Albiglutide had the lowest risk of nausea and diarrhea, while exenatide ER had the lowest risk of vomiting (*Htike et al 2016*).
- A systematic review and network meta-analysis sponsored by the manufacturer of semaglutide (Novo Nordisk) found that in patients with T2DM who were inadequately controlled on 1 to 2 OADs, semaglutide 1.0 mg was associated with significantly greater reductions in HbA1c and weight vs all GLP-1 receptor agonist comparators after 6 months of treatment, while the 0.5 mg dose achieved statistically significant reductions in HbA1c and weight vs the majority of other GLP-1 receptor agonists (*Witkowski et al 2018a*). Similar results were found in another Novo Nordisk-sponsored systematic review of trials in patients previously receiving basal insulin (*Witkowski et al 2018b*).
- Meta-analyses have revealed that incretin-based therapies are not associated with an increased risk of pancreatitis and appear to reduce all-cause mortality, CV mortality, and the incidence of MI compared to placebo or other antidiabetic agents. However, treatment with GLP-1 receptor agonists was associated with a significant increase in the incidence of cholelithiasis (*Monami et al 2017a*, *Monami et al 2017b)*.
- A meta-analysis found that overall, GLP-1 receptor agonists did not appear to be associated with an increase in the incidence of retinopathy, and there was a reduction in the incidence of nephropathy vs comparators (*Dicembrini et al 2017*).

Pramlintide

- The safety and efficacy of pramlintide in patients with T1DM have been established in PC, RCTs when administered in addition to existing insulin regimens. In a 52-week, DB, MC, PC study, pramlintide significantly reduced HbA1c from baseline compared to placebo (-0.39% vs -0.12%; p = 0.0071) and was also associated with a significant weight loss compared to placebo (p < 0.001) (*Whitehouse et al 2002*). In a second 52-week study, patients experienced a significant reduction in HbA1c when receiving pramlintide 60 mcg 3 times daily (-0.41 vs -0.18%; p = 0.012) and pramlintide 60 mcg 4 times daily (-0.39 vs -0.18%; p = 0.013) at 26 weeks. Treatment with pramlintide 3 or 4 times daily continued to maintain reductions in HbA1c at 52 weeks compared to treatment with placebo (p = 0.011 and p = 0.001 for the 3- and 4 times daily dosing, respectively) (*Ratner et al 2004*).
- A systematic review and meta-analysis of 10 randomized, PC studies (N = 3297) evaluating the effect of pramlintide as adjunctive therapy to insulin in patients with T1DM found that, compared to placebo, pramlintide resulted in significant

reductions in HbA1c (p < 0.001), total daily insulin dose (p = 0.024), mean mealtime insulin dose (p < 0.001), body weight (p < 0.001), and PPG (p = 0.002) (*Qiao et al 2017*).

- A systematic review and meta-analysis of 8 PC, RCTs assessed the effect of pramlintide in patients with T2DM and in obese patients without diabetes. Four T2DM studies (N = 930; 16 to 52 weeks duration) and 4 obesity studies (N = 686; 6 to 24 weeks duration) were included. Of the T2DM studies, 3 studies used meal-time placebo as the comparator while 1 study used rapid-acting insulin as the comparator. When endpoint data from all T2DM studies were combined, pramlintide was associated with a small but significant reduction in HbA1c (mean difference: -0.33% [95% CI, -0.51 to -0.14]; p = 0.0004). In the meta-analysis of the T2DM studies, patients on pramlintide were 1.52 times more likely to reach the HbA1c goal ≤ 7% than patients in the control group; however, this difference was not significant (p = 0.18). Pramlintide was associated with a significant change in body weight in patients with T2DM compared to the control group (-2.57 kg [95% CI, -3.44 to -1.70]; p < 0.00001) (*Singh-Franco et al 2011*).

CLINICAL GUIDELINES

- According to current clinical guidelines, metformin remains the cornerstone of most T2DM treatment regimens. If A1C remains above target with metformin alone and the patient does not have ASCVD or CKD, clinicians should consider combining metformin with any one of the following: a sulfonylurea, TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or basal insulin. The choice of which agent to add is based on drug-specific effects and patient factors. Clinical guidelines note a lower rate of hypoglycemia, established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing PPG, and the potential for weight loss as advantages associated with the incretin mimetics compared to other antidiabetic agents. The ADA guidelines recommend that lifestyle management and metformin should be initiated in patients with T2DM and established ASCVD . For patients in whom ASCVD, heart failure, or CKD predominates, the best choice for a second agent is a GLP-1 receptor agonist or SGLT2 inhibitor with demonstrated CV risk reduction. The GLP-1 receptor agonist with the strongest evidence for a CV benefit is liraglutide, followed by semaglutide, then exenatide ER. For all patients who require further intensification to injectable agents, a GLP-1 receptor agonist should be the first choice, ahead of insulin. Current clinical guidelines do not support the use of amylinomimetics in the management of T2DM. Among T1DM patients, there is limited evidence available to support the routine use of adjunctive therapies, including pramlintide, to insulin therapy (*ADA 2019, Chiang et al 2018, Davies et al 2018, Garber et al 2019, Inzucchi et al 2015*).
- The American College of Cardiology (ACC) published an expert consensus decision pathway for patients with T2DM and ASCVD (*Das 2018*). It focuses on the use of SGLT2 inhibitors and GLP-1 receptor agonists in appropriate patients to reduce adverse CV outcomes. For the GLP-1 receptor agonists, liraglutide is the only agent in the class with definitive proven benefits of reducing CV events. In contrast, lixisenatide is not associated with a reduction in ASCVD event risk. Thus, both the ACC pathway and ADA guideline consider liraglutide as the preferred GLP-1 receptor agonist in patients with established ASCVD (*ADA 2019, Das 2018*).

SAFETY SUMMARY

- GLP-1 receptor agonists are contraindicated in patients with hypersensitivity to any component of the products. With the exception of exenatide and lixisenatide, they are also contraindicated in those with a personal or family history of medullary thyroid carcinoma (MTC) or multiple endocrine neoplasia syndrome, type 2 (MEN 2).
- All GLP-1 receptor agonists, except exenatide and lixisenatide, carry a boxed warning for risk of thyroid C-cell tumors. Other safety risks include pancreatitis (including fatal and non-fatal hemorrhagic or necrotizing pancreatitis), serious hypersensitivity reactions, immunogenicity, serious hypoglycemia when used in combination with SFUs or insulin, and renal impairment. Liraglutide also has a warning for acute gallbladder disease. Semaglutide carries a warning for diabetic retinopathy complications due to the results of the SUSTAIN 6 trial, which found a higher rate of events in patients treated with semaglutide vs placebo; the absolute risk was larger among patients with a history of diabetic retinopathy at baseline compared to those without. Common AEs with these drugs include: nausea, diarrhea, vomiting, headache, and injection site reactions.
- Pramlintide is contraindicated in patients with hypersensitivity to any component of the drug and in those with hypoglycemia unawareness and confirmed gastroparesis. It has a boxed warning for increased risk of hypoglycemia, particularly in patients with T1DM. Common AEs include nausea, headache, anorexia, and vomiting; the incidence of nausea tends to be higher at the beginning of treatment and decreases with time in most patients. Gradual titration of the dose minimizes the incidence and severity of nausea.
- Exenatide and pramlintide are Pregnancy Category C. Dulaglutide, exenatide ER, liraglutide, semaglutide, and lixisenatide are uncategorized in accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR).

- There are no adequate and well-controlled studies in pregnant women. These drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It is not known whether these drugs are excreted in human milk.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Adlyxin (lixisenatide)	Injection	SC	Once daily	Inject in the abdomen, thigh, or upper arm. Administer within 1 hour before the first meal of the day, preferably the same meal each day.
Bydureon (exenatide ER)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food. Administer immediately after the powder is suspended.
Bydureon BCise (exenatide ER)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food. Administer immediately after the autoinjector is prepared.
Byetta (exenatide)	Injection	SC	Twice daily	Inject in the thigh, abdomen, or upper arm. Inject within 60 minutes prior to the morning and evening meals (or before the 2 main meals of the day, approximately 6 hours or more apart).
Ozempic (semaglutide)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food.
Symlin (pramlintide)	Injection	SC	Prior to major meals	Inject in the thigh or abdomen. Administer immediately prior to each major meal. Reduce mealtime insulin doses by 50%. Adjust insulin doses to optimize glycemic control once the target dose of pramlintide is achieved and nausea (if experienced) has subsided. The dose should be decreased if significant nausea persists.
Trulicity (dulaglutide)	Injection	SC	Once weekly	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food.
Victoza (liraglutide)	Injection	SC	Once daily	Inject in the thigh, abdomen, or upper arm. May be given any time of day, with or without food.

CONCLUSION

- The GLP-1 receptor agonists exenatide, exenatide ER, dulaglutide, liraglutide, lixisenatide, and semaglutide are incretin-based antidiabetic therapies that are FDA-approved as adjunctive therapy to diet and exercise in adult patients with T2DM. Additionally, liraglutide is indicated to reduce the risk of major adverse CV events in patients with established CV disease. Pramlintide is the only agent within the amylinomimetic medication class and is FDA-approved as adjunctive

therapy in patients with T1DM or T2DM who use mealtime insulin therapy and who have failed to achieve desired glucose control despite optimal insulin therapy.

- The incretin mimetics are available as SC injections to be administered in the abdomen, thigh, or upper arm. Exenatide is administered twice daily (60 minutes prior to meals); liraglutide is administered once daily (independent of meals); and lixisenatide is administered once daily (1 hour prior to the first meal of the day). Exenatide ER, dulaglutide, and semaglutide are administered once weekly. Pramlintide is available as a SC injection to be administered immediately prior to each major meal.
- The incretin mimetics have been studied extensively in combination with, and in comparison to, a variety of antidiabetic therapies. The agents are significantly more effective than placebo in reducing HbA1c, FPG, PPG, and body weight. Efficacy data comparing treatment to an SFU, TZD, DPP-4 inhibitor or insulin is mixed, with the GLP-1 agonists achieving significantly greater or comparable benefits in glycemic outcomes.
- Several CV outcomes trials evaluating GLP-1 receptor agonists in patients with T2DM and high CV risk have been published. The LEADER trial and Harmony Outcomes trial demonstrated a statistically significant CV risk reduction with liraglutide and albiglutide, respectively, vs placebo (*Hernandez et al 2018, Marso et al 2016a*), whereas the ELIXA trial did not demonstrate a statistically significant difference between lixisenatide vs placebo (*Pfeffer et al 2015*) and the EXSCEL trial did not demonstrate a statistically significant difference between exenatide ER vs placebo (*Holman et al 2017*). Although the risk of MACE was lower with semaglutide vs placebo in the SUSTAIN 6 trial, a superiority analysis was not prespecified (*Marso et al 2016b*). A larger CV outcome study is ongoing (*Bain et al 2019*). Preliminary results of the REWIND trial have reported that dulaglutide is also associated with statistically significant CV risk reduction compared to placebo (*Lilly press release 2018).*
- Overall, the AE profiles of the GLP-1 receptor agonists are similar. With the exception of lixisenatide and exenatide, all of the agents have a boxed warning regarding the risk of thyroid C-cell tumors. Other warnings include increased risks of pancreatitis (including fatal and non-fatal hemorrhagic or necrotizing pancreatitis), serious hypersensitivity reactions, immunogenicity, serious hypoglycemia when used in combination with SFUs or insulin, and renal impairment. Liraglutide also has a warning for acute gallbladder disease, while semaglutide has a warning for diabetic retinopathy complications.
- According to current clinical guidelines, metformin remains the cornerstone of most T2DM treatment regimens. If A1C remains above target with metformin alone and the patient does not have ASCVD or CKD, clinicians should consider combining metformin with any one of the following: a sulfonylurea, TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or basal insulin. The choice of which agent to add is based on drug-specific effects and patient factors. Clinical guidelines note a lower rate of hypoglycemia, established efficacy and safety profile when used in combination with metformin, demonstrated effectiveness in reducing PPG, and the potential for weight loss as advantages associated with the incretin mimetics compared to other antidiabetic agents. The ADA guidelines recommend that lifestyle management and metformin should be initiated in patients with T2DM and established ASCVD. For patients in whom ASCVD, heart failure, or CKD predominates, the best choice for a second agent is a GLP-1 receptor agonist or SGLT2 inhibitor with demonstrated CV risk reduction. The GLP-1 receptor agonist with the strongest evidence for a CV benefit is liraglutide, followed by semaglutide, then exenatide ER. For all patients who require further intensification to injectable agents, a GLP-1 receptor agonist should be the first choice, ahead of insulin. Current clinical guidelines do not support the use of amylinomimetics in the management of T2DM. Among T1DM patients, there is limited evidence available to support the routine use of adjunctive therapies, including pramlintide, to insulin therapy (*ADA 2019, Chiang et al 2018, Davies et al 2018, Garber et al 2019, Inzucchi et al 2015*).

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INTRODUCTION

- Diabetes mellitus is defined as a group of metabolic disorders characterized by hyperglycemia that result from defects in the secretion and action of insulin *(American Diabetes Association [ADA] Diabetes Basics 2019).*
- The classification of diabetes includes four clinical classes: 1) Type 1 diabetes (T1DM) which results from beta-cell (β-cell) destruction, usually leading to absolute insulin deficiency; 2) Type 2 diabetes (T2DM) which results from a progressive insulin secretory defect on the background of insulin resistance; 3) Other specific types of diabetes due to other causes, e.g., genetic defects in β-cell function, genetic defects in insulin action, diseases of the exocrine pancreas (such as cystic fibrosis), and drug- or chemical-induced (such as in the treatment of HIV/AIDS or after organ transplantation; and 4) Gestational diabetes mellitus (diabetes diagnosed during pregnancy that is not clearly overt diabetes) *(ADA 2019).*
- In 2015, an estimated 30.3 million people, or 9.4%, of the United States (US) population had diabetes mellitus, with 7.2 million estimated to be undiagnosed *(Centers for Disease Control and Prevention [CDC] 2017).*
- The insulin products are approved for use in the management of both T1DM and T2DM. Other pharmacologic options for T2DM include sulfonylureas, biguanides, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) agonists, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and combination products.
- Insulin is used as replacement therapy in patients with diabetes, replacing deficient endogenous insulin and temporarily restoring the ability of the body to properly utilize carbohydrates, fats, and proteins. Insulin is secreted by the β-cells in the pancreas and lowers blood glucose by facilitating peripheral glucose uptake into cells and by inhibiting gluconeogenesis in the liver. In addition to its glycemic effects, insulin has anabolic properties, enhancing protein synthesis, inhibiting lipolysis in adipocytes, and stimulating lipogenesis *(Powers 2018)*.
- The first insulin products were derived from animal sources, primarily pork and beef; however, they are no longer available in the US. These older products have been replaced with human insulin and insulin analogs. Human insulin is biosynthesized utilizing recombinant deoxyribonucleic acid (DNA) with strains of *Escherichia coli* or *Saccharomyces cerevisiae* (baker's yeast) and is structurally identical to endogenous insulin. Insulin analogs are also derived from recombinant DNA technology. They are structurally different from human insulin but have comparable glucose-lowering effects. The insulin analogs differ in the addition, deletion, or substitution of amino acids on the B chain *(Powers 2018)*. Insulin analogs available today include insulin aspart, insulin degludec, insulin detemir, insulin glargine, insulin glulisine, and insulin lispro. The primary differences between commercially available insulin products revolve around pharmacodynamic and pharmacokinetic properties, particularly onset and duration of action. Individual insulin products are often classified into categories based on their onset and duration of action.
  - Bolus insulin products, also known as rapid- or short-acting insulin, include insulin aspart, insulin glulisine, insulin lispro, and certain human insulins. Unique formulations within this category include a rapid-acting, human insulin inhalation powder, and a higher strength of rapid-acting insulin lispro that provides 200 units (U) per milliliter (U-200). In September 2017, Fiasp (insulin aspart) was approved *(Novo Nordisk news release 2017).* Fiasp is a new formulation of Novolog that contains niacinamide. Niacinamide helps to increase the speed of initial insulin absorption, resulting in an onset of appearance in the blood in an estimated 2.5 minutes. Additionally, in December 2017, Admelog (insulin lispro) was the first short-acting insulin approved as a "follow-on" product through the Food and Drug Administration's (FDA) abbreviated 505(b)(2) pathway *(FDA news release 2017).*
  - Basal insulin products, also known as intermediate- or long-acting insulin, include neutral protamine Hagedorn (NPH) isophane, insulin degludec, insulin detemir, and insulin glargine. Unique products within this category include a formulation of insulin glargine that provides 300 U of insulin glargine per mL and enables patients to utilize a higher dose in one injection. Additionally, Basaglar (insulin glargine) was approved under the FDA 505(b)(2) pathway. *(Fierce Biotech FDA press release 2015, Drugs@FDA 2019).*
- Insulin therapy is usually administered by subcutaneous (SC) injection, which allows for prolonged absorption and less pain compared to intramuscular (IM) injection. Currently there are no generic insulin products available. Of note, insulin products are available by prescription, as well as over-the-counter (OTC) (short- and intermediate-acting products only).
- This review will focus on the insulin preparations and combination insulin/GLP-1 agonist products outlined in Table 1 for their respective FDA-approved indications. FDA-approved products that do not have upcoming launch plans, such as

Ryzodeg 70/30 (insulin degludec/insulin aspart), have been excluded from this review *(Novo Nordisk press release 2015*).

- Medispan Class: Antidiabetics, Insulin

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Rapid-Acting Insulins	
Admelog, Admelog Solostar (insulin lispro)	-
Afrezza (insulin human) inhalation powder	-
Apidra, Apidra SoloStar (insulin glulisine)	-
Fiasp, Fiasp FlexTouch (insulin aspart)	-
Humalog, Humalog Kwikpen, Humalog Junior Kwikpen (insulin lispro)	-
Novolog, Novolog PenFill, Novolog FlexPen (insulin aspart)	-
Short-Acting Insulins	
Humulin R (insulin, regular, human recombinant)	-
Humulin R U-500, Humulin R U-500 Kwikpen (insulin, regular, human recombinant)	-
Novolin R, Novolin R ReliOn (insulin, regular, human recombinant)	-
Intermediate-Acting Insulins	
Humulin N, Humulin N Kwikpen (insulin, NPH human recombinant isophane)	-
Novolin N, Novolin N ReliOn (insulin, NPH human recombinant isophane)	-
Long-Acting Insulins	
Basaglar (insulin glargine)	-
Lantus, Lantus SoloStar (insulin glargine)	-
Levemir, Levemir FlexTouch (insulin detemir)	-
Toujeo SoloStar, Toujeo Max SoloStar (insulin glargine U-300)	-
Tresiba FlexTouch (insulin degludec)	-
Combination Insulins, Rapid-Acting and Intermediate-Acting	
Humalog Mix 50/50, Humalog Mix 50/50 KwikPen (50% insulin lispro protamine/50% insulin lispro)	-
Humalog Mix 75/25, Humalog Mix 75/25 Kwikpen (75% insulin lispro protamine/25% insulin lispro)	-
Novolog Mix 70/30, Novolog Mix 70/30 FlexPen (70% insulin aspart protamine/30% insulin aspart)	-
Combination Insulins, Short-Acting and Intermediate-Acting	
Humulin 70/30, Humulin 70/30 KwikPen (70% NPH, human insulin isophane/30% regular human insulin)	-
Novolin 70/30, Novolin 70/30 ReliOn, Novolin 70/30 FlexPen (70% NPH, human insulin isophane/30% regular human insulin)	-
Combination, Long-Acting Insulin and GLP-1 Receptor Agonist	
Soliqua 100/33 (insulin glargine/lixisenatide)	-
Xultophy 100/3.6 (insulin degludec/liraglutide)	-

(Drugs@FDA 2019)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications – Insulins

Product	Control of hyperglycemia in patients with diabetes mellitus	Improve glycemic control in adults with diabetes mellitus	Improve glycemic control in adults and children with diabetes mellitus
Rapid-Acting Insulins			
Admelog			✔
Afrezza		✔ §	
Apidra			✔
Fiasp		✔	
Humalog			✔
Novolog			✔
Short-Acting Insulins			
Humulin R			✔ *
Novolin R			✔
Intermediate-Acting Insulins			
Humulin N			✔
Novolin N			✔
Long-Acting Insulins†			
Basaglar			✔ ‡
Lantus			✔ ‡
Levemir			✔
Toujeo		✔	
Tresiba			✔ ‖
Combination Insulins, Rapid-Acting and Intermediate-Acting			
Humalog Mix 50/50 Humalog Mix 75/25	✔		
Novolog Mix 70/30		✔	
Combination Insulins, Short-Acting and Intermediate-Acting			
Humulin 70/30		✔	
Novolin 70/30			✔

* Humulin R U-500 is useful for the treatment of insulin-resistant patients with diabetes requiring daily doses of more than 200 units.
† Limitations of use: Not recommended for treating diabetic ketoacidosis. Use intravenous, rapid-acting or short-acting insulin instead.
‡ Not indicated for children with T2DM.
§ Limitations of use: Must use with a long-acting insulin in patients with T1DM. Not recommended for treating diabetic ketoacidosis. Not recommended in patients who smoke.
‖ Indicated for patients 1 year of age and older with diabetes mellitus; the U-100 vial is recommended for pediatric patients requiring < 5 units daily.

(Prescribing information: Admelog 2018, Afrezza 2018, Apidra 2018, Basaglar 2018, Fiasp 2018, Humalog 2018, Humalog Mix 50/50 2018, Humalog Mix 75/25 2018, Humulin 70/30 2018, Humulin N 2018, Humulin R U-100 2018, Humulin R U-500 2018, Lantus 2018, Levemir 2019, Novolin 70/30 2018, Novolin N 2018, Novolin R 2018, Novolog 2018, Novolog Mix 70/30 2018, Toujeo 2018, Tresiba 2018)

Table 3. Food and Drug Administration Approved Indications – Insulins and GLP-1 Receptor Agonists

Indication	**Soliqua** (insulin glargine/ lixisenatide)	**Xultophy** (insulin degludec/ liraglutide)
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	✔	✔
Limitations of Use		
Not recommended as first-line therapy for patients inadequately controlled on diet and exercise.	--	✔
Has not been studied in patients with a history of unexplained pancreatitis. Other antidiabetic therapies should be considered in patients with a history of pancreatitis.	✔	--
Not recommended for use in combination with any other product containing another GLP-1 receptor agonist.	✔	✔
Not for treatment of T1DM or diabetic ketoacidosis.	✔	✔
Not recommended for use in patients with gastroparesis.	✔	--
Has not been studied in combination with prandial insulin.	✔	✔

(*Prescribing information: Soliqua 2019, Xultophy 2019*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Rapid- and Short-Acting Insulins

- Clinical trials conducted with the newer insulin analogs have shown that they are at least as effective as the older insulin formulations. A large meta-analysis revealed that both insulin aspart and insulin lispro produced comparable lowering of glycosylated hemoglobin (HbA1c) in patients with T2DM compared to regular insulin *(Plank et al 2005).* In patients with T1DM, insulin lispro and insulin aspart produced small, but significant differences in lowering HbA1c compared to regular insulin. Clinical trials comparing insulin glulisine to regular insulin demonstrated similar results, with at least comparable decreases in HbA1c and a few trials reporting a significantly greater decrease in HbA1c when compared to regular insulin in patients with T1DM and T2DM *(Dailey et al 2004, Fullerton et al 2016, Garg et al 2005, Rayman et al 2007).*
- The rapid-acting analogs have demonstrated a more favorable post-prandial glycemic profile compared to regular insulin in patients with T1DM or T2DM *(Anderson et al 1997a, Chen et al 2006, Dailey et al 2004, Melo et al 2019, Raskin et al 2000, Vignati et al 1997).* Most trials reported comparable rates of hypoglycemia between rapid-acting insulin analogs and regular insulin *(Anderson et al 1997b, Bretzel et al 2004, Chen et al 2006, Colquitt et al 2003, Dailey et al 2004, Fairchild et al 2000, Garg et al 2005, Home et al 2006, McSorley et al 2002, Mortensen et al 2006, Plank et al 2005, Raskin et al 2000, Vignati et al 1997).* One large trial of patients with T1DM reported a 12% lower incidence of hypoglycemia with insulin lispro compared to regular insulin ($p < 0.001$) *(Anderson et al 1997a).* In another trial, a significantly lower frequency of nocturnal hypoglycemia was reported in patients with T2DM patients with insulin glulisine compared to regular insulin (9.1% vs 14.5%; $p = 0.029$) *(Rayman et al 2007).* A meta-analysis comparing rapid-acting agents with regular insulin in patients with T1DM found that rapid-acting agents are associated with less total hypoglycemic episodes (risk ratio [RR], 0.93; 95% confidence interval [CI], 0.87 to 0.99), nocturnal hypoglycemia (RR, 0.55; 95% CI, 0.40 to 0.76), severe hypoglycemia (RR, 0.68; 95% CI, 0.60 to 0.77), post-prandial glucose (mean difference [MD], -19.44 mg/dL; 95% CI, -21.49 to -17.39), and lower HbA1c (MD, -0.13%; 95% CI, -0.16 to -0.10) (*Melo et al 2019).* In contrast, in a Cochrane review comparing rapid-acting insulins with regular insulin in adult, non-pregnant patients with T2DM, no clear significant differences were found between the groups for all-cause mortality or hypoglycemia events (*Fullerton et al 2018*).

- Afrezza was evaluated in both T1DM and T2DM patients; in a 24-week open-label (OL), active-controlled (AC), non-inferiority trial, patients with T1DM on basal insulin were randomized to receive prandial Afrezza or insulin aspart. Afrezza met the prespecified non-inferiority margin of 0.4% reduction of HbA1c from baseline, but reductions were significantly less with Afrezza compared to insulin aspart and fewer Afrezza patients achieved a HbA1c target of < 7% *(Bode et al 2015).* T2DM patients inadequately controlled on oral antidiabetic agents (OADs) were randomized to receive Afrezza or placebo in a double-blind (DB) trial. At week 24, treatment with Afrezza provided a statistically significantly greater mean reduction in HbA1c than placebo *(Rosenstock et al 2015[a]).*
- Fiasp was evaluated in the Onset clinical trial program. Onset 1 *(Russell-Jones et al 2017)* was a 26-week, Phase 3, AC, RCT that compared Fiasp (mealtime and postmeal) to Novolog in patients with T1DM. Both mealtime and postmeal Fiasp were demonstrated to be noninferior to Novolog in change in HbA1c (Estimated treatment difference [ETD], -0.15; p < 0.0001; ETD 0.04%; p < 0.0001, respectively). Onset 2 *(Bowering et al 2017)* was a 26-week, Phase 3, DB, AC, RCT in T2DM patients on insulin and OADs. Patients were randomized to receive mealtime Fiasp (n = 345) or Novolog (n = 344). Fiasp demonstrated noninferiority to Novolog in HbA1c lowering (ETD -0.02%; p < 0.0001). Onset 3 *(Rodbard et al 2017)* was an 18-week, Phase 3, OL, RCT in T2DM patients inadequately controlled on basal insulin and OADs. Patients were randomized to receive mealtime Fiasp + basal insulin (n = 116), or basal insulin alone (n = 120). The addition of Fiasp to basal insulin demonstrated superior HbA1c lowering from baseline (ETD -0.94%; p < 0.0001 for superiority) and significantly more patients achieved an HbA1c < 7.0% (60.3% vs 18.3%; OR, 9.31; p < 0.0001); however, with the addition of Fiasp, there was an increase in the frequency of severe or blood glucose (BG)-confirmed hypoglycemic episodes (RR, 8.24; p < 0.0001) and modest weight gain.
- The safety and efficacy of Admelog, the first “follow-on” rapid-acting insulin, were evaluated in two 26-wk, Phase 3, OL, PG, RCTs in both T1DM (N = 506) (SORELLA 1; *Garg et al 2017)* and T2DM (N = 505) patients (SORELLA 2; *Derwahl et al 2018).* Patients were randomized to receive Admelog or its reference product, Humalog. Change in HbA1c in Admelog-treated patients was found to be noninferior in both trials (SORELLA 1: least squares mean difference [LSMD], 0.06%; 95% CI, -0.084 to 0.197; SORELLA 2: LSMD, -0.07%; 95% CI, -0.215 to 0.067). Rates of hypoglycemia were similar between the treatment arms in both trials.
- Head-to-head trials of rapid-acting analogs suggest comparable effectiveness in terms of decreasing HbA1c, achieving similar self-monitored glucose profiles, rates of hypoglycemia, and achieving glycemic goals in patients with T1DM *(Dreyer et al 2005, Philotheou et al 2011, Van Ban et al 2011).*

Long-Acting Insulins

- While not consistently demonstrated, data suggest that long-acting insulin analogs are superior to isophane (NPH) insulin in decreasing HbA1c, as well as the incidence of hypoglycemia in patients with T1DM and T2DM as demonstrated by the results of several active-comparator trials and meta-analyses *(Bartley et al 2008, Bazzano et al 2008, Buse et al 2009, Chase et al 2008, De Leeuw et al 2005, Fritsche et al 2003, Garber et al 2007, Haak et al 2005, Heller et al 2009, Hermansen et al 2004, Hermansen et al 2006, Home et al 2004, Horvath et al 2007, Kølendorf et al 2006, Lee et al 2012, Montañana et al 2008, Pan et al 2007, Pieber et al 2005, Philis-Tsimikas et al 2006, Raslová et al 2007, Ratner et al 2000, Riddle et al 2003, Robertson et al 2007, Rosenstock et al 2005, Russell-Jones et al 2004, Siegmund et al 2007, Standl et al 2004, Tan et al 2004, Tricco et al 2014, Vague et al 2003, Yenigun et al 2009, Yki-Järvinen et al 2000, Yki-Järvinen et al 2006).*
- The safety and efficacy of the long-acting analog Toujeo (insulin glargine U-300) have been compared to that of Lantus (insulin glargine U-100) in OL, randomized, active-controlled, parallel studies of up to 26 weeks in patients with T1DM and T2DM. The reductions in HbA1c and fasting plasma glucose with Toujeo were found to be similar to that of Lantus, including patients aged ≥ 65 years *(Home et al 2018, Bolli et al 2015, Home et al 2015, Riddle et al 2014[b], Ritzel et al 2018, Yki-Järvinen et al 2014).*
- A 2018 meta-analysis comparing Toujeo with Lantus in patients with T1DM and T2DM found that Toujeo was associated with a reduced risk of nocturnal hypoglycemia (RR, 0.81; 95% CI, 0.69 to 0.95) and a slight benefit in HbA1 reduction (effect size, -0.08; 95% CI, -0.14 to -0.01) (*Diez-Fernandez et al 2018*).
- Tresiba (insulin degludec) was evaluated in more than 5,600 T1DM and T2DM patients throughout 9 pivotal studies and 5 extension studies (BEGIN clinical program).
  - In 8 of the pivotal trials, Tresiba was non-inferior to Lantus (insulin glargine U-100) or Levemir (insulin detemir) in lowering HbA1c from baseline, with similar rates of hypoglycemia; in 5 trials, the rate of nocturnal hypoglycemia was significantly lower with Tresiba compared to Lantus or Levemir *(Davies et al 2014, Garber et al 2012, Gough et al 2013, Heller et al 2012, Mathieu et al 2013, Meneghini et al 2013[a], Onishi et al 2013, Zinman et al 2012).* It is

noteworthy that 2 of the 8 Tresiba trials resulted in a nominally lower reduction in HbA1c for Tresiba compared to the active comparator basal insulin agents *(Davies et al 2014, Heller et al 2012).* The HbA1c and hypoglycemia trends were also observed in the published extension trials *(Bode et al 2013, Davies et al 2016, Hollander et al 2015, Rodbard et al 2013).* In the ninth pivotal trial, Tresiba lowered HbA1c significantly more than oral sitagliptin 100 mg once daily in patients with T2DM who were receiving 1 or 2 concomitant background OAD agents (treatment difference, -0.43; 95% CI, -0.61 to -0.24; p < 0.001), but there were significantly more episodes of overall confirmed hypoglycemia (p < 0.0001) *(Philis-Tsimikas et al 2013).*

  - Across the BEGIN trials, a consistently increased risk of major adverse cardiovascular events (MACE) was observed with Tresiba. At the request of an FDA Advisory Committee, Novo Nordisk conducted a pre-specified meta-analysis of MACE, which included a pooled analysis of 8,068 patients from 16 Phase 3 trials conducted for Tresiba monotherapy and insulin degludec/insulin aspart (Ryzodeg). According to the 2012 analysis, there was a consistent trend towards harm in the pooled insulin degludec groups compared to active comparators (hazard ratio [HR], 1.67; 95% CI, 1.01 to 2.75). Additional post-hoc analyses consistently trended towards harm regardless of endpoint, effect measure, analysis method, and subgroup analyses *(FDA Briefing Document 2012, Novo Nordisk Briefing Document 2012).*
  - The large, DB, active-comparator DEVOTE trial was subsequently initiated to prospectively and rigorously compare the cardiovascular (CV) safety of Tresiba to Lantus in patients with T2DM at high risk for CV events. The primary composite endpoint of death from CV causes, nonfatal myocardial infarction (MI), or nonfatal stroke occurred in 8.5% of the Tresiba group and 9.3% of the Lantus group (HR, 0.91; 95% CI, 0.78 to 1.06; p < 0.001 for non-inferiority), confirming non-inferiority of Tresiba to Lantus in terms of CV safety. Tresiba also demonstrated statistically significantly lower rates of severe hypoglycemia (odds ratio [OR] for severe hypoglycemic events, 0.73; 95% CI, 0.60 to 0.89; p < 0.001 for superiority) *(Marso et al 2017).*
- The efficacy of Tresiba vs Lantus in reducing the rate of symptomatic hypoglycemic episodes in patients with T1DM and T2DM was examined in the SWITCH 1 and SWITCH 2 trials, respectively. These 65-week, DB, crossover trials enrolled patients with hypoglycemia risk factors to receive Tresiba or Lantus. In both trials, Tresiba was found to cause fewer symptomatic hypoglycemic episodes (SWITCH 1: estimated rate ratio [ERR], 0.89; p < 0.001; SWITCH 2: ERR, 0.70; p < 0.001) and nocturnal hypoglycemic episodes (SWITCH 1: ERR, 0.64; p < 0.001; SWITCH 2: ERR, 0.58; p < 0.001) during the maintenance period than Lantus *(Lane et al 2017, Wysham et al 2017)*.
- A meta-analysis of 18 trials with 16,791 patients compared the safety and efficacy of Tresiba to Lantus, and similarly found that Tresiba was associated with a significant reduction in risk for all confirmed hypoglycemia during the maintenance treatment period (ERR, 0.81; 95% CI, 0.72 to 0.92; p=0.001), nocturnal confirmed hypoglycemia during the entire (ERR, 0.71; 95% CI, 0.63 to 0.80; p,0.001) and maintenance treatment periods (ERR, 0.65; 95% CI, 0.59 to 0.71; p,0.001), and a significantly lower fasting plasma glucose level (ETD -0.28 mmol/L; 95% CI, -0.44 to -0.11 mmol/L; p=0.001). Tresiba was found to reduce the incidence of severe hypoglycemia in patients with T2D, but not T1D (*Zhang et al 2018)*.
- Additionally, Tresiba was evaluated for safety and efficacy in pediatric patients (ages 1 to 17) (N = 350) with T1DM in a 26-week, randomized, OL trial. Tresiba was non-inferior to Lantus with a difference in HbA1c reduction from baseline of 0.15% (95% CI, -0.03 to 0.33%) between the groups (pre-specified non-inferiority margin, 0.4%) *(Tresiba prescribing information 2016).*
- The safety and efficacy of Basaglar (insulin glargine U-100) compared to Lantus (insulin glargine U-100) were evaluated in 2 pivotal studies enrolling 534 and 744 patients with T1DM (ELEMENT 1 trial) and T2DM (ELEMENT 2 trial), respectively. Both trials were multicenter, parallel group, randomized controlled trials (RCTs); ELEMENT 1 was OL and ELEMENT 2 was DB. Both trials were conducted over 24 weeks; however, ELEMENT 1 also included a 28-week comparative safety extension period. Mealtime insulin lispro was administered 3 times daily in both groups within the ELEMENT 1 trial. OAD medication was permitted in conjunction with insulin treatment within the ELEMENT 2 trial. The primary efficacy endpoint tested the non-inferiority of agents by the reduction in HbA1c from baseline to 24 weeks. In both ELEMENT 1 and ELEMENT 2, Basaglar and Lantus had similar and significant (p < 0.001) within-group decreases in HbA1c values from baseline. Basaglar met non-inferiority criteria compared to Lantus for change in HbA1c from baseline to 24 weeks in both trials (ELEMENT 1: -0.35% vs -0.46%, respectively; LSMD, 0.108%; 95% CI, -0.002 to 0.219; p > 0.05; ELEMENT 2: -1.29% vs -1.34%, respectively; LSMD, 0.052%; 95% CI, -0.07 to 0.175; p > 0.05). There were no statistically significant differences between treatment groups for the rate of each category of hypoglycemia (total, nocturnal, severe) at 24 or 52 weeks in ELEMENT 1 and at 24 weeks in ELEMENT 2 (p > 0.05 for all treatment comparisons). No significant differences between treatment groups were seen for change from baseline in body weight (ELEMENT 1, week 24 and 52: both p > 0.05; ELEMENT 2, week 24: p > 0.05) *(Blevins et al 2015, Rosenstock et al*

2015[b]). Basaglar has also been compared to Lantus when used in combination with OADs in patients with T2DM. ELEMENT 5 was a 24-week trial and included predominately Asian (48%) and White (46%) patients. Basaglar met non-inferiority criteria compared to Lantus for change in HbA1c from baseline to 24 weeks (-1.25% vs -1.22%; LSMD, -0.04%; 95% CI, -0.22 to 0.15). Other 24-week efficacy and safety outcomes were similar between groups (*Pollom et al 2019*).

- At this time, there is a lack of substantial head-to-head data demonstrating the superiority of one long-acting insulin analog over another. When comparing the long-acting insulin analogs head-to-head, several trials have demonstrated non-inferiority among the products when used in the management of T1DM and as add-on therapy in patients with T2DM *(Heller et al 2009, Hollander et al 2008, Pieber et al 2007, Raskin et al 2009, Rosenstock et al 2008, Swinnen et al 2010).*
  - In one head-to-head trial of Lantus and metformin vs Levemir and metformin, Lantus had greater HbA1c lowering, but Levemir demonstrated less weight gain and hypoglycemia *(Meneghini et al 2013[b]).*
  - A 2011 Cochrane review (included 4 trials; N = 2250) concluded that Lantus and Levemir are equally effective in achieving and maintaining glycemic control (HbA1c). The review also found no differences in overall, nocturnal, and severe hypoglycemic events *(Swinnen et al 2011).* A 2018 meta-analysis similarly found no differences in HbA1c reduction between insulin degludec, determir, or glargine in T1DM and T2DM patients, but the incidence of hypoglycemia was less with degludec as compared to glargine (nocturnal hypoglycemia; T1DM: RR, 0.68; 95% CI, 0.56 to 0.81; T2DM: RR, 0.73; 95% CI, 0.65 to 0.82) (*Holmes et al 2018).*
  - To further inform the differences between basal insulin agents, a network meta-analysis (included 41 trials, of which 25 trials included patients on basal-oral therapy; N = 15,746) evaluated the safety and efficacy of Toujeo (insulin glargine U-300) vs other basal insulin therapies in the treatment of T2DM. The authors found that the change in HbA1c was comparable between Toujeo and Levemir (difference, -0.08; 95% credible interval [CrI], -0.4 to 0.24) and Tresiba (difference, -0.12; CrI, -0.42 to 0.2). Additionally, there were no differences in nocturnal or documented symptomatic hypoglycemic events *(Freemantle et al 2016).*

Combination Insulins

- A direct comparative trial evaluating 2 types of premixed biphasic insulin (insulin lispro 50/50 and insulin aspart 70/30) demonstrated similar results in terms of reducing HbA1c *(Domeki et al 2014).* Another trial comparing biphasic insulin to basal plus prandial insulin in T2DM demonstrated that basal plus prandial insulin therapy was slightly more effective than premixed insulin with less hypoglycemia *(Riddle et al 2014[a]).*

Other Evidence

- A systematic review that included 11 studies and compared the efficacy and safety of biosimilar insulins (Basaglar and Admelog) to their reference products found comparable pharmacokinetic and/or pharmacodynamic parameters, clinical efficacy and immunogenicity, and adverse events between the biosimilar agents and their reference products (*Tieu et al 2018)*.
- Insulin therapies have been compared to GLP-1 agonists with mixed study results. A study comparing glycemic control with Lantus vs exenatide demonstrated that better glycemic control was sustained with exenatide *(Diamant et al 2012).* Other studies have demonstrated that GLP-1 agonists are statistically non-inferior to Lantus for change in HbA1c *(Inagaki et al 2012, Weissman et al 2014).* Studies comparing the addition of GLP-1 agonists to Lantus were found to be non-inferior to the addition of thrice daily insulin lispro to Lantus *(Diamant et al 2014, Rosenstock et al 2014).*
- In terms of clinical outcomes, the Diabetes Control and Complications Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) have demonstrated that intensive glycemic control with insulin significantly reduces the rate of onset and progression of diabetic complications when compared to standard therapy (DCCT 1993, UKPDS 1998). Neither trial indicated the specific insulin formulations utilized; however, in the UKPDS, the risk reduction in microvascular complications was related more toward tight glycemic control rather than to one specific therapy (UKPDS, 1998).

Combination Products: Long-Acting Insulin and GLP-1 Receptor Agonist

- A 2017 systematic review and meta-analysis evaluated the efficacy and safety of insulin degludec/liraglutide vs insulin glargine/lixisenatide treatment in T2DM (*Cai 2017*). The analysis included 8 trials. The absolute HbA1c change relative to baseline with insulin glargine/lixisenatide was -1.50% and -1.89% with insulin degludec/liraglutide; comparisons

between the groups revealed no significant differences. Additionally, there was no significant difference between the groups with regard to body weight changes.

Soliqua (insulin glargine/lixisenatide)

- The efficacy and safety of insulin glargine/lixisenatide were evaluated over 30 weeks in 2 Phase 3, active-comparator (AC), OL, RCTs, titled the LIXILAN trials:
  - T2DM patients uncontrolled on basal insulin: The LIXILAN-L trial was a 2-treatment arm study in 731 T2DM patients. At baseline, patients were receiving basal insulin for at least 6 months at stable daily doses ± OADs. Patients who had an insulin glargine daily dose of 20 to 50 U were randomized to either insulin glargine/lixisenatide 100/33 (n = 366) or insulin glargine 100 U/mL (n = 365). The maximum dose of insulin glargine allowed in the trial was 60 U for both groups. For the primary endpoint, HbA1c reduction after 30 weeks of treatment, the LSMD between insulin glargine/lixisenatide and insulin glargine was statistically significant favoring combination therapy over monotherapy (LSMD, −0.5%; 95% CI, −0.6 to −0.4; p < 0.0001) *(Aroda et al 2016, FDA briefing document [Soliqua] 2016, FDA summary review [Soliqua] 2016).*
  - Comparative data vs GLP-1 receptor agonists: The LIXILAN-O trial was a 3-treatment arm study in 1167 patients with T2DM who were inadequately controlled on metformin ± OADs. Patients who met HbA1c goals based on prior therapy were then randomized to either insulin glargine/lixisenatide 100/33 (n = 468), insulin glargine 100 U/mL (n = 466), or lixisenatide (n = 233). The maximum dose of insulin glargine allowed in the trial was 60 U. For the primary endpoint, insulin glargine/lixisenatide required a non-inferior HbA1c reduction over 30 weeks compared to insulin glargine (non-inferiority upper margin of 0.3%). After 30 weeks of treatment, the LSMD in HbA1c reduction met non-inferiority compared to insulin glargine (LSMD, −0.3%; 95% CI, −0.4 to −0.2; p < 0.0001) and also demonstrated superiority for the endpoint (p < 0.0001). At week 30, the LSMD in HbA1c reduction between insulin glargine/lixisenatide and lixisenatide was also statistically significant (LSMD, −0.8%; 95% CI, −0.9 to −0.7; p < 0.0001) *(Rosenstock et al 2016, FDA briefing document [Soliqua] 2016, FDA summary review [Soliqua] 2016).*
  - Weight and hypoglycemic events: Treatment with insulin glargine/lixisenatide was associated with mean weight losses of up to 0.7 kg from baseline across the aforementioned trials. Hypoglycemic rates were comparable for insulin glargine/lixisenatide and insulin glargine; however, fewer lixisenatide-treated patients experienced documented symptomatic hypoglycemic events compared to insulin glargine/lixisenatide (6.4% vs 25.6%, respectively) *(Aroda et al 2016, Rosenstock et al 2016, FDA summary review [Soliqua] 2016).*

Xultophy (insulin degludec/liraglutide)

- The efficacy and safety of insulin degludec/liraglutide were evaluated over 26 weeks in 9 Phase 3, parallel-group, AC, RCTs, titled the DUAL trials *(Xultophy dossier 2016).* Currently, results from DUAL I through VII are available, and DUAL VIII and IX trials are ongoing; therefore, these trials will not be discussed. The DUAL I, IV, VI, and VII trials were conducted in patients uncontrolled while administered OADs, and since insulin degludec/liraglutide is not FDA-approved for use in patients previously uncontrolled on OADs, these trials have been excluded from this review:
  - T2DM patients uncontrolled on basal insulin and OADs:
    - The DUAL II trial was a 2-treatment arm, DB study in 413 T2DM patients that compared insulin degludec/liraglutide (n = 207) to insulin degludec (n = 206). Prior to randomization, uncontrolled patients were receiving basal insulin (20 to 40 U) and metformin ± OADs. The maximum dose of insulin degludec allowed in the trial was 50 U, and the maximum allowed dose of liraglutide was 1.8 mg. HbA1c reduction from baseline after 26 weeks of treatment, the primary endpoint, was 1.9% for insulin degludec/liraglutide and 0.9% for insulin degludec. The estimated treatment difference (ETD) for HbA1c statistically favored combination injectable therapy over monotherapy (ETD, −1.1%; 95% CI, −1.3 to −0.8; p < 0.0001) *(Buse et al 2014).*
    - The DUAL V trial was a 2-treatment arm, OL, non-inferiority study in 557 T2DM patients that compared insulin degludec/liraglutide (n = 278) to insulin glargine (n = 279) and metformin. Prior to randomization, uncontrolled patients were receiving insulin glargine (20 to 50 U) and metformin. The trial maximum dose of insulin degludec/liraglutide was 50 U of insulin degludec and 1.8 mg of liraglutide; there was no maximum dose for insulin glargine. For the primary endpoint, an upper bound of the 95% CI < 0.3% was required for non-inferiority, which was achieved. The HbA1c reduction from baseline after 26 weeks of treatment was -1.8% for insulin degludec/liraglutide and -1.1% for insulin glargine. The ETD for HbA1c statistically favored combination injectable therapy over monotherapy (ETD, −0.59%; 95% CI, −0.74 to −0.45; p < 0.001 for non-inferiority) *(Lingvay et al 2016).*
  - T2DM patients uncontrolled on GLP-1 receptor agonists:

- The DUAL III trial was a 2-treatment arm, OL study in 438 T2DM patients that compared insulin degludec/liraglutide (n = 292) to the currently administered maximum dose of GLP-1 receptor agonist (n = 146) and metformin ± OAD therapy. Prior to randomization, patients were receiving maximum doses of liraglutide once daily or exenatide twice daily, according to the local labeling, and metformin ± OADs. The trial maximum dose of insulin degludec/liraglutide was 50 U of insulin degludec and 1.8 mg of liraglutide. HbA1c reduction from baseline after 26 weeks of treatment, the primary endpoint, was 1.4% for insulin degludec/liraglutide and 0.3% for unchanged doses of GLP-1 receptor agonists. The ETD for HbA1c statistically favored combination injectable therapy over monotherapy (ETD, −0.94%; 95% CI, −1.1 to −0.8; p < 0.001) *(Linjawi et al 2017).*

- Weight and hypoglycemic events: Treatment with insulin degludec/liraglutide was associated with mean weight losses of up to 2.7 kg and weight gain of 2 kg from baseline across the aforementioned trials. Hypoglycemia rates with insulin degludec/liraglutide were comparable to insulin degludec. However, compared to GLP-1 receptor agonists, the estimated rate ratio (ERR) was 25.36 (95% CI, 10.63 to 60.51; p < 0.001), demonstrating a statistically significantly higher rate of hypoglycemic episodes in the insulin degludec/liraglutide group vs the GLP-1 receptor agonist group. Conversely, the ERR favored insulin degludec/liraglutide over insulin glargine with a statistically significantly higher rate of hypoglycemic episodes in the insulin glargine group (ERR, 0.43; 95% CI, 0.3 to 0.61; p < 0.001) *(Buse et al 2014, Lingvay et al 2016, Linjawi et al 2017, Xultophy dossier 2016).*

Cardiovascular (CV) outcomes

- A number of key CV studies have been conducted with insulin glargine, insulin degludec, liraglutide, and lixisenatide; of these, only liraglutide has demonstrated CV-positive outcomes. Studies with adequate power have not been conducted with the long-acting insulin and GLP-1 receptor agonist combination products.
  - The ORIGIN trial was a randomized trial without blinding conducted in 12,612 patients with CV risk factors plus impaired fasting glucose, impaired glucose tolerance, or T2DM. Patients were randomized to receive insulin glargine or standard of care therapy, which included continuing their pre-existing glycemic control regimen. CV risk factors at baseline included previous MI, stroke, angina, or revascularization. After a median 6.2 year follow-up, no significant difference in the co-primary outcomes of nonfatal MI, nonfatal stroke, or death from CV causes, and these events plus revascularization or hospitalization for heart failure (HF), were observed. The rates of incident CV outcomes were similar in the insulin glargine and standard care groups: 2.94 and 2.85 per 100 person-years, respectively, for the first co-primary outcome (HR, 1.02; 95% CI, 0.94 to 1.11; p = 0.63) and 5.52 and 5.28 per 100 person-years, respectively, for the second co-primary outcome (HR, 1.04; 95% CI, 0.97 to 1.11; p = 0.27) *(Gerstein et al 2012).*
  - ELIXA, a multi-center (MC), DB, randomized, placebo-controlled (PC) trial (N = 6068) was conducted to evaluate the long-term effects of lixisenatide vs placebo on CV outcomes in patients with T2DM who had a recent acute coronary syndrome event within 180 days of screening. The primary endpoint was a composite of the first occurrence of any of the following: death from CV causes, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina. The median follow-up was 25 months. It was found that the primary endpoint event occurred in 13.4% of patients in the lixisenatide group and 13.2% in the placebo group (HR, 1.02; 95% CI, 0.89 to 1.17), which demonstrated non-inferiority of lixisenatide to placebo (p < 0.001), but did not demonstrate superiority (p = 0.81). The rates of the individual CV components of the primary endpoint were similar between the lixisenatide and placebo groups *(Pfeffer et al 2015)*.
  - LEADER, a MC, DB, randomized, PC trial (N = 9340) was conducted to evaluate the long-term effects of liraglutide vs placebo on CV outcomes in patients with T2DM and high CV risk. The median follow-up was 3.8 years. It was found that the primary composite outcome (CV death, nonfatal MI, or nonfatal stroke) occurred in fewer patients in the liraglutide group (13%) vs the placebo group (14.9%) (HR, 0.87; 95% CI, 0.78 to 0.97; p < 0.001 for noninferiority; p = 0.01 for superiority). Mortality from CV causes was lower in the liraglutide group (4.7%) vs the placebo group (6%) (HR, 0.78; 95% CI, 0.66 to 0.93; p = 0.007). Additionally, the rate of death from any cause was lower in the liraglutide group (8.2%) vs the placebo group (9.6%) (HR, 0.85; 95% CI, 0.74 to 0.97; p = 0.02).The rates of nonfatal MI, nonfatal stroke, and hospitalization for heart failure were nonsignificantly lower in the liraglutide group than in the placebo group *(Marso et al 2016).*

CLINICAL GUIDELINES

- Insulin is the mainstay of therapy for adult and pediatric patients with T1DM. Current guidelines recommend that most people with T1DM be treated with multiple daily injections (3 to 4 injections per day of basal and prandial insulin) or continuous subcutaneous insulin infusion. Either multiple daily injections or a continuous infusion can be considered,

with some recent data demonstrating modest advantages with pump therapy such as increased HbA1c lowering and reduced severe hypoglycemia rates. In addition, the guidelines suggest that most people with T1DM should use insulin analogs to reduce hypoglycemia risk *(ADA 2019, Chiang 2018, Handelsman et al 2015).*

- According to current clinical guidelines regarding the management of T2DM, consideration should be given to initiating insulin therapy (with or without other agents) at the outset of treatment in newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA1c. Insulin therapy is usually started once patients are not achieving glycemic goals with noninsulin therapies *(ADA 2019, Davies 2018, Garber et al 2019, Handelsman et al 2015).*
- Guidelines suggest that an insulin treatment program be designed specifically for an individual patient, to match the supply of insulin to his or her dietary/exercise habits and prevailing glucose trends, as revealed through self-monitoring. Anticipated glucose-lowering effects should be balanced with the convenience of the regimen in the context of an individual's specific therapy goals *(ADA 2019, Davies 2018, Garber et al 2019, Handelsman et al 2015).*
  - The American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACA) T2DM management algorithm identifies lifestyle therapies such as weight loss, comprehensive management of lipids and blood pressure, safety, and simplicity as crucial factors of a T2DM regimen. The guideline notes that patients are unlikely to achieve glycemic targets with a third oral antihyperglycemic agent if their HbA1c level > 8% or in those with long-standing disease. A GLP-1 agent may be considered, but many patients will eventually require insulin. The guideline suggests basal (long-acting) insulin for those who are symptomatic with an entry HbA1c > 9.0%. Basal insulin analogs are preferred over NPH. If an intensified regimen is needed, the addition of a GLP-1 agonist, SGLT2 inhibitor, or DPP-4 inhibitor can be considered. The combination of basal insulin with a GLP-1 receptor agonist may offer greater efficacy than the oral agents. Prandial (rapid-acting) insulin prior to meals can be considered when the total daily dose of basal insulin exceeds 0.5 U/kg *(Garber et al 2019).*
    - The guideline also states that newer basal insulin formulations (glargine U-300, and degludec U-100 and U-200) have more prolonged and stable pharmacokinetic and pharmacodynamic characteristics than glargine U-100 and detemir. RCTs have reported equivalent glycemic control and lower rates of severe or confirmed hypoglycemia, particularly nocturnal hypoglycemia, compared to glargine U-100 and detemir insulin; however, no recommendation for specific insulin products is given.
  - The ADA and European Association for the Study of Diabetes (EASD) offer similar emphasis on lifestyle modifications and CV disease risk management. In the 2019 update to the ADA standards of medical care in diabetes, the pharmacologic treatment of T2DM was significantly changed to align with the ADA-EASD consensus report. The ADA guideline states that insulin therapy (with or without additional agents) should be initiated in patients with newly diagnosed T2DM with evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when HbA1c levels (≥ 10%) or blood glucose levels (≥ 300 mg/dL) are very high. The ADA and EASD recommend that, in most patients who require an injectable therapy, a GLP-1 agonist should be the first choice ahead of insulin. Due to the progressive nature of the disease, patients may eventually require insulin therapy (*ADA 2019, Davies 2018)*.
    - Certain patient factors can influence the choice of insulin therapy. For patients with established atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CKD), insulin therapies with demonstrated CV disease safety (degludec and glargine U-100) should be considered. For patients with hypoglycemia issues, a basal insulin with lower risk of hypoglycemia should be considered (risk of hypoglycemia: degludec/glargine U-300 < glargine U-100/detemir < NPH).
    - A basal insulin/GLP-1 agonist combination can be considered when first intensifying therapy to injectable products in patients with a HbA1c > 10% and/or if the patient is above the target HbA1c by > 2%. The combination can also be considered in patients who require additional control after the addition of a GLP-1 agonist in the intensification algorithm.
- The American College of Cardiology published an expert consensus decision pathway for patients with T2DM and ASCVD (*Das 2018*). For the GLP-1 agonists, liraglutide is the only agent in the class with proven benefits of reducing CV events. In contrast, lixisenatide is not associated with a reduction in ASCVD event risk. Thus, both the ACC pathway and ADA guideline considers liraglutide as the preferred GLP-1 agent (*ADA 2019, Das 2018*).

SAFETY SUMMARY

Insulins

- Contraindications:

- Insulins are contraindicated during episodes of hypoglycemia and with hypersensitivity to any ingredient of the product.
- In addition, Afrezza is also contraindicated in patients with chronic lung disease, such as asthma or chronic obstructive pulmonary disease (COPD), because of the risk of acute bronchospasm.

- Boxed Warnings:
  - Afrezza has a Boxed Warning for the risk of acute bronchospasm in patients with chronic lung disease. Before initiating Afrezza, a detailed medical history, physical examination, and spirometry should be performed to identify potential lung disease in all patients.
- Warnings/Precautions:
  - Insulin pens must never be shared between patients, even if the needle is changed. Patients using insulin vials must never reuse or share needles or syringes with another person. Sharing poses a risk for transmission of blood-borne pathogens.
  - Frequent glucose monitoring and insulin dose reduction may be required in patients with renal or hepatic impairment.
  - All insulins can cause hypokalemia, which if untreated, may result in respiratory paralysis, ventricular arrhythmia, and death.
  - Long-term use of insulin can cause lipodystrophy at the site of repeated insulin injections.
  - Accidental mix-ups between basal insulin products and other insulins, particularly rapid-acting insulins, have been reported. To avoid medication errors, patients should be instructed to always check the insulin label before each injection.
  - Severe, life-threatening, generalized allergy, including anaphylaxis, can occur with insulin products. If hypersensitivity reactions occur, the insulin product should be discontinued.
  - Administration of Humulin R U-500 in syringes other that U-500 insulin syringes has resulted in dosing errors. Patients should be prescribed U-500 syringes for use with Humulin R U-500 vials. The prescribed dose should always be expressed in units of insulin.
  - Afrezza has additional respiratory-related warnings and precautions associated with its use including acute bronchospasm in patients with chronic lung disease, decline in pulmonary function, and lung cancer.
- Adverse Events (AEs):
  - Hypoglycemia is the most commonly observed AE. Hypoglycemia can impair concentration ability and reaction time which may place an individual and others at risk in situations where these abilities are important. Severe hypoglycemia can cause seizures, may be life-threatening, or cause death. Self-monitoring of blood glucose plays an essential role in the prevention and management of hypoglycemia.
  - Weight gain, sodium retention and edema, and injection site reactions can occur.
  - Additional AEs observed with the inhaled insulin, Afrezza, include cough, throat pain or irritation, headache, diarrhea, productive cough, fatigue, nausea, decreased pulmonary function test, bronchitis, and urinary tract infection.
- Drug Interactons:
  - β-blockers, clonidine, guanethidine, and reserpine may mask hypoglycemic reactions.
  - Thiazolidinediones can cause dose-related fluid retention, particularly when used in combination with insulin.
  - Refer to the prescribing information for all drugs that can increase or reduce the glucose-lowering ability of insulin.
- Risk Evaluation and Mitigation Strategy (REMS)
  - The FDA previously required a communication plan to inform health care professionals about the serious risk of acute bronchospasm associated with Afrezza; however, in April 2018, the FDA determined that the communication plan has been completed and REMS is no longer needed. (https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2018/022472Orig1s017ltr.pdf).

Combination, Long-Acting Insulin and GLP-1 Receptor Agonist

- Contraindications:
  - Both combination agents are contraindicated in patients with hypersensitivity to any component of the products and during episodes of hypoglycemia.
  - Xultophy (insulin degludec/liraglutide) is also contraindicated in and has a boxed warning for patients with a personal or family history of medullary thyroid carcinoma (MTC) or in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).
- Warnings/Precautions:

- Warnings and precautions are consistent with each individual agent and include pancreatitis, serious hypersensitivity reactions/allergic reactions, hypoglycemia or hyperglycemia, the potential for overdose due to medication errors, acute kidney injury, hypokalemia, and the potential for fluid retention and heart failure with use of thiazolidinediones. Prefilled pens should never be shared between patients (even if the needle is changed) due to the risk of transmission of blood-borne pathogens.
- Additional warnings and precautions for Soliqua include immunogenicity risks associated with the development of antibodies to insulin glargine and lixisenatide resulting in a loss of glycemic control and a lack of clinical studies showing macrovascular risk reduction. Additional warnings for Xultophy include a potential increased risk for acute gallbladder disease.

- AEs:
  - The most common AEs reported with these agents include nausea, nasopharyngitis, diarrhea, headache, and upper respiratory tract infection.
  - Additional common AEs include hypoglycemia and allergic reactions with Soliqua and increased lipase with Xultophy.
- Drug Interactions:
  - The GLP-1 receptor agonist components may cause delayed gastric emptying of oral medications. Certain medications may require administration 1 hour before (ie, antibiotics, acetaminophen, oral contraceptives, or other medications dependent on threshold concentrations for efficacy) or 11 hours after (ie, oral contraceptives) administration of the GLP-1 receptor agonist.
  - Monitor use closely when administered concomitantly with other medications that may affect glucose metabolism.
  - Antiadrenergic medications (ie, beta blockers, clonidine, guanethidine, and reserpine) may mask the signs and symptoms of hypoglycemia.
- REMS programs:
  - The FDA previously required a REMS program for Xultophy, which included a communication plan for alerting healthcare professionals about the risk of acute pancreatitis and the potential risk of MTC; however, in December 2017, the FDA determined that the communication plan is no longer necessary and that a REMS is no longer required (https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2017/208583Orig1s001ltr.pdf).
- Lixisenatide and liraglutide slow gastric emptying. Patients with gastroparesis were excluded from trials; therefore, agents are generally not recommended in cases of severe gastroparesis.

DOSING AND ADMINISTRATION

- Injection sites should be rotated within the same region (abdomen, thigh or upper arm) from one injection to the next to reduce the risk of lipodystrophy.
- Dose adjustments in patients with renal and/or hepatic dysfunction may be required with the insulin products.
- In elderly patients, caution should be taken with initial insulin dosing and subsequent dose changes to avoid hypoglycemic reactions.

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
Rapid-Acting Insulins				
Admelog (insulin lispro)	100 U/mL: SoloStar pen, vial	SC, IV	Administer within 15 minutes before a meal or immediately after a meal. Use in a regimen with intermediate- or long-acting insulin when administered by SC injection.	Safety and efficacy in children < 3 years with T1DM and in children with T2DM have not been established. Use SoloStar pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Afrezza (insulin human)	Single-use cartridges: 4, 8, 12 units Available in cartons	Inhalation	Generally given 3 times daily at the beginning of a meal	Safety and efficacy in pediatric patients or in renal or hepatic dysfunction have not been established.

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
	with a single dosage and in titration packs with multiple dosages			
Apidra (insulin glulisine)	100 U/mL: SoloStar pen, vial	SC, IV	Administer within 15 minutes before a meal or within 20 minutes after starting a meal. Dose and frequency are individualized per patient needs. Use in a regimen with intermediate- or long-acting insulin when administered by SC injection.	Safety and efficacy in children < 4 years with T1DM or in children with T2DM have not been established. Use SoloStar pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Fiasp (insulin aspart)	100 U/mL: FlexTouch pen, vial, PenFill cartridges	SC, IV	Administer at the start of a meal or within 20 minutes after starting a meal. Use in a regimen with intermediate- or long-acting insulin when administered by SC injection.	Safety and efficacy have not been established in children. Use FlexTouch pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Humalog (insulin lispro)	100 U/mL: Cartridge, KwikPen, Junior KwikPen, vial 200 U/mL: KwikPen	SC, IV (U-100 only)	Administer within 15 minutes before a meal or immediately after a meal. Use in a regimen with intermediate- or long-acting insulin when administered by SC injection.	Safety and efficacy in children < 3 years with T1DM and in children with T2DM have not been established. Use KwikPen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Novolog (insulin aspart)	100 U/mL: Cartridge (PenFill), FlexPen, Vial	SC, IV	Novolog: Should be injected immediately (within 5 to 10 minutes) before a meal. Use in a regimen with intermediate- or long-acting insulin when administered by SC injection.	Safety and efficacy in children < 2 years with T1DM and in children with T2DM have not been established. Use FlexPen and PenFill cartridges with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Short-Acting Insulins				
Humulin R (insulin, regular, human recombinant)	100 U/mL: Vial 500 U/mL KwikPen, vial	SC, IV (U-100 only)	When given SC, generally given 3 or more times daily before meals (within 30 minutes). U-500: Generally given 2 to 3 times daily before meals.	U-500: well-controlled studies in children not available. Dosing in pediatric patients must be individualized. Dose conversion should not be performed when using the U-

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
			U-100: Often used concomitantly with intermediate- or long-acting insulin when administered by SC injection.	500 KwikPen or a U-500 insulin syringe. Only a U-500 insulin syringe should be used with the Humulin U-500 vial. Use KwikPen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Novolin R Novolin R ReliOn (insulin, regular, human recombinant)	100 U/mL: Vial	SC, IV	Administration should be followed by a meal within 30 minutes of administration. Often used in combination with intermediate- or long-acting insulin when administered by SC injection.	Safety and efficacy in children < 2 years with T1DM or in children with T2DM have not been established. Use in pumps is not recommended due to risk of precipitation.
Intermediate-Acting Insulins				
Humulin N (insulin, NPH, human recombinant isophane)	100 U/mL: KwikPen, vial	SC	Generally given in 1 to 2 injections per day 30 to 60 minutes before a meal or bedtime.	Has not been studied in children. Dosing in pediatric patients must be individualized. Use KwikPen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Novolin N Novolin N ReliOn (insulin, NPH, human recombinant isophane)	100 U/mL: Vial	SC	Generally given in 1 to 2 injections per day 30 to 60 minutes before a meal or bedtime.	
Long-Acting Insulins				
Basaglar (insulin glargine)	100 U/mL: KwikPen	SC	Daily May be administered at any time of day, but at same time every day.	Safety and efficacy in children < 6 years with T1DM and in children with T2DM have not been established. Use with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Lantus (insulin glargine)	100 U/mL: SoloStar pen, vial	SC	Daily May be administered at any time of day, but at same time every day.	Safety and efficacy in children < 6 years with T1DM and in children with T2DM have not been established. Use SoloStar pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Levemir (insulin	100 U/mL:	SC	Daily to twice daily	Safety and efficacy in children <

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
detemir)	FlexTouch pen, vial		Once daily administration should be given with evening meal or at bedtime. Twice daily administration should be given in the morning and then 12 hours later with evening meal or at bedtime.	2 years with T1DM and in children with T2DM have not been established. Use FlexTouch pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Toujeo (insulin glargine U-300)	300 U/mL: SoloStar pen, Max SoloStar pen	SC	Daily Administer at the same time each day.	Safety and efficacy in children have not been established. To minimize the risk of hypoglycemia, the dose of Toujeo should be titrated no more frequently than every 3 to 4 days. The Toujeo Max SoloStar pen carries 900 U of Toujeo U-300 (twice as many as the regular SoloStar pen) and is recommended for patients that require at least 20 U per day Use with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Tresiba (insulin degludec)	100 U/mL: FlexTouch pen, vial 200 U/mL: FlexTouch pen	SC	Daily May be administered at any time of day (should be same time of day in pediatric patients).	Safety and efficacy in children < 1 year have not been established (use in children ≥ 1 year with T2DM is supported by evidence from adult T2DM studies). The recommended number of days between dose increases is 3 to 4 days. Pediatric patients requiring < 5 units daily should use the U-100 vial. Use FlexTouch pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Combination Insulins, Rapid-Acting and Intermediate-Acting				
Humalog Mix 50/50 Humalog Mix 75/25	100 U/mL: KwikPen, vial	SC	Administer within 15 minutes before meals. Typically	Safety and efficacy in children have not been established.

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
(insulin lispro protamine/insulin lispro)			dosed twice daily.	Use Humalog Mix KwikPen and Novolog Mix FlexPen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Novolog Mix 70/30 (insulin aspart protamine/insulin aspart)	100 U/mL: FlexPen, vial	SC	Twice daily T1DM: administer within 15 minutes before meals T2DM: administer within 15 minutes before or after meal	
Combination Insulins, Short-Acting and Intermediate-Acting				
Humulin 70/30 (NPH, human insulin isophane/regular human insulin)	100 U/mL: KwikPen, vial	SC	Twice daily 30 to 45 minutes before a meal	Safety and efficacy in children have not been established. Use KwikPen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Novolin 70/30 Novolin 70/30 ReliOn (NPH, human insulin isophane/regular human insulin)	100 U/mL: FlexPen, vial	SC	Twice daily 30 to 60 minutes before a meal	
Combination Products, Long-Acting Insulin and GLP-1 Receptor Agonist				
Soliqua 100/33 (insulin glargine/lixisenatide)	100 U/mL; 33 mcg/mL: SoloStar pen	SC	Once daily within the hour prior to the first meal of the day	The pen delivers doses from 15 to 60 U of insulin glargine with each injection. Not recommended for use in end-stage renal disease (ESRD). Frequent BG monitoring and dose adjustment may be necessary in hepatic impairment.
Xultophy 100/3.6 (insulin degludec/liraglutide)	100 U/mL; 3.6 mg/mL: pen	SC	Once daily at the same time each day with or without food	The pen delivers doses from 10 to 50 U of insulin degludec with each injection. Has not been studied in patients with renal or hepatic impairment.

Abbreviations: BG = blood glucose, IV = intravenous, SC = subcutaneous, T1DM = type 1 diabetes mellitus, T2DM = type 2 diabetes mellitus, U = unit

(Clinical Pharmacology 2019)

*Dose and frequency of insulin products should be individualized per patient needs.
See the current prescribing information for full details

CONCLUSION

Insulins

- The insulin products are approved for use in the management of both T1DM and T2DM. The primary differences between commercially available insulin products revolve around pharmacodynamic and pharmacokinetic properties, particularly onset and duration of action.
- Individual insulin products are classified by their onset and duration of actions and may fall into one of four categories: rapid-, short-, intermediate-, or long-acting insulins. Insulin therapy is usually administered by SC injection, which allows for prolonged absorption and less pain compared to IM injection. No generic insulin products are currently available.
- Afrezza is a rapid-acting inhaled insulin. The inhalation route offers a less invasive alternative route of administration and improved convenience of administration compared with injectable rapid-acting insulins. Due to this different route of administration, the most common AEs associated with Afrezza in clinical trials were hypoglycemia, cough, and throat pain or irritation.
- The safety and efficacy of insulin therapy in the management of diabetes are well established. Clinical trials have demonstrated that the newer rapid- and long-acting insulin analogs are as effective as regular and isophane (NPH) insulin in terms of glucose management. The data also suggest that long-acting insulin analogs are superior to NPH in decreasing HbA1c and are associated with a lower incidence of hypoglycemic events. Furthermore, head-to-head data do not consistently demonstrate the superiority of one rapid- or long-acting insulin analog over another.
- In terms of clinical outcomes, intensive glycemic control with insulin has been shown to significantly reduce the rate of onset and progression of diabetic complications when compared to standard therapy.
- Insulin is the mainstay of therapy for adult and pediatric patients with T1DM. Current guidelines recommend that most people with T1DM be treated with multiple daily injections (3 to 4 injections per day of basal and prandial insulin) or continuous subcutaneous insulin infusion. In addition, the guidelines suggest that most people with T1DM should use insulin analogs to reduce hypoglycemia risk *(ADA 2019, Chiang 2018, Handelsman et al 2015).*
- According to current clinical guidelines regarding the management of T2DM, consideration should be given to initiating insulin therapy (with or without other agents) at the outset of treatment in newly diagnosed patients with markedly symptomatic and/or elevated blood glucose levels or HbA1c. Insulin therapy is usually started once patients are not achieving glycemic goals with noninsulin therapies *(ADA 2019, Davies 2018, Garber et al 2019, Handelsman et al 2015).*
- Guidelines suggest that an insulin treatment program be designed specifically for an individual patient, to match the supply of insulin to his or her dietary/exercise habits and prevailing glucose trends, as revealed through self-monitoring. Anticipated glucose-lowering effects should be balanced with the convenience of the regimen in the context of an individual's specific therapy goals *(ADA 2019, Davies 2018, Garber et al 2019, Handelsman et al 2015).*
- The ADA and EASD recommend that in most patients who require an injectable therapy a GLP-1 agonist should be the first choice, ahead of insulin. Certain patient factors can influence the choice of insulin therapy and recommendations for certain products are made for those with ASCVD, CKD, and those with hypoglycemia issues (*ADA 2019, Davies 2018)*.

Combination, Long-Acting Insulin and GLP-1 Receptor Agonist

- Insulin glargine/lixisenatide (Soliqua) and insulin degludec/liraglutide (Xultophy) are long-acting insulin and incretin-based antidiabetic combination therapies that are FDA-approved as adjunctive therapy to diet and exercise to improve glycemic control in adult T2DM patients.
- The medications are administered through a fixed ratio pen. Soliqua may be administered in doses of 15 to 60 U of insulin glargine and 5 to 20 mcg of lixisenatide, while Xultophy may be administered in doses of 10 to 50 U of insulin degludec and 0.36 to 1.3 mcg of liraglutide SC once daily depending on prior treatment and dosages. Individualized dosing is recommended based on metabolic needs, blood glucose monitoring, glycemic control, type of diabetes, and prior insulin use of the patient.
- These agents have been studied in combination with metformin, sulfonylureas, pioglitazone, and meglitinides. In studies, Soliqua demonstrated HbA1c reductions ranging from 0.3 to 0.5% vs insulin glargine and 0.8% vs lixisenatide. Xultophy demonstrated estimated treatment differences in HbA1c reductions of 1% vs insulin degludec monotherapy, 0.6% vs insulin glargine monotherapy, and 0.9% vs a GLP-1 receptor agonist (eg, liraglutide or exenatide twice daily). Across trials, Xultophy and Soliqua were associated with both weight losses and gains. Hypoglycemia rates were mostly similar to those observed within the basal insulin monotherapy arms; however, the GLP-1 receptor agonists were associated with less hypoglycemic events *(Aroda et al 2016, Buse et al 2014, FDA summary review [Soliqua] 2016, Lingvay et al 2016, Linjawi et al 2017, Rosenstock et al 2016).* Several CV outcomes trials have been conducted in patients with T2DM who were administered basal insulin monotherapy or GLP-1 receptor agonist monotherapy. Of these trials, the

only trial which demonstrated a reduced CV risk was the LEADER trial, which compared liraglutide to placebo *(Gerstein et al 2012, Marso et al 2016, Marso et al 2017, Pfeffer et al 2015).*

- Overall, the safety profiles of these agents are similar. Xultophy has a boxed warning regarding the risk of thyroid C-cell tumors and is contraindicated in patients with a history of MTC or MEN 2. Other key warnings for these products include increased risks of pancreatitis, hypoglycemia or hyperglycemia, the potential for overdose due to medication errors, acute kidney injury, hypokalemia, and the potential for fluid retention and heart failure with use of thiazolidinediones. Soliqua has an additional warning and precaution regarding immunogenicity risks associated with the development of antibodies which may result in the loss of glycemic control. Common AEs include gastrointestinal effects (eg, nausea, diarrhea, etc), nasopharyngitis, headache, and upper respiratory tract infection.
- The ADA and EASD guidelines note that a basal insulin/GLP-1 agonist combination can be considered when first intensifying therapy to injectable products in patients with a HbA1c > 10% and/or if above the target HbA1c by over 2%. The combination can also be considered in patients who require additional control after the addition of a GLP-1 agonist in the intensification algorithm (*ADA 2019, Davies 2018).*

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Therapeutic Class Overview
Meglitinides

INTRODUCTION

- Diabetes mellitus affects more than 30 million people in the United States. More than 84 million American adults have prediabetes, with 90% of this population unaware that they have the condition (*Centers for Disease Control and Prevention [CDC] 2018*).
- Type 2 diabetes mellitus (T2DM) is the most common form of diabetes, and is characterized by elevated fasting and postprandial glucose concentrations. It is a chronic illness that requires continuing medical care and ongoing patient self-management, education and support to prevent acute complications and to reduce the risk of long-term complications (*American Diabetes Association [ADA] 2019, CDC 2018*).
- Complications of T2DM include heart disease, stroke, vision loss, kidney disease, and lower-limb amputations. It is the leading cause of kidney failure, lower-limb amputations, and adult-onset blindness and the seventh leading cause of death in the United States (*CDC 2018*).
- Medical costs for patients with diabetes are double the costs for patients without diabetes (*CDC 2018*).
- Classes of oral medications for the management of blood glucose levels in patients with T2DM may exert their effects through various mechanisms, including decreasing hepatic glucose production, increasing insulin secretion, increasing insulin sensitivity, decreasing the rate of carbohydrate absorption, decreasing glucagon secretion, and blocking glucose reabsorption by the kidney (*Davies et al 2018*).
- Key pharmacologic options for T2DM include sulfonylureas, biguanides, thiazolidinediones (TZDs), meglitinides (or glinides), alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose cotransporter 2 (SGLT2) inhibitors, and insulin (*Davies et al 2018*). Many patients with T2DM will require combination therapy (*Garber et al 2018*).
- Meglitinides are rapid-acting oral antidiabetic agents that lower blood glucose levels by stimulating insulin secretion from the pancreas in a beta-cell dependent manner. They are structurally unrelated to the oral sulfonylurea insulin secretagogues.
- This review will focus on the 2 approved meglitinides, repaglinide and nateglinide. Repaglinide is also Food and Drug Administration (FDA)-approved as a combination product with metformin.
- Medispan class: Endocrine and Metabolic Drugs; Meglitinide Analogues; Meglitinide-Biguanide Combination

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Starlix (nateglinide)	✔
Prandin (repaglinide)	✔
Prandimet (repaglinide/metformin)*	✔ *

*The brand product, Prandimet, is no longer marketed. Additionally, generic repaglinide/metformin has experienced a long-term backorder and may not be available.

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication*	**Starlix** (nateglinide)	**Prandin** (repaglinide)	**Prandimet** (repaglinide/ metformin)
Adjunct to diet and exercise to improve glycemic control in adults with T2DM	✔	✔	
Combination product indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM who are already treated with a meglitinide and metformin or who have inadequate glycemic control on a meglitinide alone or metformin alone			✔

*Limitation of use: not for treatment of type 1 diabetes mellitus or diabetic ketoacidosis

(Prescribing information: Prandimet 2017, Prandin 2019, Starlix 2018)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The effectiveness of repaglinide and nateglinide as monotherapy and in combination with other oral antidiabetic agents has been demonstrated in numerous clinical trials. Meglitinides have been compared to other antidiabetic agents including sulfonylureas, metformin, and insulin (*Bellomo et al 2011, Cesur et al 2007, Derosa et al 2003, Fang et al 2014, Hollander et al 2003, Omori et al 2018, Ozbek et al 2006, Wolffenbuttel et al 1999*). There were at least 3 studies comparing repaglinide to nateglinide head-to-head (*Li J et al 2007, Raskin et al 2003, Rosenstock et al 2004*). The meglitinides were used as monotherapy in *Rosenstock et al* and in combination with metformin in *Raskin et al*.
  - In the monotherapy trial comparing repaglinide to nateglinide (N = 150), a clinically significant reduction in hemoglobin A1c (HbA1c) was seen in both groups with a mean reduction of 1.6% in those randomized to repaglinide vs 1% in those randomized to nateglinide (p = 0.002) (*Rosenstock et al 2004*). At the end of the study, 54% of the repaglinide-treated patients had HbA1c values less than 7% vs 42% of the nateglinide-treated patients; however, the difference did not reach statistical significance (p = 0.18). There were no major hypoglycemic episodes in either treatment group. Patients receiving repaglinide experienced more weight gain than those receiving nateglinide (1.8 kg vs 0.7 kg; p = 0.04).
  - In the second study comparing repaglinide to nateglinide (N = 192), both in combination with metformin, a clinically significant reduction in HbA1c was seen in both groups with the greatest reduction in the repaglinide group (1.3 vs 0.7%, respectively; p < 0.001). The percent of patients who achieved final HbA1c values of less than 7% was 59% for the repaglinide group and 47% for the nateglinide group (p value not reported). Mean changes in fasting plasma glucose were significantly greater for patients receiving repaglinide than nateglinide (p = 0.002) (*Raskin et al 2003*).
  - In a Chinese study, both repaglinide and nateglinide had similar effects on fasting blood glucose and postprandial glucose (p > 0.05) (*Li J et al 2007*).
- A meta-analysis of 4 clinical trials in Chinese patients (N = 955) found that nateglinide and repaglinide had similar reductions in HbA1c and fasting blood glucose and had similar adverse events (*Li C et al 2009*).
- A multicenter, open-label, randomized trial, conducted in Japan, enrolled 57 lean elderly patients with T2DM who were being treated with a sulfonylurea. Patients were randomized to switch to repaglinide or continue on the sulfonylurea for 12 weeks. Patients switching to repaglinide had comparable HbA1c levels to those remaining on a sulfonylurea (-0.07% and +0.02%, respectively; p = 0.37). There was also no significant difference in the number of hypoglycemic episodes (*Omori et al 2018*).
- Additionally, monotherapy with repaglinide was compared to metformin in patients with newly diagnosed T2DM who were naïve to oral antihyperglycemic agents. Repaglinide and metformin achieved comparable results in reduction of HbA1c, fasting plasma glucose and post-prandial glucose (*Fang et al 2014*).
- In a double-blind, placebo-controlled trial, 289 patients were randomized to nateglinide 30 mg, 60 mg, 120 mg, 180 mg, or placebo for 12 weeks. Increased insulin secretion was observed with maximal values seen at 30 minutes and a return to normal values in 3 to 4 hours. HbA1c values were compared between baseline and 12 weeks, and significant reductions were seen for the 60 mg, 120 mg, and 180 mg doses in the range of 0.45% to 0.64% (*Hanefeld et al 2000*).
- Additional studies have demonstrated that when nateglinide or repaglinide was added to metformin therapy, the changes from baseline for HbA1c and fasting plasma glucose levels for either combination were significantly greater than either meglitinide monotherapy or metformin monotherapy (*Black et al 2007, Horton et al 2000, Marre et al 2002, Moses et al 1999).* This additive effect was also seen when repaglinide was given with rosiglitazone (*Raskin et al 2004*). The change in HbA1c and fasting plasma glucose from baseline was significant for repaglinide plus rosiglitazone when compared to either as monotherapy.
- In a systematic review of 136 trials, results from clinical trials showed that most oral agents, including TZDs, metformin, and repaglinide, improved glycemic control to the same degree as sulfonylureas (absolute decrease in HbA1c level of about 1%) (moderate-to-high strength of evidence) (*Bolen et al 2007*). Nateglinide and alpha-glucosidase inhibitors have slightly weaker effects, on the basis of indirect comparisons of placebo-controlled trials (low strength of evidence). TZDs were the only class with a beneficial effect on high-density lipoprotein (HDL) levels (mean relative increase, 3 to 5 mg/dL) but a harmful effect on low-density lipoprotein (LDL) levels (mean relative increase, 10 mg/dL) compared with

other oral agents. Metformin decreased LDL levels by about 10 mg/dL, whereas other oral agents had no effects on LDL (moderate strength of evidence). TZDs, second-generation sulfonylureas, and metformin had similarly minimal effects on systolic blood pressure (moderate strength of evidence). Most agents except metformin increased body weight by 1 to 5 kg (moderate strength of evidence).

- A network meta-analysis was conducted to determine whether the addition of various antidiabetic drug regimens to metformin monotherapy in patients with T2DM led to significant reductions in HbA1c. All agents reduced HbA1c more than placebo but at varying levels. Insulin glargine, sulfonylureas, and nateglinide were associated with increased hypoglycemia risk when compared to placebo, but repaglinide, GLP-1 receptor agonists, DPP-4 inhibitors, and TZDs were not (*Mearns et al 2015*).
- According to studies comparing the efficacy of a meglitinide to other oral diabetic agents, meglitinides may offer an alternative to be used when side effects of other oral agents are intolerable or when those agents are contraindicated. From the data presented, there is no evidence available to indicate what effects meglitinides will have on important long-term outcomes, and it is difficult to determine if one meglitinide offers an advantage in glycemic control or safety over the other.

CLINICAL GUIDELINES

- Current guidelines recommend that metformin, along with lifestyle intervention, should be the initial pharmacologic therapy for T2DM in the absence of specific contraindications.
  - According to the ADA and a joint consensus report from the ADA and the European Association for the Study of Diabetes (EASD), dual therapy or triple therapy can be considered in patients not achieving their HbA1c goal on metformin monotherapy (*ADA 2019, Davies et al 2018*). Choice of add-on therapy should be determined based on 1) whether the patient has established atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CKD); and 2) whether there is a compelling need to minimize hypoglycemia or a compelling need to minimize weight gain or promote weight loss in patients without established ASCVD or CKD.
    - If ASCVD predominates, a GLP-1 receptor agonist with proven cardiovascular disease (CVD) benefit or an SGLT2 inhibitor with proven CVD benefit (if estimated glomerular filtration rate [eGFR] is adequate) is recommended.
    - If heart failure or CKD predominates, an SGLT2 inhibitor with evidence of reducing heart failure and/or CKD progression is preferred if the eGFR is adequate. If the SGLT2 inhibitor is not tolerated or contraindicated, or if the eGFR is less than adequate, a GLP-1 receptor agonist with proven CVD benefit is recommended.
    - In patients without established ASCVD or CKD:
      - If there is a compelling need to minimize hypoglycemia, recommendations include a DPP-4 inhibitor, a GLP-1 receptor agonist, an SGLT2 inhibitor, or a TZD.
      - If there is a compelling need to minimize weight gain or promote weight loss, a GLP-1 receptor agonist with good efficacy for weight loss or an SGLT2 inhibitor is recommended.
    - The early introduction of basal insulin is a well-established approach to treatment in patients who have very high HbA1c levels (> 11%), symptoms of hyperglycemia, or evidence of ongoing catabolism (eg, weight loss) (*Davies et al 2018*).
    - In most patients who need the greater glucose-lowering effect of an injectable medication (ie, HbA1c is above target despite dual/triple therapy), GLP-1 receptor agonists are preferred to insulin.
    - Meglitinides are not used commonly in the United States (*Davies et al 2018*). Advantages of these products include a reduction in postprandial glucose excursions, dosing flexibility, and safe use in advanced renal disease with cautious dosing (especially repaglinide). Disadvantages include a risk of hypoglycemia, weight gain, frequent dosing schedule, and uncertain cardiovascular safety.
  - According to the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE), the choice of diabetic therapies must be individualized based on attributes specific to the patient and the medication (*Garber et al 2018*). Metformin is recommended as the preferred initial agent for monotherapy in patients with an entry HbA1c < 7.5%; however, monotherapy with other agents may be considered. Combination therapies including metformin plus 1 or 2 additional agents are recommended for patients with an entry HbA1c ≥ 7.5%. Several options for dual- and triple-therapy are presented in a hierarchy, with GLP-1 receptor agonists and SGLT2 inhibitors listed as the top 2 options to be added. In patients with an entry HbA1c > 9%, dual- or triple therapy should be considered if patients are asymptomatic, and insulin considered if patients are symptomatic (*Garber et al 2018*).

- Meglitinides have somewhat lower HbA1c-lowering effects and a shorter half-life, and therefore have a lower risk of prolonged hypoglycemia compared to sulfonylureas. Meglitidines are not generally preferred as monotherapy, but may be appropriate for select patients.

SAFETY SUMMARY

- Contraindications:
  - Hypersensitivity to the drug or any of its ingredients
  - Concomitant use with gemfibrozil: repaglinide and repaglinide/metformin
  - Severe renal impairment (eGFR < 30 mL/min/1.73 m^2): repaglinide/metformin
  - Acute or chronic metabolic acidosis, including diabetic ketoacidosis: repaglinide/metformin
- Boxed warning – repaglinide/metformin:
  - Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as renal impairment, concomitant use of certain drugs (eg, carbonic anhydrase inhibitors such as topiramate), excessive alcohol intake, age ≥ 65 years, hepatic impairment, and hypoxic states (eg, acute congestive heart failure).
  - If lactic acidosis is suspected, repaglinide/metformin should be discontinued and the patient hospitalized immediately. Prompt hemodialysis is recommended.
- Warnings/Precautions:
  - Hypoglycemia
  - No clinical studies have conclusively established evidence of macrovascular risk reduction with therapy.
  - Repaglinide and repaglinide/metformin should not be used with NPH insulin (risk of serious cardiovascular adverse reactions).
  - See prescribing information for other warnings for repaglinide/metformin due to its metformin component.
- Adverse Effects:
  - The most common adverse effects for the class include hypoglycemia, headache, nausea, dyspepsia, back pain, diarrhea, upper respiratory tract infection, flu symptoms, dizziness, sinusitis, and arthropathy/arthralgia.
- Drug Interactions:
  - Repaglinide
    - Cyclosporine, gemfibrozil, clopidogrel, cytochrome P450 (CYP) 2C8 inhibitors (eg, trimethoprim, gemfibrozil, montelukast, clopidogrel), and CYP3A4 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, erythromycin) may increase the plasma concentrations of repaglinide.
    - Drugs that induce CYP3A4 and/or CYP2C8 enzyme systems (eg, rifampin, barbiturates, and carbamazepine) may reduce the glucose-lowering effect of repaglinide.
  - Nateglinide
    - Nonsteroidal anti-inflammatory drugs, salicylates, monoamine oxidase inhibitors, non-selective beta-adrenergic-blocking agents, anabolic hormones, guanethidine, and CYP2C9 inhibitors (eg, fluconazole, voriconazole, amiodarone) may increase the glucose-lowering action of nateglinide and increase susceptibility to hypoglycemia.
    - Thiazides, corticosteroids, thyroid products, sympathomimetics, somatropin, somatostatin analogues, and CYP inducers (eg, rifampin, phenytoin, St. John's Wort) may reduce the hypoglycemic action of nateglinide and increase susceptibility to hyperglycemia.
  - This section is not a comprehensive list of potential drug interactions. See prescribing information for additional products that may increase the risk of hypoglycemia or decrease the blood glucose lowering effect of the meglitinides as well as drug interactions based on the metformin component of repaglinide/metformin.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Starlix (nateglinide)	Tablets	Oral	3 times daily	Should be taken up to 30 minutes prior to meals. If a meal is skipped, the scheduled dose should be skipped to reduce the risk of hypoglycemia.
Prandin (repaglinide)	Tablets	Oral	2 to 4 times daily (max daily dose: 16 mg)	Should be taken within 30 minutes of a meal. If a meal is skipped, the scheduled dose should be skipped to reduce the risk of hypoglycemia. In severe renal impairment (creatinine clearance 20 to 40 mL/min), should be initiated at a low dose (0.5 mg) and gradually titrated.
Prandimet (repaglinide/ metformin)	Tablets	Oral	2 to 3 times daily (max dose: 10/2500 mg daily or 4/1000 mg per meal)	Should be taken within 15 to 30 minutes of a meal. If a meal is skipped, the scheduled dose should be skipped to reduce the risk of hypoglycemia. In patients inadequately controlled with metformin, the recommended starting dose of repaglinide/metformin is 1/500 mg administered twice daily. In patients inadequately controlled with meglitinide monotherapy, the recommended starting dose of the metformin component is 500 mg twice daily. If eGFR < 30 mL/min/1.73 m^2, repaglinide/metformin is contraindicated and should be discontinued. The combination should not be initiated in patients with eGFR between 30 to 45 mL/min/1.73 m^2. If eGFR falls below 45 mL/min/1.73 m^2, the benefits and risks of continuing therapy should be assessed; if eGFR falls below 30 mL/min/1.73 m^2, the combination should be discontinued.

CONCLUSION

- The meglitinides are a class of oral antidiabetic agents that increase insulin secretion in the pancreas. They are FDA approved as an adjunct to diet and exercise either alone or in combination with other therapies for the treatment of T2DM.
- The pharmacokinetic and pharmacodynamic properties of this drug class suggest they have the potential to produce a rapid, short-lived insulin secretory response.
- The effectiveness of these agents as monotherapy and in combination with other oral antidiabetic agents has been demonstrated in a number of clinical trials. In studies comparing meglitinides to placebo, repaglinide and nateglinide resulted in reductions in HbA1c of 0.1% to 2.1% and 0.2% to 0.6%, respectively. Combination studies with metformin demonstrated that combined therapy produced clinically (and statistically) significant reductions in HbA1c compared with metformin alone without any reported severe hypoglycemia or other adverse events, but at the expense of a statistically significant weight gain (repaglinide and metformin) (*Black et al 2007*).
- Head-to-head clinical trials comparing the efficacy of repaglinide to nateglinide are limited. In one study, a clinically significant reduction in HbA1c was seen in those randomized to repaglinide (1.6%) compared to those randomized to nateglinide (1%). However, the proportion of patients achieving an HbA1c < 7% did not differ between treatment groups. There were no major hypoglycemic episodes in either treatment group. In another study comparing repaglinide to

nateglinide, both in combination with metformin, a clinically significant reduction in HbA1c was seen in both groups with the greatest reduction in the repaglinide group (1.3% vs 0.7%, respectively; p < 0.001) (*Raskin et al 2003*).

- Based on studies comparing the efficacy of a meglitinide to other oral diabetic agents, meglitinides may be considered alternative oral antihyperglycemic agents of similar potency to metformin and sulfonylureas, and can be used where side effects of the other oral diabetic agents are intolerable or where those agents are contraindicated. There is no evidence available to indicate what effects meglitinides will have on important long-term outcomes, and it is difficult to determine if one meglitinide offers an advantage in glycemic control or safety over the other.
- Adverse events associated with meglitinides include hypoglycemia, headache, nausea, dyspepsia, back pain, diarrhea, upper respiratory tract infection, flu symptoms, dizziness, sinusitis, and arthropathy/arthralgia.
- Current guidelines recommend that metformin, along with lifestyle intervention, should be the initial pharmacologic therapy for T2DM in the absence of specific contraindications (*ADA 2019, Garber et al 2018, Davies et al 2018*). Meglitinides are listed as one of several potential alternatives or add-on therapies; however, other classes are generally preferred in combination with metformin as dual or triple combination therapy for patients with T2DM (*ADA 2018, Davies et al 2018*). According to a joint consensus report by the ADA and EASD, advantages of meglitinides include a reduction in postprandial glucose excursions, dosing flexibility, and safe use in advanced renal disease with cautious dosing (especially repaglinide) (*Davies et al 2018*). Disadvantages include a risk of hypoglycemia, weight gain, frequent dosing schedule, and uncertain cardiovascular safety.
- The 2018 AACE/ACE guidelines note that the meglitinides have somewhat lower HbA1c-lowering effects and shorter half-lives, and thus a lower risk of prolonged hypoglycemia, relative to sulfonylureas (*Garber et al 2018*).

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Therapeutic Class Overview
Sodium-Glucose Cotransporter-2 Inhibitors

INTRODUCTION

- In the United States (US), diabetes mellitus affects more than 30 million people and is the 7th leading cause of death (*Centers for Disease Control and Prevention [CDC] 2018*).
- Type 2 diabetes mellitus (T2DM) is the most common form of diabetes and is characterized by elevated fasting and postprandial glucose concentrations *(American Diabetes Association [ADA] 2019[a])*. It is a chronic illness that requires continuing medical care and ongoing patient self-management education and support to prevent acute complications and to reduce the risk of long-term complications *(ADA 2019[b])*.
  - Complications of T2DM include hypertension, heart disease, stroke, vision loss, nephropathy, and neuropathy *(ADA 2019[a])*.
- In addition to dietary and lifestyle management, T2DM can be treated with insulin, one or more oral medications, or a combination of both. Many patients with T2DM will require combination therapy *(Garber et al 2019)*.
- Classes of oral medications for the management of blood glucose levels in patients with T2DM focus on increasing insulin secretion, increasing insulin responsiveness, or both, decreasing the rate of carbohydrate absorption, decreasing the rate of hepatic glucose production, decreasing the rate of glucagon secretion, and blocking glucose reabsorption by the kidney *(Garber et al 2019)*.
- Pharmacologic options for T2DM include sulfonylureas (SFUs), biguanides, thiazolidinediones (TZDs), meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogs, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, combination products, and insulin.
- The SGLT2 inhibitor class consists of 4 unique molecular entities, canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin, and their combination products with metformin or a DPP-4 inhibitor.
  - SGLT2 is the predominant transporter responsible for reabsorption of glucose from the glomerular filtrate back into the circulation. Inhibition of SGLT2 reduces renal reabsorption of filtered glucose and lowers the renal threshold for glucose, thereby increasing urinary glucose excretion.
- Medispan class: Antidiabetics, Sodium-glucose cotransporter 2 inhibitors

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Dapagliflozin products	
Farxiga (dapagliflozin)	-
Xigduo XR (dapagliflozin/metformin hydrochloride extended-release [ER])	-
Qtern (dapagliflozin/saxagliptin)	-
Canagliflozin products	
Invokana (canagliflozin)	-
Invokamet (canagliflozin/metformin hydrochloride)	-
Invokamet XR (canagliflozin/metformin ER)	-
Empagliflozin products	
Jardiance (empagliflozin)	-
Glyxambi (empagliflozin/linagliptin)	-
Synjardy (empagliflozin/metformin)	-
Synjardy XR (empagliflozin/metformin ER)	-
Ertugliflozin products	
Steglatro (ertugliflozin)	-
Segluromet (ertugliflozin/metformin)	-

Drug	Generic Availability
Steglujan (ertugliflozin/sitagliptin)	-

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indications	Single-Entity				Combination Products						
	Farxiga (dapagliflozin)	Invokana (canagliflozin)	Jardiance (empagliflozin)	Steglatro (ertugliflozin)	Glyxambi (empagliflozin/ linagliptin)	Qtern (dapagliflozin/ saxagliptin)	Invokamet, Invokamet XR* (canagliflozin/ metformin)	Synjardy, Synjardy XR* (empagliflozin/ metformin)	Xigduo XR* (dapagliflozin/ metformin ER)	Segluromet (ertugliflozin/ metformin)	Steglujan (ertugliflozin/ sitagliptin
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM	✓	✓	✓	✓							
To reduce the risk of CV death in adult patients with T2DM and established CVD			✓								
To reduce the risk of MACE (CV death, nonfatal myocardial infarction and nonfatal stroke) in adults with T2DM and established CVD		✓									
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both components is appropriate.					✓†		✓†	✓†	✓		✓
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM who have inadequate control with dapagliflozin or who are already treated with dapagliflozin and saxagliptin						✓					
As an adjunct to diet and exercise to improve glycemic control in adults with T2DM who have inadequate control with ertugliflozin and/or metformin										✓	

Abbreviations: CV = cardiovascular; CVD = cardiovascular disease; MACE = major adverse cardiovascular events; T2DM = type 2 diabetes mellitus

* These combination products contain metformin ER.

† Labeling for combination products containing empagliflozin and canagliflozin state that the single-entity products are additionally indicated to reduce CV risk; however, the effectiveness of the combination products for CV risk reduction has not been established.

Limitations of use: Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin are not recommended in patients with type 1 diabetes mellitus (T1DM) or for the treatment of diabetic ketoacidosis (DKA). Glyxambi and Steglujan have not been studied in patients with a history of pancreatitis. Qtern should only be used in patients who tolerate 10 mg dapagliflozin.

(*Prescribing information: Farxiga 2019, Glyxambi 2018, Invokana 2018, Invokamet/Invokamet XR 2018, Jardiance 2018, Qtern 2018, Segluromet 2018, Steglatro 2018, Steglujan 2018, Synjardy 2018, Synjardy XR 2018, Xigduo XR 2019*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The safety and efficacy of the SGLT2 inhibitors were evaluated in patients that were drug-naïve or in patients whose glucose was inadequately controlled with other oral agents and/or insulin. SGLT2 inhibitors have demonstrated efficacy in lowering glycosylated hemoglobin (HbA1c) levels by ~0.5% to 1.5% *(Davies et al 2018)*. They have been studied as monotherapy and in combination with other antidiabetic agents. Most trials evaluated the addition of an SGLT2 inhibitor to one or more classes of antidiabetic agents.
- The SGLT2 inhibitors have consistently shown significant beneficial effects on HbA1c, fasting plasma glucose (FPG), weight gain, post-prandial glucose (PPG), and blood pressure when used as monotherapy or in combination therapy:
  - As monotherapy *(Bailey et al 2012, Ferrannini et al 2010, Ferrannini et al 2013, Inagaki et al 2014, Stenlöf et al 2013, Terra et al 2017)*
  - With metformin *(Bailey et al 2010, Haring et al 2014, Henry et al 2012, Leiter et al 2015, Rosenstock et al 2013, Rosenstock et al 2016, Rosenstock et al 2018, Ross et al 2015)*
  - With an SFU *(Fulcher et al 2015, Strojek et al 2011, Strojek et al 2014, Wilding et al 2013)*
  - With metformin and an SFU *(Dagogo-Jack et al 2018, Haring et al 2013, Matthaei et al 2015)*
  - As add-on therapy to TZDs *(Forst et al 2014, Kovacs et al 2014, Rosenstock et al 2012)*
  - As add-on therapy or compared to DPP-4 inhibitors *(Jabbour et al 2014, Lavalle-Gonzalez et al 2013, Roden et al 2013, Rosenstock et al 2015[a], Schernthaner et al 2013)*
  - As add-on therapy to insulin *(Neal et al 2015, Rosenstock et al 2014, Rosenstock et al 2015[b], Wilding et al 2012)*
- The combination of SGLT2 inhibitors with metformin lowers HbA1c compared to placebo. These studies use the coadministration of the two components instead of fixed-dose combination tablets for Invokamet, Segluromet, Synjardy, and Xigduo XR. The bioequivalency of Invokamet XR and Synjardy XR to the immediate release combination products in healthy subjects was used to support the Food and Drug Administration (FDA) approval of these extended-release combination products.
- Glyxambi (empagliflozin/linagliptin) was the first FDA-approved SGLT2-inhibitor/DPP-4 inhibitor combination product. A 52-week, phase 3, double-blind, parallel-group, randomized controlled trial (RCT) in patients with T2DM demonstrated reductions in HbA1c with Glyxambi that were superior to those of empagliflozin or linagliptin alone as add-on to metformin *(DeFronzo et al 2015)*. Qtern (dapagliflozin/saxagliptin) was approved in February 2017; efficacy and safety were observed as add-on therapy with saxagliptin in patients on dapagliflozin plus metformin at 24 weeks *(Matthaei et al 2015)* and at 52 weeks *(Matthaei et al 2016)*; with dapagliflozin added to saxagliptin plus metformin at 24 weeks *(Mathieu et al 2015)* and 52 weeks *(Mathieu et al 2016)*; and with saxagliptin plus dapagliflozin addition vs the single addition of saxagliptin or dapagliflozin to metformin at 24 weeks *(Rosenstock et al 2015[a])*. Additionally, the add-on combination of dapagliflozin and saxagliptin resulted in improved glycemic control compared to glimepiride in patients on metformin monotherapy (*Muller-Wieland et al 2018)*. Steglujan (ertugliflozin/sitagliptin) was approved in December 2017; efficacy and safety of co-initiation of ertugliflozin and sitagliptin were observed at 26 weeks in patients inadequately controlled on diet and exercise (*Miller et al 2018*). In patients inadequately controlled with metformin, ertugliflozin plus sitagliptin was more effective in glycemic control at weeks 26 and 52 as compared to individual components alone (*Pratley et al 2018*).
- The SGLT2 inhibitors have also shown noninferiority in decreasing HbA1c in direct comparisons when compared to SFUs:
  - Dapagliflozin vs glipizide, both in combination with metformin *(Nauck et al 2011)*
  - Canagliflozin vs glimepiride *(Cefalu et al 2013)*
  - Empagliflozin vs glimepiride *(Ridderstrale et al 2014, Ridderstrale et al 2018)*
  - Ertugliflozin vs glimepiride (*Hollander et al 2018*)

- Additional studies have demonstrated the safety and efficacy of SGLT2 inhibitors in special populations:
  - Patients with T2DM and chronic kidney disease *(Barnett et al 2014, Fioretto et al 2018, Grunberger et al 2018, Kohan et al 2014, Yale et al 2014, Yale et al 2013)*
  - Patients with T2DM and CV disease (CVD) *(Leiter et al 2014)*
  - Patients with T2DM and nonalcoholic fatty liver disease *(Kuchay et al 2018)*
  - Elderly patients *(Bode et al 1995, Bode et al 2015, Sinclair et al 2014, Sinclair et al 2016)*
    - A pooled analysis of six phase 3, double-blind, placebo-controlled, RCTs compared the efficacy and safety of canagliflozin in patients < 75 years and ≥ 75 years of age. Canagliflozin 100 mg and 300 mg were associated with placebo-subtracted mean reductions in HbA1c in patients < 75 years (-0.69% and -0.85%, respectively) and ≥ 75 years (-0.65% and -0.55%, respectively). Dose-related reductions in FPG, body weight, and blood pressure were also seen with canagliflozin 100 mg and 300 mg in patients in both age groups. Overall adverse event incidences were 67.1% with canagliflozin 100 mg, 68.6% with canagliflozin 300 mg, and 65.9% with non-canagliflozin (pooled group of comparators in all studies) in patients < 75 years, and 72.4%, 79.1%, and 72.3%, respectively, in patients ≥ 75 years, with a similar safety profile in both groups *(Sinclair et al 2016).*
- Various long-term studies have been conducted that provide data on the safety and efficacy after at least one year of treatment with the SGLT2 inhibitors *(Araki et al 2015, Aronson et al 2018, Bailey et al 2015, Bode et al 2015, Del Prato et al 2015, Kovacs et al 2015, Nauck et al 2014, Yale et al 2017)*.
- Other post-hoc analyses of pooled data from RCTs have further evaluated the effects of SGLT2 inhibitors on parameters such as blood pressure, weight gain, and adverse events *(Davies et al 2015, Ptaszynska et al 2014, Weir et al 2014)*.
- Furthermore, various meta-analyses have been conducted that have demonstrated the individual efficacy of the SGLT2 inhibitors *(Liakos et al 2014, Orme et al 2014, Sun et al 2014, Yang et al 2014, Zhang et al 2018)*.

Comparative efficacy

- While there are no head-to-head studies comparing the efficacy and safety of the SGLT2 inhibitors, a 2016 systematic review and network meta-analysis found that canagliflozin 300 mg reduced HbA1c, FPG, and systolic blood pressure, while increasing low-density lipoprotein cholesterol (LDL-C) to a greater extent compared with other inhibitors (dapagliflozin and empagliflozin) at any dose *(Zaccardi et al 2016)*.
- Another systematic review and network meta-analysis found similar results *(Shyangdan et al 2016)*. When used as monotherapy, a greater proportion of patients achieved a HbA1c <7% on canagliflozin 300 mg than on canagliflozin 100 mg and dapagliflozin 10 mg, but there were no significant differences compared with either dose of empagliflozin. Canagliflozin 300 mg reduced HbA1c more than other SGLT2 inhibitors, with the mean difference ranging from 0.20% to 0.64%. There were no significant differences between the SGLT2 inhibitors with respect to weight reduction.
- Another systematic review and network meta-analysis found that ertugliflozin 15 mg reduced HbA1c more than dapagliflozin 10 mg and empagliflozin 25 mg, both as monotherapy and in combination with metformin (*McNeill et al 2019*).
- The Agency for Healthcare Research and Quality (AHRQ) updated its review of the diabetes medications for adults with T2DM to include the results from an additional eight studies *(Bolen et al 2016)*. Findings related to the SGLT2 inhibitors included some of the following:
  - Body weight was maintained or reduced by metformin, DPP-4 inhibitors, GLP-1 agonists, and SGLT2 inhibitors.
  - Systolic blood pressure was reduced by 3 to 5 mm Hg by SGLT2 inhibitors and GLP-1 agonists compared to metformin.
  - Some adverse events were higher with specific classes of drugs including gastrointestinal (GI) events (metformin and GLP-1 agonists) and risk of genital mycotic infection (SGLT2 inhibitors).

Cardiovascular (CV) outcome studies

- EMPA-REG OUTCOME was the first study to demonstrate a positive benefit on CV outcomes due to glucose lowering with empagliflozin as add-on to standard of care in T2DM patients with high CV risk *(Zinman et al 2015)*. Empagliflozin significantly reduced the risk of the composite MACE endpoint (CV death, nonfatal myocardial infarction [MI], or nonfatal stroke) by 14% vs placebo ($p < 0.001$ for noninferiority; $p = 0.04$ for superiority). In addition, there was a 38% reduction in CV death, 35% reduction in hospitalization for heart failure (HHF), and 32% reduction in death from any cause associated with its use; however, there were no significant between-group differences in the rates of MI or stroke. The underlying mechanism of empagliflozin and its effect on CV outcomes are not clearly understood. Recently updated guidelines acknowledge the established CV benefit with empagliflozin *(ADA 2019, Das et al 2018, Davies et al 2018, Garber et al 2019)*.

- A recently published follow-up to the EMPA-REG OUTCOME study examined the pre-specified secondary objective of the effect of empagliflozin on microvascular outcomes, and in particular, progression of kidney disease in patients with T2DM at high risk for CV events. In this new analysis, incident or worsening nephropathy occurred in 525 of 4124 patients taking empagliflozin and 388 of 2061 in the placebo group (12.7% vs 18.8%; hazard ratio [HR]: 0.61; 95% confidence interval [CI], 0.53 to 0.70; p < 0.001). This renal end point consisted of a combination of progression to macroalbuminuria, a doubling of serum creatinine, the start of renal-replacement therapy, or renal death. A relative risk reduction of 38% was seen with the endpoint of progression to macroalbuminuria, which occurred in 459 of 4091 patients taking empagliflozin compared with 330 of 2033 patients on placebo (11.2% vs 16.2%; HR, 0.62; 95% CI, 0.54 to 0.72; p < 0.001) *(Wanner et al 2016)*.

- The CANVAS Program was comprised of 2 trials, the Canagliflozin Cardiovascular Assessment Study (CANVAS) and CANVAS-Renal (CANVAS-R), that included a total of 10,142 patients with T2DM and high CV risk *(Neal et al 2017)*. The studies were designed to assess the CV safety and efficacy of canagliflozin, as well as to evaluate the balance between potential benefits of the drug and its associated risks (eg, genitourinary infection, DKA, fracture). Significantly fewer participants in the canagliflozin group had a primary outcome event (composite of CV death, nonfatal MI, or nonfatal stroke) vs placebo: 26.9 vs 31.5 participants with an event per 1000 patient-years (HR, 0.86; 95% CI, 0.75 to 0.97; p < 0.001 for noninferiority; p = 0.02 for superiority). Recently updated guidelines acknowledge the established CV benefit with canagliflozin, but also note the increased risk of amputation (*ADA 2019, Das et al 2018, Davies et al 2018, Garber et al 2019*).
- The DECLARE-TIMI 58 study (N = 17,160) evaluated CV outcomes with dapagliflozin in patients with established CVD or multiple risk factors. After a median follow up of 4.2 years, dapagliflozin demonstrated noninferiority to placebo for the primary outcome of MACE (upper boundary of the 95% CI < 1.3; p < 0.001 for noninferiority); however, dapagliflozin was not statistically significantly superior to placebo with respect to MACE (8.8% vs 9.4%; HR, 0.93; 95% CI, 0.84 to 1.03; p = 0.17) (*Wiviott et al 2019*).
  - Dapagliflozin significantly reduced a composite outcome of CV death and HHF (4.9% vs 5.8%; HR, 0.83; 95% CI, 0.73 to 0.95; p = 0.0005). The significant result was driven by reductions in HHF (HR, 0.73; 95% CI, 0.61 to 0.88), as there was no difference between groups in the rate of CV death (HR, 0.98; 95% CI, 0.82 to 1.17).
  - Patients who received dapagliflozin were associated with a higher risk of DKA (p = 0.02) and serious genital infections vs placebo (p < 0.001).
- The VERTIS CV study (N = 8237) will evaluate CV outcomes with ertugliflozin in patients with established CVD. Estimated study completion is in the second half of 2019 (*ClinicalTrials.gov*).
- A meta-analysis of the 3 published CV outcome trials (N = 34,322) evaluated the CV and renal benefits of the SGLT2 inhibitor class. SGLT2 inhibitors were associated with an 11% reduction in MACE vs placebo (HR, 0.89; 95% CI, 0.83 to 0.96; p = 0.0014). MACE risk reduction was statistically significant in the subgroup of patients with established CVD (HR, 0.86; 95% CI, 0.80 to 0.93), but not in the subgroup of patients with only risk factors for CVD (HR, 1.00; 95% CI, 0.87 to 1.16; p for interaction = 0.0501). SGLT2 inhibitors significantly reduced the risk for a composite outcome of HHF or CV death (HR, 0.77; 95% CI, 0.71 to 0.84; p < 0.0001) and progression to renal disease (HR, 0.55; 95% CI, 0.48 to 0.64; p < 0.0001), with consistent results across the subgroups of patients with and without established CVD (*Zelniker et al 2019*).
- A meta-analysis evaluating the CV effects of SGLT2 inhibitors in patients with T2DM pooled 35 studies that reported at least 1 CV outcome (*Usman et al 2018*). As compared to placebo, the pooled analysis found that SGLT2 inhibitors were associated with a reduction in all-cause mortality (odds ratio [OR], 0.79; 95% CI, 0.70 to 0.89), (MACE (OR, 0.8; 95% CI 0.76 to 0.92), non-fatal MI (OR, 0.85; 95% CI, 0.73 to 0.98) and HHF (OR, 0.67; 95% CI, 0.59 to 0.76).
- A network meta-analysis evaluated the CV effects of empagliflozin compared to DPP-4 inhibitors in patients with T2DM with established CVD or at high risk for CV outcomes (*Balijepalli et al 2018)*. The analysis pooled 4 studies and found that empagliflozin was superior to saxagliptin (HR, 0.60; 95% credible interval [CrI], 0.46 to 0.80) and sitagliptin (HR, 0.60; 95% CrI, 0.46 to 0.79) in reducing the risk of CV mortality. Similar results were found for all-cause mortality (empagliflozin vs saxagliptin: HR, 0.61; 95% CrI, 0.49 to 0.76; and vs sitagliptin: HR, 0.67; 95% CrI, 0.54 to 0.83).
- The Comparative Effectiveness of Cardiovascular Outcomes in New Users of SGLT2 Inhibitors (CVD-REAL) study is the first large real-world study of > 300,000 patients with T2DM, both with and without established CVD that evaluated outcomes of HHF and all-cause death in patients with T2DM treated with SGLT2 inhibitors vs other glucose-lowering drugs. Data were collected from patients living in 6 countries (United States, Germany, Sweden, Norway, Denmark, and the United Kingdom) *(Kosiborod et al 2017)*. Overall, treatment with SGLT2 inhibitors vs other agents was associated with a 39% relative risk reduction in HHF, a 51% reduction in all-cause death, and a 46% reduction in the HHF or death composite.

- An additional observational analysis from the CVD-REAL investigators evaluated the risk of CVD and CV mortality in patients initiating SGLT2 inhibitors compared to other glucose-lowering drugs in the CVD-REAL Nordic study (*Birkeland et al 2017*). Approximately 90,000 patients were identified from registries in Denmark, Norway, and Sweden. The baseline prevalence of CVD was 25%. Use of SGLT2 inhibitors was found to be associated with a reduced risk of CV events, HHF, and CV mortality compared to other glucose-lowering drugs, with relative risk reductions of 22%, 30%, and 47%, respectively.
  - The CVD-REAL Nordic study also evaluated MACE in approximately 40,000 patients with T2DM, both with and without CVD, who were new users of dapagliflozin or DPP-4 inhibitors (*Persson et al 2018)*. Dapagliflozin use was associated with a 21% relative reduction in MACE, 38% relative reduction in HHF, and a 41% relative reduction in all-cause mortality as compared to DDP-4 inhibitor use.
- The EASEL cohort study evaluated patients with T2DM and established CVD and compared those who were initiated on SGLT2 inhibitors versus other glucose-lowering drugs (*Udell et al 2018*). The propensity-matched population included 25,258 patients. Initiation of a SGLT2 inhibitor, as compared to a non-SGLT2 inhibitor, was associated with a relative risk reduction of 43% for the combined endpoint of all-cause mortality and HHF, and a 33% relative risk reduction for MACE. However, SGLT2 inhibitor use was also associated with a higher risk of below-knee amputation (HR, 1.99; 95% CI, 1.12 to 3.51), mainly driven by patients exposed to canagliflozin.

CLINICAL GUIDELINES

Overview

- Professional society guidelines are consistent in recommending metformin as the optimal first-line pharmacologic therapy for treatment-naïve patients with T2DM, unless the patient has contraindications or intolerance. SGLT2 inhibitors are among the second-line options for subsequent therapy. All guidelines emphasize individualized therapy based upon patient-specific factors such as comorbidities, weight, risk of hypoglycemia, and duration of diabetes *(ADA 2019, Copeland et al 2013, Davies et al 2018, Garber et al 2019)*. Metformin is considered the drug of choice for children with T2DM *(Copeland et al 2013)*.
- A 2018 American College of Cardiology expert consensus decision pathway on CV risk reduction in patients with T2DM and atherosclerotic CV disease (ASCVD) suggests adding an SGLT2 inhibitor or GLP-1 receptor agonist that has demonstrated beneficial CV outcomes to other guideline-directed therapy for diabetes (specifically, metformin). Among the SGLT2 inhibitors with CV outcome data at the time that the pathway was written (canagliflozin and empagliflozin), empagliflozin was the preferred SGLT2 inhibitor based on the available evidence and overall risk to benefit ratio *(Das et al 2018)*.

- **ADA/European Association for the Study of Diabetes (EASD): Management of Hyperglycemia in Type 2 Diabetes, 2018** *(Davies et al 2018)*
  - The goals of T2DM therapy are to prevent or delay complications and maintain quality of life, which requires glycemic control, CV risk factor management, regular follow-up, and a patient-centered approach to enhance patient engagement in self-care activities. Careful consideration of patient-specific factors and preferences must inform the process of individualizing treatment goals and strategies.
  - Due to new evidence of benefit with specific agents in the reduction of mortality, heart failure (HF), and progression of renal disease, the overall approach to glucose-lowering medication in T2DM for the ADA/EASD consensus report was updated in 2018. A history of CVD, CKD, and HF should be taken into consideration early in the process of treatment selection. Additionally, the guideline recommends early consideration of weight, hypoglycemic risk, treatment cost, and other patient-related factors that may influence the choice of drug therapy.
    - Among patients with T2DM who have established ASCVD, SGLT2 inhibitors or GLP-1 receptor agonists with proven CV benefit are recommended as part of glycemic management.
    - For patients with ASCVD with concomitant HF, SGLT2 inhibitors are recommended.
    - For patients with T2DM and CKD (with or without ASCVD), an SGLT2 inhibitor shown to reduce CKD progression should be considered. If SGLT2 inhibitors are contraindicated or not preferred, a GLP-1 receptor agonist shown to reduce CKD progression should be considered.
  - Initial monotherapy: Metformin remains the preferred drug for initial monotherapy based on its efficacy, safety, tolerability, low cost, and extensive clinical experience.

- Add-on to metformin: The selection of a second agent added to metformin is based on patient preference and clinical characteristics. Important clinical characteristics include the presence of established ASCVD and other comorbidities such as HF or CKD; the risk for specific AEs, particularly hypoglycemia and weight gain; as well as safety, tolerability, and cost.
- Intensification beyond 2 medications: Intensification of treatment beyond dual therapy to maintain glycemic targets requires consideration of the impact of medication side effects on comorbidities, as well as the burden of treatment and cost.
- Addition of injectable medications: For patients who require the greater glucose-lowering effect of an injectable medication, GLP-1 receptor agonists are preferred over insulin. For patients with extreme and symptomatic hyperglycemia, insulin is recommended.
- Beyond basal insulin: Patients who are unable to maintain glycemic targets on basal insulin in combination with oral medications can have treatment intensified with GLP-1 receptor agonists, SGLT2 inhibitors, or prandial insulin.

- **ADA: Standards of Medical Care in Diabetes – 2019** *(ADA 2019)*
  - SGLT2 inhibitors provide insulin-independent glucose lowering by blocking glucose reabsorption in the proximal renal tubule by inhibiting SGLT2. These agents provide modest weight loss and blood pressure reduction in T2DM. None of the available 4 agents are FDA-approved for the treatment of patients with T1DM.

  - Pharmacological therapy for T2DM:
    - Metformin (if not contraindicated and if tolerated) is the preferred initial pharmacological agent for T2DM (level A).
    - Metformin should be continued when used in combination with other agents, including insulin, if not contraindicated and if tolerated (level A).
    - Dual therapy should be considered in patients with newly diagnosed T2DM who have HbA1c ≥ 1.5% above their glycemic target (level E).
    - Early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when HbA1c levels (> 10%) or blood glucose levels (> 300 mg/dL) are very high (level E).
    - A patient-centered approach should be used to guide the choice of pharmacologic therapy. Considerations include comorbidities (ASCVD, HF, CKD), hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences (level E).
    - In patients with T2DM and established ASCVD, SGLT2 inhibitors or GLP-1 receptor agonists with demonstrated CVD benefit are recommended as part of the antihyperglycemic regimen (level A).
    - In patients with T2DM and established ASCVD with a high risk of or existing HF, SGLT2 inhibitors are preferred (level C).
    - In patients with T2DM and CKD, use of SGLT2 inhibitors or GLP-1 receptor agonists shown to reduce the risk of CKD progression, CV events, or both should be considered (level C).
    - In most patients who require the greater glucose-lowering effect of an injectable medication, GLP-1 receptor agonists are preferred over insulin (level B).
    - The medication regimen should be reevaluated at regular intervals (every 3 to 6 months) and adjusted as needed to incorporate new patient factors (level E).
  - Initial therapy
    - Metformin should be initiated at the time T2DM is diagnosed if there are no contraindications.
    - For patients with contraindications or intolerance to metformin, initial therapy with an SGLT2 inhibitor, GLP-1 receptor agonist, DPP-4 inhibitor, TZD, SFU (2nd generation), or insulin should be considered based on patient factors.
  - Combination therapy
    - Dual therapy is recommended for patients who do not achieve their HbA1c goal after 3 months of monotherapy.
    - For patients without ASCVD or CKD, an agent from any of the 6 preferred classes (SFU, TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or basal insulin) can be added to metformin, with the choice of agent based on drug-specific effects (ie, avoidance of adverse effects such as hypoglycemia and weight gain) and patient factors (ie, cost and personal preference).
    - For patients with ASCVD, HF, or CKD, the best choice for add-on therapy is a GLP-1 receptor agonist or SGLT2 inhibitor with demonstrated benefit.
    - Similar considerations are applied in patients who require a third agent to achieve glycemic goals.

Table 3. ADA Factors to Consider for Antihyperglycemic Therapies in T2DM

Class*	Efficacy	Hypoglycemia	Weight	ASCVD	CHF	Route	DKD	Additional considerations
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Oral	Neutral	GI AEs common B12 deficiency
SGLT2i	Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, empagliflozin	Oral	Benefit: canagliflozin, empagliflozin	Boxed warning for amputation: canagliflozin Genitourinary infections
GLP-1ra	High	No	Loss	Neutral: lixisenatide Benefit: liraglutide > semaglutide > exenatide ER	Neutral	SQ	Benefit: liraglutide	Boxed warning for thyroid C-cell tumors (liraglutide, albiglutide, dulaglutide, exenatide ER)
DPP-4i	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin, alogliptin	Oral	Neutral	Potential risk of acute pancreatitis Joint pain
TZD	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Oral	Neutral	Boxed warning for CHF (pioglitazone, rosiglitazone)
SFU (2nd generation)	High	Yes	Gain	Neutral	Neutral	Oral	Neutral	FDA special warning on increased risk of CV mortality based on studies of an older SFU (tolbutamide)
Insulin	Highest	Yes	Gain	Neutral	Neutral	SQ	Neutral	Injection site reactions

Abbreviations: AE = adverse event; ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; CV = cardiovascular; DKD = diabetic kidney disease; DPP-4i = dipeptidyl peptidase 4 inhibitor; ER = extended-release; GI = gastrointestinal; GLP-1ra = glucagon-like peptide-1 receptor agonist; SFU = sulfonylurea; SGLT2i = sodium-glucose cotransporter-2 inhibitor; SQ = subcutaneous; T2DM = type 2 diabetes mellitus; TZD = thiazolidinediones

* Other antidiabetic drugs not shown in above table (eg, inhaled insulin, alpha-glucosidase inhibitors (AGIs), colesevelam, bromocriptine, and pramlintide) may be tried in specific situations; however, considerations include modest efficacy in T2DM, frequency of administration, potential for drug interactions, cost, and/or side effects.

- **American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) - Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm** *(Garber et al 2019)*
  - Founding principles of the Comprehensive Type 2 Diabetes Management Algorithm:
    - Lifestyle optimization is essential for all patients with diabetes.
    - Minimizing the risk of both severe and non-severe hypoglycemia is a priority. Minimizing risk of weight gain is also a priority.
    - The HbA1c target should be individualized based on numerous factors, such as age, life expectancy, comorbid conditions, duration of diabetes, risk of hypoglycemia or adverse consequences from hypoglycemia, patient motivation, and adherence. A target HbA1c ≤ 6.5% is considered optimal if it can be achieved in a safe and affordable manner, but higher targets may be appropriate for certain individuals and may change for a given individual over time.
    - Glycemic control targets include fasting and post-prandial glucose as determined by self-monitoring of blood glucose.
    - The choice of diabetes therapies must be individualized based on attributes specific to both patients and the medications themselves. Medication attributes include antihyperglycemic efficacy, mechanism of action, risk of inducing hypoglycemia, risk of weight gain, other AEs, tolerability, ease of use, likely adherence, cost, and safety or risk reduction in heart, kidney, or liver disease. Patient-specific considerations include initial A1C, duration of T2D, and obesity status.
      - The choice of therapy depends on the individual patient's cardiac, cerebrovascular, and renal status. Combination therapy is usually required and should involve agents with complementary mechanisms of action.

- Therapy must be evaluated frequently (eg, every 3 months) until the patient is stable, using multiple criteria (eg, HbA1c, self-monitoring of blood glucose records, lipid and blood pressure levels, hypoglycemia events, AEs).

○ Glycemic control algorithm for T2DM:

- In patients with recent-onset T2DM or mild hyperglycemia (HbA1c < 7.5%), lifestyle therapy plus antihyperglycemic monotherapy (preferably with metformin) is recommended. For patients with ASCVD or CKD, GLP-1 receptor agonists and SGLT2 inhibitors with proven benefits may be preferred.
  - Other acceptable alternatives to metformin include DPP-4 inhibitors and TZDs; AGIs, SFUs, and meglitinides may also be appropriate as monotherapy for select patients.
- In patients who do not achieve their HbA1c goal after 3 months of monotherapy or patients who present with HbA1c ≥ 7.5%, dual therapy should be started by adding 1 of the following agents to metformin (in order of preference): GLP-1 receptor agonist, SGLT2 inhibitor, DPP-4 inhibitor, TZD, basal insulin, colesevelam, bromocriptine quick release (QR), AGI, SFU, or meglitinide.
- If dual therapy does not achieve the HbA1c goal in 3 months, triple therapy should be started by adding 1 of the following agents to metformin plus a second-line agent (in order of preference): GLP-1 receptor agonist, SGLT2 inhibitor, TZD, basal insulin, DPP-4 inhibitor, colesevelam, bromocriptine QR, AGI, SFU, or meglitinide.
- If triple therapy fails to achieve the HbA1c goal in 3 months, then the patient should proceed to or intensify insulin therapy.
- In patients with entry HbA1c > 9.0%, dual therapy or triple therapy is recommended if the patient is asymptomatic. If the patient is symptomatic, insulin therapy alone or in combination with other agents is recommended.

○ SGLT2 inhibitor-specific information:

- SGLT2 inhibitors have a glucosuric effect that results in decreased HbA1c, weight, and systolic blood pressure.
- Empagliflozin was associated with significantly lower rates of all-cause and CV death and lower risk of HHF in the EMPA-REG OUTCOME trial.
- Canagliflozin was associated with a reduction in risk for the combined CV outcome of CV death, MI, or nonfatal stroke, as well as a lower risk for HHF. Canagliflozin was also associated with an increased risk of amputation in the CANVAS trial.
- Dapagliflozin was associated with a reduction in the composite outcome of CV death and HHF in the DECLARE-TIMI 58 trial; however, dapagliflozin did not significantly decrease the risk for the composite outcome of CV death, nonfatal MI, and stroke.
- Safety concerns with treatment include increased risks of mycotic genital infections, slightly increased LDL-C levels, limited efficacy in patients with an estimated glomerular filtration rate (eGFR) < 45 mL/min/1.73 m^2, and hypotension due to increased diuresis. Postmarketing reports of SGLT2 inhibitor-associated DKA are still being investigated. Reports were primarily in T1DM and T2DM patients with less than expected hyperglycemia (euglycemic DKA).

Table 4. AACE/ACE Profiles of Antidiabetic Medications

	Hypoglycemia	Weight	Renal/GU	GI	Cardiac	Bone	Ketoacidosis
Metformin	Neutral	Slight loss	eGFR < 30: contraindicated	Moderate	Neutral	Neutral	Neutral
GLP-1ra	Neutral	Loss	Possible benefit: liraglutide Exenatide not indicated CrCl < 30	Moderate	Liraglutide FDA approved for prevention of MACE	Neutral	Neutral
SGLT2i	Neutral	Loss	Genital mycotic infections Not indicated eGFR < 45 Possible CKD benefit	Neutral	Empagliflozin FDA approved to reduce CV mortality Canagliflozin FDA approved to reduce MACE	Neutral	DKA can occur
DPP-4i	Neutral	Neutral	Dose adjustment necessary (except linagliptin) Albuminuria reduction	Neutral	Alogliptin, saxagliptin: Possible increased HHF	Neutral	Neutral
AGI	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral
TZD	Neutral	Gain	Neutral	Neutral	Moderate CHF risk May reduce stroke risk	Moderate fracture risk	Neutral

SFU	Moderate/severe	Gain	More hypoglycemia risk	Neutral	Possible ASCVD risk	Neutral	Neutral
Meglitinide	Mild	Gain	More hypoglycemia risk	Neutral	Possible ASCVD risk	Neutral	Neutral
Colesevelam	Neutral	Neutral	Neutral	Mild	ASCVD benefit	Neutral	Neutral
Bromocriptine QR	Neutral	Neutral	Neutral	Moderate	Safe	Neutral	Neutral
Insulin	Moderate to severe	Gain	More hypoglycemia risk	Neutral	CHF risk	Neutral	Neutral
Pramlintide	Neutral	Loss	Neutral	Moderate	Neutral	Neutral	Neutral

Abbreviations: AGI = alpha-glucosidase inhibitor; ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; CrCl = creatinine clearance; CV = cardiovascular; DKA = diabetic ketoacidosis; DPP-4i = dipeptidyl peptidase 4 inhibitor; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; GI = gastrointestinal; GLP-1ra = glucagon-like peptide-1 receptor agonist; GU = genitourinary; HHF = hospitalization for heart failure; MACE = major adverse cardiovascular events; QR = quick release; SFU = sulfonylurea; SGLT2i = sodium-glucose cotransporter-2 inhibitor; TZD = thiazolidinedione

SAFETY SUMMARY

- Contraindications:
  - History of serious hypersensitivity reaction to canagliflozin, dapagliflozin, empagliflozin, or ertugliflozin.
  - Severe renal impairment (eGFR < 30 mL/min/1.73 m^2), end-stage renal disease, or dialysis.
  - Metformin-containing products have the following contraindications:
    - Severe renal impairment (Segluromet: eGFR < 30 mL/min/1.73 m^2; Invokamet, Invokamet XR, Synjardy, Synjardy XR: eGFR < 45 mL/min/1.73 m^2; Xigduo XR: eGFR < 60 mL/min/1.73 m^2), end-stage renal disease, or dialysis
    - Known hypersensitivity to metformin hydrochloride
    - Acute or chronic metabolic acidosis, including DKA, with or without coma. DKA should be treated with insulin.
  - Linagliptin-containing products have the following contraindications:
    - History of hypersensitivity reactions to linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticarial, or bronchial hyperreactivity.
  - Saxagliptin-containing products have the following contraindications:
    - History of a serious hypersensitivity reaction to dapagliflozin or to saxagliptin, including anaphylaxis, angioedema or exfoliative skin conditions.
    - Moderate to severe renal impairment (eGFR < 45 mL/min/1.73 m^2), end-stage renal disease, or dialysis.
  - Sitagliptin-containing products have the following contraindications:
    - History of hypersensitivity reactions to sitagliptin, such as anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome.
- Boxed Warnings:
  - Canagliflozin-containing products carry a Boxed Warning for lower limb amputation. An approximately 2-fold increased risk of lower limb amputations associated with canagliflozin use was observed in the CANVAS and CANVAS-R trials in patients with T2DM who had established CVD or were at risk for CVD. Amputations of the toe and midfoot were most frequent; however, amputations involving the leg were also observed. Some patients had multiple amputations, some involving both limbs. Before initiating, consider factors that may increase the risk of amputation. Monitor patients receiving canagliflozin for infections or ulcers of the lower limbs, and discontinue if these occur.
  - Metformin-containing products carry a Boxed Warning for lactic acidosis. Lactic acidosis can occur due to metformin accumulation. The risk increases with conditions such as concomitant use of certain drugs, age > 65 years, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. Symptoms include malaise, myalgias, respiratory distress, increasing somnolence, and abdominal pain. Laboratory abnormalities include increased lactate/pyruvate ratio, anion gap acidosis, metformin plasma levels generally > 5 mcg/mL, and elevated blood lactate. If acidosis is suspected, discontinue treatment and hospitalize the patient immediately.
- Warnings and Precautions
  - Several FDA drug safety communications have been issued for canagliflozin.
    - The FDA published a drug safety communication in June 2016 stating that the existing warning about the risk of acute kidney injury for canagliflozin (Invokana, Invokamet, Invokamet XR) and dapagliflozin (Farxiga, Xigduo XR)

has been strengthened. Based on recent confirmed cases of acute kidney injury, the warning in the drug label has been revised to include more specific parameters regarding the monitoring of renal function and discontinuation in cases of renal impairment *(FDA Drug Safety Communication 2016[b])*.

- The drug safety communication issued in May 2016 with interim safety results from the CANVAS and CANVAS-R studies has since culminated in a formal boxed warning on all canagliflozin-containing agents for the risk of lower limb amputation *(FDA Drug Safety Communication 2016[a] and 2017)*.
- The FDA issued a drug safety communication regarding the risk of fracture and bone density in 2016.
  - The FDA evaluated the incidence of bone fractures based on a pooled analysis of nine clinical trials (n = 10,194) with patients ages 55 to 80 who had a mean duration of exposure to canagliflozin of 85 weeks. The incidence rates of bone fractures were greater with canagliflozin 100 mg and 300 mg vs placebo or an active comparator (1.4 and 1.5 vs 1.1 per 100 patient-years of exposure, respectively). Fractures were observed as early as 12 weeks after treatment initiation and were more likely to be low trauma (eg, fall from no more than standing height), and affect the upper extremities *(Watts et al 2016)*.
  - Based on an FDA-required post-marketing trial, canagliflozin caused greater loss of bone mineral density at the hip and lower spine than placebo over two years in elderly individuals (55 to 80 years of age) with poorly controlled T2DM. Placebo-corrected declines in bone mineral density at the total hip were 0.9% and 1.2%, respectively for canagliflozin 100 mg and 300 mg, and were 0.1% at the femoral neck for both canagliflozin doses. Placebo-adjusted bone mineral density decline at the distal forearm was 0.4% with canagliflozin 300 mg and 0% with canagliflozin 100 mg *(Bilezikian et al 2016, FDA Drug Safety Communication 2015)*.
  - A pooled analysis of data from clinical trials did not find an increased risk of fracture with empagliflozin vs placebo or glimepiride *(Kohler et al 2018)*.
- The FDA issued a drug safety communication regarding rare occurrences of necrotizing fasciitis of the perineum (also referred to as Fournier's gangrene) in 2018 (*FDA Drug Safety Communication 2018*).
  - From March 2013 to May 2018, the FDA identified 12 cases (7 males and 5 females) of Fournier's gangrene in patients taking an SGLT2 inhibitor. The infection developed within several months of starting an SGLT2 inhibitor, and all 12 patients were hospitalized and required surgery.
  - In comparison, only 6 cases of Fournier's gangrene (all in men) were identified in review of other antidiabetic drug classes over a period of more than 30 years.

Table 5. Warnings and Precautions

Warnings and Precautions	Single-Entity Products				Combination Products						
	Farxiga (dapagliflozin)	Invokana (canagliflozin)	Jardiance (empagliflozin)	Steglatro (ertugliflozin)	Glyxambi (empagliflozin/ linagliptin)	Qtern (dapagliflozin/ saxagliptin)	Invokamet, Invokamet XR (canagliflozin/ metformin)	Synjardy, Synjardy XR (empagliflozin/ metformin)	Xigduo XR (dapagliflozin/ metformin ER)	Segluromet (ertugliflozin/ metformin)	Steglujan (ertugliflozin/ sitagliptin
Hypotension: Before initiating therapy, assess volume status and correct hypovolemia in patients with renal impairment, the elderly, in patients with low systolic blood pressure, and in patients on diuretics.	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Ketoacidosis: Assess patients who present with signs/symptoms of metabolic acidosis regardless of blood	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔

Warnings and Precautions	Single-Entity Products				Combination Products						
	Farxiga (dapagliflozin)	Invokana (canagliflozin)	Jardiance (empagliflozin)	Steglatro (ertugliflozin)	Glyxambi (empagliflozin/ linagliptin)	Qtern (dapagliflozin/ saxagliptin)	Invokamet, Invokamet XR (canagliflozin/ metformin)	Synjardy, Synjardy XR (empagliflozin/ metformin)	Xigduo XR (dapagliflozin/ metformin ER)	Segluromet (ertugliflozin/ metformin)	Steglujan (ertugliflozin/ sitagliptin
glucose level.											
Acute kidney injury: Consider temporarily discontinuing in settings of reduced oral intake or fluid losses. If acute kidney injury occurs, discontinue and promptly treat. Monitor renal function during therapy.	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Impairment in renal function: Monitor renal function during therapy. More frequent monitoring is recommended in patients with eGFR < 60 mL/min/1.73 m^2. Avoid initiation of dapagliflozin and ertugliflozin when eGFR < 60 mL/min/1.73 m^2.	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Hypoglycemia: Consider a lower dose of insulin or the insulin secretagogue to reduce the risk of hypoglycemia when used in combination.	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Macrovascular outcomes: No clinical studies have established conclusive evidence of macrovascular risk reduction.	✔	✔		✔	✔	✔	✔	✔	✔	✔	✔
Necrotizing fasciitis of the perineum (Fournier's Gangrene): Cases, which may be life-threatening, have been reported. Evaluate patients with pain, tenderness, erythema, or swelling of the genital or perineal area who also have accompanying fever or malaise. Broad spectrum antibiotics and surgical debridement are likely needed.	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Hypersensitivity reactions: Monitor for anaphylaxis and		✔	✔		✔	✔	✔	✔			✔

Warnings and Precautions	Single-Entity Products				Combination Products						
	Farxiga (dapagliflozin)	Invokana (canagliflozin)	Jardiance (empagliflozin)	Steglatro (ertugliflozin)	Glyxambi (empagliflozin/ linagliptin)	Qtern (dapagliflozin/ saxagliptin)	Invokamet, Invokamet XR (canagliflozin/ metformin)	Synjardy, Synjardy XR (empagliflozin/ metformin)	Xigduo XR (dapagliflozin/ metformin ER)	Segluromet (ertugliflozin/ metformin)	Steglujan (ertugliflozin/ sitagliptin
angioedema. Discontinue use and treat and monitor until signs and symptoms resolve.											
Genital mycotic infections: Monitor and treat if indicated.	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Increased LDL-C: Monitor LDL-C and treat per standard of care.	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Bladder cancer: An imbalance in bladder cancers was observed in clinical trials. Dapagliflozin should not be used in patients with active bladder cancer and should be used with caution in patients with a prior history of bladder cancer.	✔					✔			✔		
Lower limb amputation: An approximately 2-fold increased risk of lower limb amputations was observed with canagliflozin in patients with T2DM who had either established CVD or were at risk for CVD.		✔		✔ †			✔			✔ †	✔ †
Urosepsis and Pyelonephritis: Evaluate for signs/symptoms of UTI and treat promptly, if indicated.	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Bone fracture: An increased risk of bone fracture, occurring as early as 12 weeks after treatment initiation, was observed. Consider factors that contribute to fracture risk before initiating canagliflozin		✔					✔				
Vitamin B_{12} deficiency: Metformin may lower vitamin B_{12} levels. Monitor hematologic parameters annually.							✔	✔	✔	✔	
Pancreatitis: There have been post marketing reports of acute					✔	✔					✔

Warnings and Precautions	Single-Entity Products				Combination Products						
	Farxiga (dapagliflozin)	Invokana (canagliflozin)	Jardiance (empagliflozin)	Steglatro (ertugliflozin)	Glyxambi (empagliflozin/ linagliptin)	Qtern (dapagliflozin/ saxagliptin)	Invokamet, Invokamet XR (canagliflozin/ metformin)	Synjardy, Synjardy XR (empagliflozin/ metformin)	Xigduo XR (dapagliflozin/ metformin ER)	Segluromet (ertugliflozin/ metformin)	Steglujan (ertugliflozin/ sitagliptin
pancreatitis, including fatal pancreatitis. Discontinue if suspected.											
Arthralgia: Severe and debilitating arthralgia has been reported in patients taking DPP-4 inhibitors. Consider as a possible cause for severe joint pain and discontinue if appropriate.					✔	✔					✔
Bullous pemphigoid: Patients taking DPP-4 inhibitors have required hospitalization due to bullous pemphigoid. Patients should report development of blisters or erosions. Discontinue if suspected.					✔	✔					✔
HF: In a CV outcomes trial enrolling participants with established ASCVD or multiple risk factors for ASCVD (SAVOR trial), more patients randomized to saxagliptin (289/8280, 3.5%) were hospitalized for HF compared to patients randomized to placebo (228/8212, 2.8%). In a time-to-first-event analysis the risk of HHF was higher in the saxagliptin group (estimated HR, 1.27; 95% CI, 1.07 to 1.51). Subjects with a prior history of HF and subjects with renal impairment had a higher risk for HHF, irrespective of treatment assignment; monitor, observe, and advise patients of this risk and consider discontinuation in any patients that develop signs of HF.					✔ †	✔					✔ †
Radiologic studies with intravascular iodinated contrast							✔	✔	✔	✔	

Warnings and Precautions	Single-Entity Products				Combination Products						
	Farxiga (dapagliflozin)	Invokana (canagliflozin)	Jardiance (empagliflozin)	Steglatro (ertugliflozin)	Glyxambi (empagliflozin/ linagliptin)	Qtern (dapagliflozin/ saxagliptin)	Invokamet, Invokamet XR (canagliflozin/ metformin)	Synjardy, Synjardy XR (empagliflozin/ metformin)	Xigduo XR (dapagliflozin/ metformin ER)	Segluromet (ertugliflozin/ metformin)	Steglujan (ertugliflozin/ sitagliptin
materials: metformin can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Metformin-containing agents should be withheld at the time of or prior to the procedure (and withheld for 48 hours subsequent to the procedure). They should be reinstituted only after renal function is normal or mildly impaired.											

† Warning refers to data with another agent in the class.

- Adverse effects:
  - The most common adverse effects seen with the SGLT2 inhibitors are genital mycotic infections and urinary tract infections.
  - Most common adverse reactions associated with metformin (5% or greater incidence) are diarrhea, nausea, vomiting, flatulence, asthenia, indigestion, abdominal discomfort, and headache.
- Drug Interactions:

  All SGLT2 Inhibitors:
  - Positive urine glucose test: Monitoring glycemic control with urine glucose tests is not recommended in patients taking SGLT2 inhibitors as SGLT2 inhibitors increase urinary glucose excretion and will lead to positive urine glucose tests. Use alternative methods to monitor glycemic control.
  - Interference with 1,5-anhydroglucitol (1,5-AG) assay: Monitoring glycemic control with 1,5-AG assay is not recommended as measurements of 1,5AG are unreliable in assessing glycemic control in patients taking SGLT2 inhibitors. Use alternative methods to monitor glycemic control.

  Canagliflozin:
  - Co-administration of canagliflozin with inducers of uridine diphosphate glucuronosyltransferase (UGT) enzymes such as rifampin, phenytoin, phenobarbital, and ritonavir may result in decreased canagliflozin area under the concentration curve (AUC); consider increasing canagliflozin dosage to 300 mg once daily in patients tolerating 100 mg once daily who have an eGFR of 60 mL/min/1.73 m^2 or more and require additional glycemic control. Consider another antihyperglycemic agent in patients with eGFR of 45 to less than 60 mL/min/1.73 m^2 receiving concurrent therapy with a UGT inducer.
  - Co-administration of canagliflozin 300 mg with digoxin have been reported to increase the AUC and mean peak drug concentration of digoxin (20% and 36%, respectively).

  Dapagliflozin:
  - When dapagliflozin is used with insulin or an insulin secretagogue (eg, SFU), a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycemia.

  Empagliflozin:

- Diuretics: Co-administration of diuretics with increased urine volume and frequency of voids may increase the potential for volume depletion.
- When empagliflozin is used with insulin or an insulin secretagogue (eg, SFU), a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycemia.

Ertugliflozin:

- When ertugliflozin is used with insulin or an insulin secretagogue (eg, SFU), a lower dose of insulin or the insulin secretagogue may be required to reduce the risk of hypoglycemia.

Linagliptin-containing products:

- Efficacy of linagliptin may be reduced when used in combination with a strong inducer of cytochrome P450 (CYP) 3A4 or P-glycoprotein. Consider alternative treatments.

Saxagliptin-containing products:

- Ketoconazole significantly increased saxagliptin exposure. Similar significant increases in plasma concentrations of saxagliptin are anticipated with other strong CYP3A4/5 inhibitors; do not co-administer Qtern with strong CYP3A4/5 inhibitors.

Sitagliptin-containing products:

- Sitagliptin slightly increases serum concentration levels of digoxin. Digoxin therapy should be monitored, but no dosage adjustment is recommended.

Metformin-containing products:

- Cationic drugs such as cimetidine may reduce metformin elimination and may increase the risk for lactic acidosis. Other drugs which may increase exposure to metformin include ranolazine, vandetanib, and dolutegravir.
- Alcohol may potentiate the effect of metformin on lactate metabolism. Advise against excessive alcohol intake.
- Topiramate or other carbonic anhydrase inhibitors (eg, zonisamide, acetazolamide, or dichlorphenamide) frequently decrease serum bicarbonate and induce non-anion gap, hyperchloremic metabolic acidosis. Concomitant use of these drugs may induce metabolic acidosis and may increase the risk of lactic acidosis.
- Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, and isoniazid. When such drugs are administered, monitor for loss of blood glucose control. When such drugs are withdrawn from a patient receiving a metformin-containing drug, monitor for hypoglycemia.

DOSING AND ADMINISTRATION

Table 6. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single entity products				
Farxiga (dapagliflozin)	Tablets	Oral	Daily	Initiation is not recommended if eGFR is < 45 mL/min/1.73 m^2. Discontinue therapy if eGFR falls below 30 mL/min/1.73 m^2.
Invokana (canagliflozin)	Tablets	Oral	Daily	Limit dose to 100 mg once daily in patients who have an eGFR of 45 to < 60 mL/min/1.73 m^2. Not recommended if eGFR persistently falls below 45 mL/min/1.73 m^2. Not recommended in cases of severe hepatic impairment.
Jardiance (empagliflozin)	Tablets	Oral	Daily	Do not initiate if eGFR is < 45 mL/min/1.73 m^2. Discontinue therapy if eGFR persistently falls below 45 mL/min/1.73 m^2.
Steglatro (ertugliflozin)	Tablets	Oral	Daily	Initiation not recommended if eGFR is between 30 and 60 mL/min/1.73 m^2. Not recommended in patients with an eGFR persistently between 30 and < 60 mL/min/1.73 m^2. Discontinue therapy if eGFR falls below 30 mL/min/1.73 m^2.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Not recommended in cases of severe hepatic impairment.
Combination products				
Invokamet (canagliflozin/ metformin)	Tablets	Oral	Two times daily	Limit canagliflozin to 50 mg twice daily in patients with eGFR of 45 to < 60 mL/min/1.73 m^2. Contraindicated in patients with moderate to severe renal impairment (eGFR < 45 mL/min/1.73 m^2), end stage renal disease, or patients on dialysis. Not recommended in patients with hepatic impairment.
Invokamet XR (canagliflozin/ metformin ER)	Tablets	Oral	Daily	Limit canagliflozin to 100 mg (two 50 mg tablets) daily in patients with eGFR of 45 to < 60 mL/min/1.73 m^2. Contraindicated in patients with moderate to severe renal impairment (eGFR < 45 mL/min/1.73 m^2), end stage renal disease, or patients on dialysis. Not recommended in patients with hepatic impairment.
Xigduo XR (dapagliflozin/ metformin ER)	Tablets	Oral	Daily	Not recommended in patients with eGFR < 45 mL/min/1.73 m^2. Contraindicated in patients with eGFR < 30 mL/min/1.73 m^2. Not recommended in hepatic impairment.
Qtern (dapagliflozin/ saxagliptin)	Tablets	Oral	Daily	Do not initiate if eGFR is < 60 mL/min/1.73 m^2. Discontinue if eGFR falls persistently below 60 mL/min/1.73 m^2.
Glyxambi (empagliflozin/ linagliptin)	Tablets	Oral	Daily	Do not initiate or continue if eGFR < 45 mL/min/1.73 m^2. Discontinue if eGFR is persistently < 45 mL/min/1.73 m^2.
Synjardy (empagliflozin/ metformin)	Tablets	Oral	Two times daily	Contraindicated in patients with eGFR < 45 mL/min/1.73 m^2. Advise premenopausal females of the potential for an unintended pregnancy. Use should generally be avoided in patients with hepatic disease
Synjardy XR (empagliflozin/ metformin ER)	Tablets	Oral	Daily	Contraindicated in patients with eGFR < 45 mL/min/1.73 m^2. Advise premenopausal females of the potential for an unintended pregnancy. Use should generally be avoided in patients with hepatic disease
Segluromet (ertugliflozin/ metformin)	Tablets	Oral	Two times daily	Contraindicated in patients with eGFR < 30 mL/min/1.73 m^2. Initiation not recommended if eGFR is between 30 and 60 mL/min/1.73 m^2. Not recommended in patients with an eGFR persistently between 30 and < 60 mL/min/1.73 m^2. Advise premenopausal females of the potential for an unintended pregnancy. Not recommended in hepatic impairment.
Steglujan (ertugliflozin/ sitagliptin)	Tablets	Oral	Daily	Contraindicated in patients with eGFR < 30 mL/min/1.73 m^2. Initiation not recommended if eGFR is between 30 and 60 mL/min/1.73 m^2. Not recommended in patients with an eGFR persistently between 30 and < 60 mL/min/1.73 m^2. Not recommended in cases of severe hepatic impairment.

See the current prescribing information for full details

CONCLUSION

- Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin are inhibitors of SGLT2, the co-transporter responsible for the majority of reabsorption of glucose filtered by the kidney. By inhibiting SGLT2, these agents reduce reabsorption of filtered glucose, lower the renal threshold for glucose, and thereby increase urinary glucose excretion.
- Similar to other currently available oral antidiabetic agents, SGLT2 inhibitors are indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. SGLT2 inhibitors have demonstrated efficacy in lowering HbA1c levels by ~0.5% to 1.5%. They have been studied as monotherapy and in combination with metformin and other antidiabetic agents.
- The SGLT2 inhibitor/metformin combinations include Invokamet/Invokamet XR (canagliflozin/metformin), Synjardy/Synjardy XR (empagliflozin/metformin), Segluromet (ertugliflozin/metformin), and Xigduo XR (dapagliflozin/metformin). Glyxambi (empagliflozin/linagliptin), Qtern (dapagliflozin/saxagliptin), and Steglujan (ertugliflozin/sitagliptin) are SGLT2 inhibitor/DPP-4 inhibitor combination products.
- In clinical trials, the SGLT2 inhibitors have been evaluated in patients that were drug-naïve or in patients whose glucose was inadequately controlled with other oral agents and/or insulin. They have demonstrated effectiveness when used as monotherapy and in combination with other antidiabetic agents. Most trials evaluated the addition of an SGLT2 inhibitor to one or more classes of antidiabetic agents.
- The SGLT2 inhibitors have consistently shown significant beneficial effects on HbA1c, FPG, weight, PPG, and blood pressure when used as monotherapy or in combination therapy.
- All 4 single-entity SGLT2 inhibitors are dosed once daily. Initiation of dapagliflozin and ertugliflozin are not recommended in patients with an eGFR < 60 mL/min/1.73 m^2. Empagliflozin and canagliflozin are not recommended in patients with an eGFR < 45 mL/min/1.73 m^2. Volume depletion issues should be corrected prior to initiation of SGLT2 therapy.
- The SGLT2 inhibitors share a similar safety profile, including increased LDL-C levels, increased serum creatinine and a concomitant decrease in eGFR, volume depletion, and genital mycotic infections. Warnings for bone fractures and lower limb amputation were added for canagliflozin-containing products. Warnings for DKA, urosepsis and pyelonephritis, and necrotizing fasciitis of the perineum were also added to the labeling of SGLT2 inhibitors after increased incidences were reported post-marketing.
- Consensus guidelines generally recommend metformin as the optimal first-line drug, unless there are prevalent contraindications or intolerance to treatment. SGLT2 inhibitors may be prescribed as a part of subsequent dual or triple therapy, if the target is not achieved after three months at maximum tolerated doses. SGLT2 inhibitors are preferred add-on agents for dual therapy in patients with established ASCVD, CKD, or HF. All guidelines emphasize individualized therapy based upon a patient's specific factors such as comorbidities, weight, risk of hypoglycemia, and duration of diabetes.
- Large CV outcome trials have demonstrated a CV benefit with certain SGLT2 inhibitors. The EMPA-REG OUTCOME trial was a long-term, placebo-controlled study involving 7020 patients with T2DM at high risk for CV events. When added to standard of care, empagliflozin significantly reduced the risk of the combined endpoint (CV death, nonfatal MI, or nonfatal stroke) by 14% vs placebo ($p < 0.001$ for noninferiority; $p = 0.04$ for superiority). In the CANVAS Program, significantly fewer participants in the canagliflozin group had a primary outcome event (the composite of death from CV causes, nonfatal MI, or nonfatal stroke) vs placebo: 26.9 vs 31.5 participants with an event per 1000 patient-years (HR, 0.86; 95% CI, 0.75 to 0.97; $p < 0.001$ for noninferiority; $p = 0.02$ for superiority). In the DECLARE-TIMI 58 study, dapagliflozin was noninferior to placebo with respect to MACE ($p < 0.001$ for noninferiority; $p = 0.17$ for superiority) and significantly reduced a composite outcome of CV death and HHF (HR, 0.83; 95% CI, 0.73 to 0.95; $p = 0.0005$) in patients with established CVD or multiple risk factors for CVD.
- The SGLT2 inhibitors provide another treatment option for glycemic control in patients unable to tolerate first-line treatment with metformin or other oral antidiabetic therapies due to adverse effects or risk for hypoglycemia. Positive CV outcomes have been demonstrated with empagliflozin, canagliflozin, and dapagliflozin, suggesting that SGLT2 inhibitors may play a significant role in T2DM patients at high risk for CV events.

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Therapeutic Class Overview
Sulfonylureas

INTRODUCTION

- In the United States (US), diabetes mellitus affects more than 30 million people and is the 7th leading cause of death (*Centers for Disease Control and Prevention [CDC] 2018*).
- Type 2 diabetes mellitus (T2DM) is the most common form of diabetes and is characterized by elevated fasting and postprandial glucose concentrations *(American Diabetes Association [ADA] 2019[a])*. It is a chronic illness that requires continuing medical care and ongoing patient self-management education and support to prevent acute complications and to reduce the risk of long-term complications *(ADA 2019[b])*.
  - Complications of T2DM include hypertension, heart disease, stroke, vision loss, nephropathy, and neuropathy *(ADA 2019[a])*.
- In addition to dietary and lifestyle management, T2DM can be treated with insulin, one or more oral medications, or a combination of both. Many patients with T2DM will require combination therapy *(Garber et al 2019)*.
- Classes of oral medications for the management of blood glucose levels in patients with T2DM focus on increasing insulin secretion, increasing insulin responsiveness, or both, decreasing the rate of carbohydrate absorption, decreasing the rate of hepatic glucose production, decreasing the rate of glucagon secretion, and blocking glucose reabsorption by the kidney *(Garber et al 2019)*.
- Pharmacologic options for T2DM include sulfonylureas (SFUs), biguanides, thiazolidinediones (TZDs), meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogs, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, combination products, and insulin *(Garber et al 2019)*.
- SFUs are the oldest of the oral antidiabetic medications, and all agents are available generically. The SFUs can be divided into 2 categories: first-generation and second-generation.
- The first-generation SFUs are acetohexamide, chlorpropamide, tolazamide, and tolbutamide. Acetohexamide has been discontinued from the U.S. market and will not be further discussed in this review. Chlorpropamide, tolazamide and tolbutamide are all available as generics; the branded products (Diabinese, Tolinase, and Orinase, respectively) have been discontinued by the manufacturers.
- The second-generation SFUs are glimepiride, glipizide, and glyburide. The second-generation agents have structural characteristics that allow them to be given in much lower doses than the first-generation agents. The branded products Diabeta and Micronase have been discontinued by their respective manufacturers, but generic glyburide is still available.
- The combination products consist of an SFU and metformin (glyburide/metformin and glipizide/metformin) or an SFU and a TZD (glimepiride/pioglitazone), which also have generic formulations available. Of note, the brands Metaglip (glipizide/metformin) and Glucovance (glyburide/metformin) have been discontinued. Additionally, Avandaryl (glimepiride/rosiglitazone) has been discontinued, but not for efficacy or safety reasons. A generic formulation is not yet available but has received Food and Drug Administration (FDA) approval. This review will focus on the single entity and combination oral SFUs listed in Table 1.
- Medispan class: Antidiabetics, Sulfonylureas; Antidiabetics, Antidiabetic Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
First-generation	
chlorpropamide	✔
tolazamide	✔
tolbutamide	✔
Second-generation	
Amaryl (glimepiride)	✔
glyburide	✔
Glucotrol (glipizide)	✔

Drug	Generic Availability
Glucotrol XL (glipizide extended-release [ER])	✔
Glynase (micronized glyburide)	✔
Combination products	
Duetact (glimepiride/pioglitazone)	✔
glipizide/metformin	✔
glyburide/metformin	✔

(Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019)

INDICATIONS

Table 2. FDA-Approved Indications

Indication	1st generation			2nd generation			Combinations		
	chlorpropamide	tolazamide	tolbutamide	glimepiride	glipizide	glyburide	glimepiride/ pioglitazone	glipizide/ metformin	glyburide/ metformin
Adjunct to diet and exercise to improve glycemic control in adults with T2DM	✔	✔	✔	✔	✔	✔		✔	✔
Adjunct to diet and exercise to improve glycemic control in adults with T2DM who are already treated with a TZD and an SFU or who have inadequate glycemic control on a TZD alone or an SFU alone							✔		

(Prescribing information: Amaryl 2018, chlorpropamide 2009, Duetact 2017, glipizide and metformin 2017, glyburide 2017, glyburide/metformin 2017, Glucotrol 2018, Glucotrol XL 2018, Glynase 2017, tolazamide 2009, tolbutamide 2009)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EVIDENCE SUMMARY

- Second-generation SFUs have comparable efficacy for the treatment of T2DM *(Bell et al 2004, Inzucchi et al 2002).* Some evidence suggests that glimepiride may have less of an impact on ischemic preconditioning than glyburide and may be the preferred agent in patients with coronary heart disease; however, contrasting evidence suggests that there is no difference between agents *(Andersson et al 2011, Evans et al 2008, Lee et al 2003, Pantalone et al 2010).* Other studies show that therapy with glipizide and glyburide resulted in comparable HbA1c reductions, and similar reductions in HbA1c were observed with patients on glimepiride and glyburide therapy *(Birkeland et al 1994, Kitabchi et al 2000, Sami et al 1996).*
- A systematic review and meta-analysis of 31 DB randomized controlled trials (RCTs) evaluated the efficacy of SFUs in reducing hemoglobin A1C (HbA1c). Included studies evaluated glimepiride, glipizide, glyburide, tolbutamide, or tolazamide as monotherapy or add-on therapy. The duration of the included trials ranged from 12 weeks to 3 years, with a median duration of 16 weeks. In 9 monotherapy trials, the placebo-adjusted reduction in HbA1c with SFUs was 1.51% (95% CI, 1.25 to 1.78). In 4 add-on therapy trials, SFUs reduced HbA1c by 1.62% (95% CI, 1.0 to 2.24). In 17 trials with patients on insulin therapy, the addition of an SFU was associated with an HbA1c reduction of 0.46% (95% CI, 0.24 to 0.69) and a reduced insulin dose *(Hirst et al 2013).*

- A meta-analysis demonstrated that glyburide was not associated with a higher risk of cardiovascular (CV) events when compared to other SFUs, meglitinides, or insulin. However, glyburide was associated with a 52% higher risk of experiencing greater than 1 episode of hypoglycemia *(Gangji et al 2007).* Additional meta-analyses supported this evidence. Bolen et al compared several endpoints (eg, mortality, microvascular endpoints, macrovascular endpoints) among the following agents: second-generation SFUs, biguanides, TZDs, meglitinides, and alpha-glucosidase inhibitors. Results demonstrated that there was no definitive evidence on the comparative effectiveness of the agents on all-cause mortality, CV mortality or morbidity, peripheral arterial disease, neuropathy, retinopathy, or nephropathy. TZDs, metformin, and repaglinide improved glycemic control to the same degree as SFUs *(Bolen et al 2007).* Pantalone et al and Andersson et al also compared overall mortality among several second-generation SFUs. No statistically significant difference in the risk of overall mortality was observed among these agents. However, study results suggest that glimepiride may be the preferred SFU in those with underlying coronary artery disease *(Andersson et al 2011, Pantalone et al 2010).*
- In a double-blind (DB) randomized trial, treatment with metformin showed a significant reduction in the recurrence of composite CV events compared to glipizide *(Hong et al 2013).* In an observational study, the use of glyburide, glipizide, and rosiglitazone was associated with significantly higher mortality rates than metformin therapy *(Wheeler et al 2013).*
- Several head to head studies were conducted to evaluate the efficacy of SFUs compared to a GLP-1 agonist. Each therapy in most instances was added to existing drugs to improve glycemic control. Overall, reduction in HbA1c from baseline and improvement in glycemic control were significantly greater with the GLP-1 agonist compared to glimepiride *(Ahrén et al 2014, Gallwitz et al 2012, Garber et al 2009, Garber et al 2011, Nauck et al 2009).* In similarly designed studies, the efficacy and safety of an SFU was compared to a DPP-4 inhibitor. Overall, reductions in mean HbA1c from baseline were similar in the DPP-4 inhibitor (alogliptin, linagliptin, sitagliptin, saxagliptin) and SFU (glimepiride, glipizide) study groups *(Arechavaleta et al 2011, Del Prato et al 2014, Gallwitz et al 2012, Goke et al 2010, Rosenstock et al 2013, Seck et al 2010).* In a study comparing alogliptin to glipizide, more patients taking glipizide experienced hypoglycemic episodes compared to patients taking alogliptin *(Del Prato et al 2014, Rosenstock et al 2013).* In a 52-week extension study, patients taking saxagliptin + metformin had similar glycemic control compared to patients taking glipizide + metformin. However, the saxagliptin group had a lower incidence of hypoglycemia and less weight gain *(Goke et al 2013).*
- A meta-analysis by Amate et al compared the efficacy and safety of metformin and a DPP-4 inhibitor versus metformin and glimepiride as a second-line treatment. The results revealed a 12% greater decrease in HbA1c and a higher proportion of patients achieving HbA1c <7% in the metformin with glimepiride group *(Amate et al 2015).* Another meta-analysis compared metformin with an SFU to metformin with a DPP-4 inhibitor. The results revealed a statistically significant reduction in HbA1c levels for the SFU group during the first 12 weeks of therapy, but no difference between the 2 groups following 52 to 104 weeks of treatment. The proportion of patients reaching HbA1c <7% was not statistically different between the 2 groups *(Mishriky et al 2015).* A meta-analysis by Hou et al investigated the efficacy and safety of metformin with an SFU versus metformin with sitagliptin when used for at least 12 weeks. The results revealed no statistically significant differences between the 2 groups with regard to decrease in HbA1c levels and proportion of patients achieving HbA1c <7% *(Hou et al 2015).* Results of all meta-analyses revealed greater weight gain and more hypoglycemia in patients taking metformin with an SFU compared to patients on metformin with a DPP-4 inhibitor.
- A network meta-analysis of controlled trials comparing 2 or more SFUs assessed all-cause mortality and CV mortality. In 18 studies (N = 167,327), all-cause mortality was lowest with glimepiride, followed by glipizide, glyburide, tolbutamide, and chlorpropamide. Glimepiride was associated with a significantly lower risk of mortality than glyburide, and glipizide was associated with a similar mortality rate to glyburide. Similar associations were observed for CV mortality in 13 studies (N = 145,916). Compared to glyburide, the RR of CV-related death was 0.79 (95% credible interval [CrI], 0.57 to 1.11) for glimepiride, 1.01 (95% CrI, 0.72 to 1.43) for glipizide, 1.11 (95% CrI, 0.79 to 1.55) for tolbutamide, and 1.45 (95% CrI, 0.88 to 2.44) for chlorpropamide *(Simpson et al 2015).*
- A meta-analysis of 8 studies compared CV outcomes with metformin plus an SFU and metformin plus a DPP-4 inhibitor. The relative risk (RR) of nonfatal CV events (0.71, 95% confidence interval [CI] 0.56 to 0.90), CV mortality (0.58, 95% CI 0.41 to 0.82), and all-cause mortality (0.72, 95% CI 0.59 to 0.87) were all significantly lower with metformin plus a DPP-4 inhibitor. The RR of fatal CV events was similar with both treatment combinations *(Wang et al 2017).*
- A network meta-analysis of 170 RCTs (N = 166,371) evaluated differences in 4-point major adverse cardiovascular events (MACE) (composite of CV death, nonfatal MI, nonfatal stroke, and unstable angina) and all-cause mortality. Compared to SFUs, SGLT2 inhibitors, insulin, GLP-1 receptor agonists, and DPP-4 inhibitors were associated with

significantly lower rates of MACE. For all-cause mortality, SFUs were associated with more deaths than SGLT2 inhibitors and insulin. The ranking of CV risk was linearly correlated with the ranking of severe hypoglycemia risk, and SFUs were associated with the highest risks for both outcomes *(Zhuang et al 2018).*

- A head to head study was conducted to evaluate the efficacy and safety of glyburide when compared to nateglinide in T2DM with 2 hour postprandial glucose levels ≥11.1 mmol/L. Study results revealed that nateglinide led to greater reductions in postprandial glucose excursions compared to glyburide *(Bellomo et al 2011).*
- Clinical trials comparing the SFUs to the SGLT2 inhibitors have suggested that the SGLT2 inhibitors are noninferior to glipizide or glimepiride and are associated with less hypoglycemia and weight gain *(Nauck et al 2011, Nauck et al 2014, Ridderstrale et al 2014).*
- The effectiveness of the combination SFUs was demonstrated primarily through clinical trials designed to compare individual SFU agents in combination with other antidiabetic agents (ie, metformin). A significant improvement in glycemic control was observed when an SFU was administered as combination therapy compared to monotherapy *(Garber et al 2002, Goldstein et al 2003, Marre et al 2002).* In 2 studies where glyburide monotherapy and metformin monotherapy were compared to a combination of glyburide and metformin, the reductions in HbA1c were significantly greater with the combination *(Garber et al 2002, Marre et al 2002).* A similar outcome was seen when glipizide monotherapy and metformin monotherapy were compared to the combination of glipizide and metformin *(Goldstein et al 2003).* The addition of basal insulin to combination therapy with glimepiride and metformin resulted in a significant improvement in overall glycemic control compared with combination glimepiride and metformin *(Park et al 2014).*
- Another set of studies consisted of retrospective analyses that looked at glyburide and metformin as individual agents given concurrently compared to a combination product of glyburide and metformin *(Blonde et al 2003, Duckworth et al 2003, Gottschalk et al 2007).* These studies provided only mean doses of the individual agents and the combination products, making it difficult to determine if equivalent doses of the individual agents given concurrently were equivalent to the combination products. Thus, it is not clear if there is any advantage of the combination formulation over the individual agents when given at an equivalent dose. Finally, a meta-analysis compared the safety of SFUs in combination with metformin to metformin monotherapy. While combination therapy was more effective than metformin alone in improving HbA1c and reducing gastrointestinal effects, it had the disadvantage of decreasing high-density lipoproteins and increasing the risk of hypoglycemia and nervous system adverse events *(Zhang et al 2013).*
- A systematic review evaluated the safety and efficacy of antidiabetic classes (ie, biguanides, TZDs, SFUs, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 receptor agonists) in 216 studies of monotherapy or combination therapy for T2DM. *(Bolen et al 2016).*
  - For monotherapy, metformin, TZDs, and SFUs were associated with similar reductions in HbA1c in the short term (high strength of evidence). Compared to DPP-4 inhibitors, metformin was more effective in lowering HbA1c (difference, −0.4%). Differences in HbA1c reduction between SFUs, TZDs, DPP-4 inhibitors, and SGLT2 inhibitors as add-on therapy to metformin were either not statistically significant or not clinically meaningful (< 0.3%) (moderate strength of evidence).
  - In general, significant between-group differences were observed when comparing classes expected to increase weight (ie, SFUs, TZDs, insulin) to classes expected to decrease weight (ie, metformin, DPP-4 inhibitors, SGLT2 inhibitors, GLP-1 agonists). SFUs were associated with less weight gain than TZDs, but more weight gain than metformin and GLP-1 agonists (moderate strength of evidence). Patients with an SFU added to metformin therapy experienced significantly more weight gain compared to patients who remained on metformin alone (high strength of evidence) and patients with a DPP-4 inhibitor or SGLT2 inhibitor added to metformin (high strength of evidence).
  - Compared to metformin, SFU monotherapy was associated with a 50 to 70% higher RR of CV mortality (absolute risk difference, 0.1 to 2.9% in RCTs; moderate strength of evidence).
  - Overall, the risk of mild, moderate, or total hypoglycemia was higher with SFUs alone and in combination with metformin than with any other monotherapies and metformin-based combinations. Patients receiving SFU monotherapy had a higher risk of severe hypoglycemia than patients receiving metformin or TZD monotherapy (moderate strength of evidence). As add-on therapy to metformin, SFUs were associated with a greater risk of severe hypoglycemia than DPP-4 or SGLT2 inhibitors (moderate strength of evidence).
- Three retrospective, propensity-matched, new-user cohort studies (N = 246,558,805) with replication across 8 sites evaluated patients receiving SFUs, DPP-4 inhibitors, or TZDs as add-on therapy to metformin. No significant differences were observed between classes in the reduction of HbA1c levels to ≤ 7% or the incidence of kidney disorders. Compared to DPP-4 inhibitors, SFUs were associated with an increased risk for myocardial infarction (hazard ratio [HR], 1.12; 95% CI, 1.02 to 1.24) and eye disorders (HR, 1.15; 95% CI, 1.11 to 1.19) *(Vashisht et al 2018).*

CLINICAL GUIDELINES

Overview

- Professional society guidelines are consistent in recommending metformin as the optimal first-line pharmacologic therapy for treatment-naïve patients with T2DM, unless the patient has contraindications or intolerance. SFUs are among the second-line options for subsequent therapy. All guidelines emphasize individualized therapy based upon patient-specific factors such as comorbidities, weight, risk of hypoglycemia, and duration of diabetes *(ADA 2019, Copeland et al 2013, Davies et al 2018, Garber et al 2019)*.
- A 2018 American College of Cardiology expert consensus decision pathway on CV risk reduction in patients with T2DM and atherosclerotic CV disease (ASCVD) suggests adding an SGLT2 inhibitor or GLP-1 receptor agonist that has demonstrated beneficial CV outcomes to other guideline-directed therapy for diabetes (specifically, metformin). Among the SGLT2 inhibitors with CV outcome data at the time that the pathway was written (canagliflozin and empagliflozin), empagliflozin was the preferred SGLT2 inhibitor based on the available evidence and overall risk to benefit ratio *(Das et al 2018)*.

- **ADA/European Association for the Study of Diabetes (EASD): Management of Hyperglycemia in Type 2 Diabetes, 2018** *(Davies et al 2018)*
  - The goals of T2DM therapy are to prevent or delay complications and maintain quality of life, which requires glycemic control, CV risk factor management, regular follow-up, and a patient-centered approach to enhance patient engagement in self-care activities. Careful consideration of patient-specific factors and preferences must inform the process of individualizing treatment goals and strategies.
  - Due to new evidence of benefit with specific agents in the reduction of mortality, heart failure (HF), and progression of renal disease, the overall approach to glucose-lowering medication in T2DM for the ADA/EASD consensus report was updated in 2018. A history of CVD, chronic kidney disease (CKD), and heart failure should be taken into consideration early in the process of treatment selection. Additionally, the guideline recommends early consideration of weight, hypoglycemic risk, treatment cost, and other patient-related factors that may influence the choice of drug therapy.
    - Among patients with T2DM who have established ASCVD, SGLT2 inhibitors or GLP-1 receptor agonists with proven CV benefit are recommended as part of glycemic management.
    - For patients with ASCVD with concomitant HF, SGLT2 inhibitors are recommended.
    - For patients with T2DM and CKD (with or without ASCVD), an SGLT2 inhibitor shown to reduce CKD progression should be considered. If SGLT2 inhibitors are contraindicated or not preferred, a GLP-1 receptor agonist shown to reduce CKD progression should be considered.
  - Initial monotherapy: Metformin remains the preferred drug for initial monotherapy based on its efficacy, safety, tolerability, low cost, and extensive clinical experience.
  - Add-on to metformin: The selection of a second agent added to metformin is based on patient preference and clinical characteristics. Important clinical characteristics include the presence of established ASCVD and other comorbidities such as HF or CKD; the risk for specific AEs, particularly hypoglycemia and weight gain; as well as safety, tolerability, and cost.
  - Intensification beyond 2 medications: Intensification of treatment beyond dual therapy to maintain glycemic targets requires consideration of the impact of medication side effects on comorbidities, as well as the burden of treatment and cost.
  - Addition of injectable medications: For patients who require the greater glucose-lowering effect of an injectable medication, GLP-1 receptor agonists are preferred over insulin. For patients with extreme and symptomatic hyperglycemia, insulin is recommended.
  - Beyond basal insulin: Patients who are unable to maintain glycemic targets on basal insulin in combination with oral medications can have treatment intensified with GLP-1 receptor agonists, SGLT2 inhibitors, or prandial insulin.

- **ADA: Standards of Medical Care in Diabetes – 2019** *(ADA 2019)*
  - Pharmacological therapy for T2DM:
    - Metformin (if not contraindicated and if tolerated) is the preferred initial pharmacological agent for T2DM (level A).
    - Metformin should be continued when used in combination with other agents, including insulin, if not contraindicated and if tolerated (level A).

- Dual therapy should be considered in patients with newly diagnosed T2DM who have HbA1c ≥ 1.5% above their glycemic target (level E).
- Early introduction of insulin should be considered if there is evidence of ongoing catabolism (weight loss), if symptoms of hyperglycemia are present, or when HbA1c levels (> 10%) or blood glucose levels (> 300 mg/dL) are very high (level E).
- A patient-centered approach should be used to guide the choice of pharmacologic therapy. Considerations include comorbidities (ASCVD, HF, CKD), hypoglycemia risk, impact on weight, cost, risk for side effects, and patient preferences (level E).
- In patients with T2DM and established ASCVD, SGLT2 inhibitors or GLP-1 receptor agonists with demonstrated CVD benefit are recommended as part of the antihyperglycemic regimen (level A).
- In patients with T2DM and established ASCVD with a high risk of or existing heart failure, SGLT2 inhibitors are preferred (level C).
- In patients with T2DM and CKD, use of SGLT2 inhibitors or GLP-1 receptor agonists shown to reduce the risk of CKD progression, CV events, or both should be considered (level C).
- In most patients who require the greater glucose-lowering effect of an injectable medication, GLP-1 receptor agonists are preferred over insulin (level B).
- The medication regimen should be reevaluated at regular intervals (every 3 to 6 months) and adjusted as needed to incorporate new patient factors (level E).

○ Initial therapy
- Metformin should be initiated at the time T2DM is diagnosed if there are no contraindications.
- For patients with contraindications or intolerance to metformin, initial therapy with an SGLT2 inhibitor, GLP-1 receptor agonist, DPP-4 inhibitor, TZD, SFU (2nd generation), or insulin should be considered based on patient factors.

○ Combination therapy
- Dual therapy is recommended for patients who do not achieve their HbA1c goal after 3 months of monotherapy.
- For patients without ASCVD or CKD, an agent from any of the 6 preferred classes (SFU, TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or basal insulin) can be added to metformin, with the choice of agent based on drug-specific effects (ie, avoidance of adverse effects such as hypoglycemia and weight gain) and patient factors (ie, cost and personal preference).
- For patients with ASCVD, HF, or CKD, the best choice for add-on therapy is a GLP-1 receptor agonist or SGLT2 inhibitor with demonstrated benefit.
- Similar considerations are applied in patients who require a third agent to achieve glycemic goals.

Table 3. ADA Factors to Consider for Antihyperglycemic Therapies in T2DM

Class*	Efficacy	Hypoglycemia	Weight	ASCVD	CHF	Route	DKD	Additional considerations
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Oral	Neutral	GI AEs common B12 deficiency
SGLT2i	Intermediate	No	Loss	Benefit: canagliflozin, empagliflozin	Benefit: canagliflozin, empagliflozin	Oral	Benefit: canagliflozin, empagliflozin	Boxed warning for amputation: canagliflozin Genitourinary infections
GLP-1ra	High	No	Loss	Neutral: lixisenatide Benefit: liraglutide > semaglutide > exenatide ER	Neutral	SQ	Benefit: liraglutide	Boxed warning for thyroid C-cell tumors (liraglutide, albiglutide, dulaglutide, exenatide ER)
DPP-4i	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin, alogliptin	Oral	Neutral	Potential risk of acute pancreatitis Joint pain
TZD	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Oral	Neutral	Boxed warning for CHF (pioglitazone, rosiglitazone)
SFU (2nd generation)	High	Yes	Gain	Neutral	Neutral	Oral	Neutral	FDA special warning on increased risk of CV

								mortality based on studies of an older SFU (tolbutamide)
Insulin	Highest	Yes	Gain	Neutral	Neutral	SQ	Neutral	Injection site reactions

Abbreviations: AE = adverse event; ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; CV = cardiovascular; DKD = diabetic kidney disease; DPP-4i = dipeptidyl peptidase 4 inhibitor; ER = extended-release; GI = gastrointestinal; GLP-1ra = glucagon-like peptide-1 receptor agonist; SFU = sulfonylurea; SGLT2i = sodium-glucose cotransporter-2 inhibitor; SQ = subcutaneous; T2DM = type 2 diabetes mellitus; TZD = thiazolidinediones

* Other antidiabetic drugs not shown in above table (eg, inhaled insulin, alpha-glucosidase inhibitors (AGIs), colesevelam, bromocriptine, and pramlintide) may be tried in specific situations; however, considerations include modest efficacy in T2DM, frequency of administration, potential for drug interactions, cost, and/or side effects.

- **American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) - Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm** *(Garber et al 2019)*
  - Founding principles of the Comprehensive Type 2 Diabetes Management Algorithm:
    - Lifestyle optimization is essential for all patients with diabetes.
    - Minimizing the risk of both severe and non-severe hypoglycemia is a priority. Minimizing risk of weight gain is also a priority.
    - The HbA1c target should be individualized based on numerous factors, such as age, life expectancy, comorbid conditions, duration of diabetes, risk of hypoglycemia or adverse consequences from hypoglycemia, patient motivation, and adherence. A target HbA1c ≤ 6.5% is considered optimal if it can be achieved in a safe and affordable manner, but higher targets may be appropriate for certain individuals and may change for a given individual over time.
    - Glycemic control targets include fasting and post-prandial glucose as determined by self-monitoring of blood glucose.
    - The choice of diabetes therapies must be individualized based on attributes specific to both patients and the medications themselves. Medication attributes include antihyperglycemic efficacy, mechanism of action, risk of inducing hypoglycemia, risk of weight gain, other AEs, tolerability, ease of use, likely adherence, cost, and safety or risk reduction in heart, kidney, or liver disease. Patient-specific considerations include initial A1C, duration of T2DM, and obesity status.
      - The choice of therapy depends on the individual patient's cardiac, cerebrovascular, and renal status. Combination therapy is usually required and should involve agents with complementary mechanisms of action.
    - Therapy must be evaluated frequently (eg, every 3 months) until the patient is stable, using multiple criteria (eg, HbA1c, self-monitoring of blood glucose records, lipid and blood pressure levels, hypoglycemia events, AEs).
  - Glycemic control algorithm for T2DM:
    - In patients with recent-onset T2DM or mild hyperglycemia (HbA1c < 7.5%), lifestyle therapy plus antihyperglycemic monotherapy (preferably with metformin) is recommended. For patients with ASCVD or CKD, GLP-1 receptor agonists and SGLT2 inhibitors with proven benefits may be preferred.
      - Other acceptable alternatives to metformin include DPP-4 inhibitors and TZDs; AGIs, SFUs, and meglitinides may also be appropriate as monotherapy for select patients.
    - In patients who do not achieve their HbA1c goal after 3 months of monotherapy or patients who present with HbA1c ≥ 7.5%, dual therapy should be started by adding 1 of the following agents to metformin (in order of preference): GLP-1 receptor agonist, SGLT2 inhibitor, DPP-4 inhibitor, TZD, basal insulin, colesevelam, bromocriptine quick release (QR), AGI, SFU, or meglitinide.
    - If dual therapy does not achieve the HbA1c goal in 3 months, triple therapy should be started by adding 1 of the following agents to metformin plus a second-line agent (in order of preference): GLP-1 receptor agonist, SGLT2 inhibitor, TZD, basal insulin, DPP-4 inhibitor, colesevelam, bromocriptine QR, AGI, SFU, or meglitinide.
    - If triple therapy fails to achieve the HbA1c goal in 3 months, then the patient should proceed to or intensify insulin therapy.
    - In patients with entry HbA1c > 9.0%, dual therapy or triple therapy is recommended if the patient is asymptomatic. If the patient is symptomatic, insulin therapy alone or in combination with other agents is recommended.
  - SFU-specific information:
    - The SFUs have relatively potent HbA1c-lowering effects, but they lack durability and are associated with weight gain and hypoglycemia. SFUs have the highest risk of serious hypoglycemia of any noninsulin therapy, and

analyses of large datasets have raised concerns regarding the CV safety of this class when the comparator is metformin, which may itself have cardioprotective properties.

Table 4. AACE/ACE Profiles of Antidiabetic Medications

	Hypoglycemia	Weight	Renal/GU	GI	Cardiac	Bone	Ketoacidosis
Metformin	Neutral	Slight loss	eGFR < 30: contraindicated	Moderate	Neutral	Neutral	Neutral
GLP-1ra	Neutral	Loss	Possible benefit: liraglutide Exenatide not indicated CrCl < 30	Moderate	Liraglutide FDA approved for prevention of MACE	Neutral	Neutral
SGLT2i	Neutral	Loss	Genital mycotic infections Not indicated eGFR < 45 Possible CKD benefit	Neutral	Empagliflozin FDA approved to reduce CV mortality Canagliflozin FDA approved to reduce MACE	Neutral	DKA can occur
DPP-4i	Neutral	Neutral	Dose adjustment necessary (except linagliptin) Albuminuria reduction	Neutral	Alogliptin, saxagliptin: Possible increased HHF	Neutral	Neutral
AGI	Neutral	Neutral	Neutral	Moderate	Neutral	Neutral	Neutral
TZD	Neutral	Gain	Neutral	Neutral	Moderate CHF risk May reduce stroke risk	Moderate fracture risk	Neutral
SFU	Moderate/severe	Gain	More hypoglycemia risk	Neutral	Possible ASCVD risk	Neutral	Neutral
Meglitinide	Mild	Gain	More hypoglycemia risk	Neutral	Possible ASCVD risk	Neutral	Neutral
Colesevelam	Neutral	Neutral	Neutral	Mild	ASCVD benefit	Neutral	Neutral
Bromocriptine QR	Neutral	Neutral	Neutral	Moderate	Safe	Neutral	Neutral
Insulin	Moderate to severe	Gain	More hypoglycemia risk	Neutral	CHF risk	Neutral	Neutral
Pramlintide	Neutral	Loss	Neutral	Moderate	Neutral	Neutral	Neutral

Abbreviations: AGI = alpha-glucosidase inhibitor; ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; CrCl = creatinine clearance; CV = cardiovascular; DKA = diabetic ketoacidosis; DPP-4i = dipeptidyl peptidase 4 inhibitor; eGFR = estimated glomerular filtration rate; FDA = Food and Drug Administration; GI = gastrointestinal; GLP-1ra = glucagon-like peptide-1 receptor agonist; GU = genitourinary; HHF = hospitalization for heart failure; MACE = major adverse cardiovascular events; QR = quick release; SFU = sulfonylurea; SGLT2i = sodium-glucose cotransporter-2 inhibitor; TZD = thiazolidinedione

SAFETY SUMMARY

- The American Geriatrics Society recommends avoidance of long-acting sulfonylureas (chlorpropamide, glimepiride, and glyburide) in older adults (high quality of evidence; strong recommendation) *(Fick et al 2019)*.
  - Chlorpropamide has a prolonged half-life in older adults, which increases the risk for prolonged hypoglycemia and syndrome of inappropriate antidiuretic hormone (SIADH).
  - Glimepiride and glyburide have a higher risk of severe, prolonged hypoglycemia in older adults.

- **Contraindications:**
  - Patients with diabetic ketoacidosis or diabetic coma
  - Patients with type 1 diabetes mellitus
  - Hypersensitivity to drug or its components
  - Amaryl (glimepiride), Glucotrol XL: Patients who have a history of an allergic reaction to sulfonamide derivatives including cutaneous reactions with or without pruritus such as angioedema and Stevens-Johnson syndrome
  - Duetact: Patients with New York Heart Association Class III or IV heart failure
  - Glyburide, glyburide/metformin, Glynase: Concomitant administration with Tracleer (bosentan)
  - Glyburide/metformin, glipizide/metformin: Renal disease or renal dysfunction
- **Boxed Warnings:**

- Duetact: TZDs, including pioglitazone and rosiglitazone, cause or exacerbate congestive heart failure in some patients.
- Glyburide/metformin: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation.

- **Warnings/Precautions:**
  - The metabolism and excretion of these drugs may be slowed in patients with impaired renal and/or hepatic function.
  - There is an association between use of an SFU (tolbutamide) and increased CV mortality.
  - Post-marketing data showed that glimepiride can be associated with angioedema, Stevens-Johnson syndrome, and anaphylaxis.
  - All SFUs are capable of producing severe hypoglycemia.
  - Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with SFUs can lead to hemolytic anemia.
  - Other warnings/precautions for TZDs and metformin can be found in the product labeling.
- **Adverse events:**
  - Constipation, diarrhea, hypoglycemia, nausea, photosensitivity, rash, and vomiting are some of the most common adverse effects.
  - Weight gain
  - Chlorpropamide has unique adverse effects, including disulfiram-like reaction and a reaction identical to SIADH.
  - Adverse events for TZDs and metformin can be found in the product labeling.
- **Drug interactions:**
  - ACE inhibitors - may cause a temporary increase in insulin sensitivity, increasing the risk for hypoglycemia.
  - MAO inhibitors - may enhance the hypoglycemic action of SFUs through an unknown mechanism.
  - Salicylates, nonsteroidal anti-inflammatory agents - can reduce plasma glucose levels and enhance insulin secretion, adding to the hypoglycemic effects of SFUs.
  - Thiazide diuretics, atypical antipsychotics, corticosteroids, oral contraceptives, protease inhibitors, calcium channel blockers - may increase fasting blood glucose levels, resulting in decreased glycemic control.
  - Sulfonamides, quinolones, fluconazole - may impair the metabolism of certain SFUs and enhance the hypoglycemic effects of SFUs.
  - Colesevelam - maximum plasma concentration and total exposure to the SFU is reduced when colesevelam is coadministered with certain SFUs. Therefore, the SFU should be administered at least 4 hours prior to colesevelam.
  - Beta-blockers, clonidine – may either increase or decrease the glucose-lowering effect of SFUs, and may block signs and symptoms of hypoglycemia.
  - Chlorpropamide has a unique interaction with alcohol, which may cause a disulfiram-like reaction and increase the risk for hypoglycemia.

DOSING AND ADMINISTRATION

- SFUs are typically administered with meals. When dosed once daily, SFUs are given with breakfast or the first main meal of the day.

Table 5. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
First-generation				
chlorpropamide	Tablets	Oral	Once daily	
tolazamide	Tablets	Oral	Once daily	Twice daily dosing for doses > 500 mg
tolbutamide	Tablets	Oral	Once daily or divided throughout the day	Administered without regard to meals
Second-generation				

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Amaryl (glimepiride)	Tablets	Oral	Once daily	
glyburide	Tablets	Oral	Once daily > 10 mg: twice daily	Micronized and conventional formulations of glyburide are not bioequivalent Avoid use in patients with moderate to severe renal impairment or renal failure
Glucotrol (glipizide)	Tablets	Oral	Once daily > 15 mg: divided doses	
Glucotrol XL (glipizide extended-release [ER])	Extended-release tablets	Oral	Once daily	
Glynase (micronized glyburide)	Tablets	Oral	Once daily > 6 mg: twice daily	Micronized and conventional formulations of glyburide are not bioequivalent
Combination products				
Duetact (glimepiride/pioglitazone)	Tablets	Oral	Once daily	
glipizide/metformin	Tablets	Oral	Once or twice daily	Contraindicated for use in patients with estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2
glyburide/metformin	Tablets	Oral	Once or twice daily	Contraindicated for use in patients with eGFR < 30 mL/min/1.73 m^2

See the current prescribing information for full details

CONCLUSION

- The SFUs are FDA-approved for the treatment of T2DM. SFUs stimulate the release of insulin by binding to the SFU receptor on pancreatic β-cells and increase basal and postprandial insulin secretion; therefore, they are useful only in patients with some β-cell function. SFUs are the oldest of the oral antidiabetic medications. All single-entity agents and combination therapy agents with pioglitazone or metformin are available generically.
- The SFUs can be divided into 2 categories: first-generation and second-generation. The first-generation SFUs consist of chlorpropamide, tolazamide, and tolbutamide. The second-generation SFUs consist of glimepiride, glipizide, and glyburide. The second-generation agents have structural characteristics that allow them to be given in much lower doses than the first-generation agents. In general, the SFUs differ in their pharmacokinetic parameters; however, they are equally effective when administered in equipotent doses.
- Second-generation agents are generally more potent and may have a better safety profile than first-generation SFUs. All SFUs have similar effectiveness and lower HbA1c by approximately 1 to 2%.
- The SFUs are contraindicated in patients with type 1 diabetes or diabetic ketoacidosis.
- The labeling for each SFU contains a special warning for increased CV mortality based on an older study of tolbutamide. Other key warnings include hypoglycemia, secondary failure, and SFU-induced hemolytic anemia in patients with G6PD deficiency.
  - AEs associated with the SFU class include gastrointestinal disturbances, allergic skin reactions, and hematologic AEs.
  - Chlorpropamide is associated with unique AEs, including SIADH, hyponatremia, and disulfiram-like reaction when used with alcohol.
- The American Geriatrics Society recommends avoidance of long-acting sulfonylureas (chlorpropamide, glimepiride, and glyburide) in older adults due to the increased risk of AEs, including prolonged hypoglycemia *(Fick et al 2019).*

- According to current clinical guidelines for the management of T2DM, metformin is the preferred initial pharmacological agent for T2DM. The SFUs are among the recommended second- or third-line treatment options for patients who are not candidates for metformin or who failed to achieve glycemic goals on metformin therapy. SGLT2 inhibitors and GLP-1 receptor agonists with proven benefit are preferred over SFUs for patients with T2DM and ASCVD, CKD, or HF. When SFUs are added to ongoing treatment, use of the second-generation agents is recommended *(ADA 2019, Garber et al 2019).*

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OPTUMRx

Therapeutic Class Overview
Thiazolidinediones

INTRODUCTION

- Diabetes mellitus affects more than 30 million people in the United States (US). Greater than 84 million American adults have prediabetes and 90% of them do not know they have it (*Centers for Disease Control and Prevention [CDC] 2018*).
- Type 2 diabetes mellitus (T2DM) is the most common form of diabetes and is characterized by elevated fasting and postprandial glucose concentrations (*American Diabetes Association [ADA] Diabetes Basics, 2019*). It is a chronic illness that requires continuing medical care and ongoing patient self-management education and support to prevent acute complications and to reduce the risk of long-term complications (*ADA 2019*).
- Complications of T2DM include heart disease, stroke, vision loss, kidney disease, and amputations of toes, feet or legs. It is the leading cause of kidney failure, lower-limb amputations, and adult-onset blindness and the seventh leading cause of death in the US (*CDC 2018*).
- In addition to dietary and lifestyle management, T2DM can be treated with insulin, 1 or more oral medications, or a combination of both. Many patients with T2DM will require combination therapy (*Garber et al 2019*).
- Classes of oral medications for the management of blood glucose levels in patients with T2DM focus on increasing insulin secretion, increasing insulin responsiveness, or both, or decreasing the rate of carbohydrate absorption (*Wexler 2019*).
- Pharmacologic options for T2DM include sulfonylureas, biguanides, thiazolidinediones (TZDs), meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogs, amylinomimetics, sodium-glucose cotransporter 2 (SGLT2) inhibitors, combination products, and insulin.
- This review focuses on the TZDs. This class of agents enhances insulin sensitivity in adipose tissue, skeletal muscle, and the liver (*Clinical Pharmacology 2019*). There are currently 2 TZDs marketed in the US: Actos (pioglitazone) and Avandia (rosiglitazone).
- This review also includes fixed-dose combination products containing a TZD in combination with metformin, extended-release metformin, or glimepiride. An additional combination product, Oseni (alogliptin and pioglitazone), is reviewed with the DPP-4 inhibitor class. Combinations of pioglitazone/metformin, pioglitazone/metformin extended release, and pioglitazone/glimepiride are currently available. Combination rosiglitazone/metformin and rosiglitazone/glimepiride have been Food and Drug Administration (FDA) approved, but are not currently marketed.
- Re-analysis of safety data by the FDA has eliminated access restrictions to rosiglitazone-containing medications that had been in place since 2011 (*FDA press release 2015*). Restrictions were previously instituted due to the association of rosiglitazone with an increased risk of myocardial infarction (*GlaxoSmithKline [GSK] press release 2014*).
- Medispan class: Thiazolidinediones, Thiazolidinediones-Biguanide Combinations, Sulfonylurea-Thiazolidinedione Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Actos (pioglitazone)	✔
Actoplus Met (pioglitazone/metformin)	✔
Actoplus Met XR (pioglitazone/metformin extended-release)	-
Duetact (pioglitazone/glimepiride)	✔
Avandia (rosiglitazone)	-*
Avandamet (rosiglitazone/metformin)†	-
Avandaryl (rosiglitazone/glimepiride)†	-

*Generic rosiglitazone has been approved by the FDA, but it is not currently marketed.
†Brand Avandamet and Avandaryl have been discontinued by the manufacturer. Generic rosiglitazone/metformin and generic rosiglitazone/glimepiride have been approved by the FDA, but are not available; it is unclear whether these products will be launched in the future. Thus, at this time there is no commercially available rosiglitazone/metformin or rosiglitazone/glimepiride combination product.

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	pioglitazone	pioglitazone/ metformin	pioglitazone/ glimepiride	rosiglitazone	rosiglitazone/ metformin	rosiglitazone/ glimepiride
Adjunct to diet and exercise to improve glycemic control in adults with T2DM in multiple clinical settings as monotherapy or as combination therapy	✔					
Adjunct to diet and exercise to improve glycemic control in adults with T2DM.				✔	✔	✔
Adjunct to diet and exercise to improve glycemic control in adults with T2DM who are already treated with a TZD and a sulfonylurea or who have inadequate glycemic control on a TZD alone or a sulfonylurea alone			✔			
Adjunct to diet and exercise to improve glycemic control in adults with T2DM when treatment with both pioglitazone and metformin is appropriate		✔				

(Prescribing information: Actos 2017, Actoplus Met 2017, Actoplus Met XR 2017, Avandamet 2017, Avandaryl 2015, Avandia 2019, Duetact 2017)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Data consistently demonstrate that TZDs are associated with significant lowering of glycosylated hemoglobin (A1C) and fasting plasma glucose (FPG). Trials have demonstrated the efficacy of pioglitazone as monotherapy in treatment-naïve patients (*Russell-Jones et al 2012, Wainstein et al 2012*). Rosiglitazone (both monotherapy and in combination with metformin) has also been demonstrated to be effective in treatment-naïve patients (*Rosenstock et al 2006*).
- More frequently, TZDs have been evaluated in combination regimens in patients who failed to achieve a goal A1C with other treatment(s). In this setting, pioglitazone led to improvement in glycemic parameters when added to metformin (*Bergenstal et al 2010*), a sulfonylurea (*Hanefeld et al 2004, Kipnes et al 2001*), or an SGLT2 inhibitor (*Rosenstock et al 2012*). Rosiglitazone has also shown efficacy as add-on therapy with metformin (*Bailey et al 2005, Fonseca et al 2000, Rigby et al 2010, Scott et al 2008, Weissman et al 2005*) or a sulfonylurea (*Marre et al 2009*).
- Studies evaluating the relative A1C-lowering efficacy between TZDs and antidiabetic agents from other classes have shown varying results. In a few trials, a TZD has been shown to be less efficacious than a comparator treatment such as exenatide ER or liraglutide (*Bergenstal et al 2010, Marre et al 2009*). However, several trials have demonstrated comparable efficacy with a TZD and a comparator, such as metformin, exenatide ER, or sitagliptin (*Hanefeld et al 2004, Russell-Jones et al 2012, Scott et al 2008*). Overall A1C-lowering of TZD monotherapy is similar to metformin (*McCulloch 2017*).
- A number of trials have compared pioglitazone to rosiglitazone on various outcome measures. Most studies demonstrated no significant differences between pioglitazone and rosiglitazone for A1C, FPG, or body weight changes (*Brackenridge et al 2009, Derosa et al 2004, Derosa et al 2006, Goldberg et al 2005, Khan et al 2002*). One monotherapy trial in Japanese patients (N = 373) failed to demonstrate non-inferiority of rosiglitazone to pioglitazone for changes in A1C; however, pioglitazone was associated with higher incidences of adverse events relating to edema and weight gain (*Kikuchi et al 2012*).
- In several studies pioglitazone was demonstrated to have more beneficial effects on lipid parameters compared to rosiglitazone (*Derosa et al 2004, Derosa et al 2006, Goldberg et al 2005, Khan et al 2002*).
- The safety of TZDs has been evaluated in several large randomized controlled trials and meta-analyses (MAs).

- An MA revealed that long-term use of TZDs was associated with a significant increased risk of fracture, which was more significant in women, compared to control (no TZD) (*Loke et al 2009*).
- An increase in the risk of non-spine fractures was reported in the ACCORD BONE trial, a longitudinal observational study. The risk of fracture among women treated with a TZD (primarily as rosiglitazone) over 1 to 2 years or > 2 years was significantly higher compared to no use (hazard ratios 2.32 and 2.01, respectively). Discontinuation of TZDs (for > 1 to 2 years) resulted in a reduced risk of fracture compared to current users and a comparable risk compared to women who never used TZDs. No significant overall effect was seen among men given TZDs (*Schwartz et al 2015*).
- An MA revealed that long-term use of TZDs was associated with a significant increased risk of any and serious pneumonia or lower respiratory tract infection compared to control (placebo, sulfonylurea, metformin) (*Singh et al 2011*).
- Pioglitazone demonstrated no increased risk of cardiovascular (CV) events (composite of all-cause mortality, nonfatal myocardial infarction, nonfatal stroke, acute coronary syndrome, endovascular or surgical intervention on coronary or leg arteries, or amputation above the leg) compared to placebo. Significantly more reports of heart failure were noted with pioglitazone; however, treatment was not associated with an increased risk of death due to heart failure (*Dormandy et al 2005, Erdmann et al 2007[b], Lincoff et al 2007*).
  - Sub-analyses of this trial revealed that patients with a prior stroke were not at an increased risk of CV events with pioglitazone, and that pioglitazone significantly decreased the risk of fatal and nonfatal myocardial infarction in patients with a previous myocardial infarction (*Erdmann et al 2007[a], Wilcox et al 2007*).
- Various MAs and interim analyses concluded that rosiglitazone may be associated with a significant increased risk of myocardial infarction (*Nissen et al 2007, Singh et al 2007*) and an insignificant increased risk of CV death (*Nissen et al 2007*) compared to control (placebo or active comparator); however, other MAs have not supported these findings (*Bach et al 2013, Home et al 2007, Lu et al 2015*). None of these analyses demonstrated an increased risk of all-cause mortality with rosiglitazone (*Home et al 2007, Lu et al 2015, Nissen et al 2007, Singh et al 2007*).
- A post-hoc analysis of BARI 2D concluded that rosiglitazone is not associated with increased rates of major adverse ischemic CV events among patients with T2DM and established CAD (*Bach et al 2013*).
- The readjudication of the RECORD safety trial performed by the Duke Clinical Research Institute (DCRI) confirmed the initial finding of the trial that rosiglitazone was not associated with an increased risk for CV events (*Mahaffey et al 2013*). However, all parties did agree that the underlying design flaws of RECORD, in particular, its open-label, non-inferiority design, mean that data from the trial will never provide definitive assurance about the safety of rosiglitazone (*Mitka 2013*). The FDA also conducted an MA to assess the CV risk associated with rosiglitazone. Overall, a statistically significant increased risk of myocardial infarction and a non-significant increased risk of major adverse CV events (MACE) were observed with rosiglitazone vs. pooled comparators. In the included placebo-controlled trials, a statistically significant increased risk of myocardial infarction and statistically non-significant increased risk of MACE with rosiglitazone were observed; however, no increased risk of myocardial infarction or MACE was observed in the active-controlled trials (*Avandia prescribing information 2016, FDA Drug Safety Communication 2013*). Based on this data, and continued monitoring of rosiglitazone-containing products since 2013 which have not identified new pertinent safety information, the FDA announced in December 2015 that a Risk Evaluation and Mitigation Strategy (REMS) was no longer necessary to ensure the benefits of rosiglitazone-containing medicines outweigh their risks (*FDA press release 2015*).
- In several studies, pioglitazone had more favorable effects on lipid parameters compared to rosiglitazone. Rosiglitazone has been associated with significant increases in total cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, and apolipoprotein B (apo B), while pioglitazone has usually been associated with neutral or favorable effects on lipid parameters (*Derosa et al 2004, Derosa et al 2006, Goldberg et al 2005, Khan et al 2002*).
- Two MAs concluded that pioglitazone confers a modest but clinically significant increased risk of bladder cancer and the risk is higher with increased cumulative dose or duration of exposure (*Turner et al 2014, Ferwana et al 2013*). A third MA could not exclude an association between pioglitazone exposure and bladder cancer (*Monami et al 2014*). More recently, results from cohort and nested case-control analyses revealed that pioglitazone use was not associated with a statistically significant increased risk of bladder cancer, although an increased risk, as previously observed, could not be excluded (*Lewis et al 2015*).

CLINICAL GUIDELINES

- Guidelines on the treatment of diabetes are available from the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE), the ADA, the European Association for the Study of Diabetes (EASD), and the American College of Physicians (ACP) (*ADA 2019, Garber et al 2019, Qaseem et al 2017, Davies et al 2018*).
- In the 2019 update to the ADA standards of medical care in diabetes, the pharmacologic treatment of T2DM was significantly changed to align with the ADA-EASD consensus report. The ADA/EASD state that metformin, if not contraindicated and if tolerated, is the preferred initial pharmacologic agent for treatment of T2DM. If A1C remains above target with metformin alone and the patient does not have atherosclerotic cardiovascular disease (ASCVD) or chronic kidney disease (CKD), clinicians should consider combining metformin with any one of the following: a sulfonylurea, TZD, DPP-4 inhibitor, SGLT2 inhibitor, GLP-1 receptor agonist, or basal insulin. The choice of which agent to add is based on drug-specific effects and patient factors. For patients in whom ASCVD, heart failure, or CKD predominates, the best choice for a second agent is a GLP-1 receptor agonist or SGLT2 inhibitor with demonstrated CV risk reduction. If a third agent is required to achieve glycemic goals, drug choice should be based on avoidance of adverse effects, cost, and patient preferences. There is very little trial-based evidence to guide this choice. Of note, for the first time in the ADA annual diabetes management guideline, the ADA has also aligned its recommendations with those of the American College of Cardiology (ACC) for CV risk reduction in patients with T2DM. This focuses on the use of SGLT2 inhibitors and GLP-1 agonists in appropriate patients in order to reduce adverse CV outcomes (*ADA 2019, Davies et al 2018*).
- The AACE/ACE 2019 algorithm has stratified pharmacologic recommendations for T2DM based on an A1C < 7.5%, ≥ 7.5%, and > 9%. For those entering treatment with A1C < 7.5%, monotherapy with metformin is preferred; acceptable alternatives include a GLP-1 agonist, an SGLT2 inhibitor, a DPP-4 inhibitor, or a TZD. Alpha-glucosidase inhibitors, sulfonylureas, and meglitinides may be appropriate for monotherapy in certain situations. Patients entering treatment with A1C ≥ 7.5% should be initiated on dual therapy consisting of metformin (or another first-line agent) plus a second agent. If A1C is > 9% and the patient has no symptoms, dual therapy or triple therapy should be initiated; however, symptomatic patients would derive greater benefit from the addition of insulin. At all levels of treatment, caution is advised with use of TZDs, sulfonylureas, and meglitinides. Side effects that have limited TZD use include weight gain, increased fracture risk in postmenopausal women and elderly men, and an elevated risk for chronic edema or heart failure (*Garber et al 2019*).
  - Although various MAs had pointed to a modest but clinically significant increased risk of bladder cancer with pioglitazone, a cohort and nested case-control analyses revealed that pioglitazone use was not associated with a statistically significant increased risk of bladder cancer (*Ferwana et al 2013, Lewis et al 2015, Monami et al 2014, Turner et al 2014*). The results from this analysis led the authors of the 2019 AACE guidelines to state that "a possible association with bladder cancer has largely been refuted" (*Garber et al 2019*). Despite this statement from the AACE guideline, the FDA states that discrepant findings from studies combined with limitations in study design and the inherent difficulty of investigating moderate effect sizes in long latency endpoints, render the totality of the evidence regarding pioglitazone and bladder cancer risk inconclusive (*Hampp et al 2017*). Therefore, the urinary bladder tumor warning remains in the pioglitazone labeling.
- The ACP recommends that clinicians prescribe metformin to patients with T2DM when pharmacologic therapy is needed. They also recommend that clinicians consider adding either a sulfonylurea, a TZD, an SGLT-2 inhibitor, or a DPP-4 inhibitor to metformin when a second oral therapy is considered (*Qaseem et al 2017*).

SAFETY SUMMARY

- Contraindications:
  - Hypersensitivity to any of the components of the products.
  - Do not initiate in New York Heart Association (NYHA) Class III or IV patients.
  - For metformin containing products:
    - Do not use in patients with severe renal impairment (estimated glomerular filtration rate [eGFR] < 30 mL/min/1.73 m^2) or in acute or chronic metabolic acidosis including diabetic ketoacidosis.
- Boxed warnings:
  - Pioglitazone-containing products:

- Can cause or exacerbate congestive heart failure. When initiating or increasing dose, watch for signs and symptoms. If heart failure develops, manage appropriately and either discontinue the drug or decrease the dose.
- Rosiglitazone-containing products:
  - Can cause or exacerbate congestive heart failure. When initiating or increasing dose, watch for signs and symptoms. If heart failure develops, manage appropriately and either discontinue the drug or decrease the dose.
- Metformin-containing products:
  - Postmarketing cases of metformin-associated lactic acidosis have resulted in death, hypothermia, hypotension, and resistant bradyarrhythmias. Risk factors include renal impairment, concomitant use of certain drugs, age ≥ 65 years old, radiological studies with contrast, surgery and other procedures, hypoxic states, excessive alcohol intake, and hepatic impairment. If lactic acidosis is suspected, the drugs should be discontinued and general supportive measures should be instituted in a hospital setting. Prompt hemodialysis is recommended.

- Selected Warnings/Precautions:
  - Fluid retention and edema can occur.
  - Use with caution in NYHA Class I and II patients.
  - Dose-related weight gain may occur.
  - Increased risk of fractures especially in females.
  - Macular edema can occur; regular eye exams are recommended.
  - Periodic monitoring of liver enzymes is recommended.
  - Avoid metformin use in patients with hepatic disease or those using alcohol.
  - Pioglitazone may increase the risk of bladder cancer; do not use in patients with active bladder cancer and use cautiously in patients with a history of bladder cancer.
  - Hypersensitivity reactions with glimepiride have been reported, including anaphylaxis, angioedema, and Stevens - Johnson syndrome.
- Adverse effects with TZDs:
  - Edema and weight gain.
- Drug interactions with TZDs:
  - Enzyme inducers or inhibitors of CYP2C8 may affect the plasma levels of both pioglitazone and rosiglitazone.
  - Topiramate may decrease pioglitazone concentrations.
  - Patients taking concomitant colesevelam, should take pioglitazone/glimepiride or rosiglitazone/glimepiride 4 hours before colesevelam.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Actos (pioglitazone)	Tablet	Oral	Once daily. Max dose: 45 mg once daily.	Max dose is 15 mg daily when used in combination with gemfibrozil or other strong CYP2C8 inhibitors.
Actoplus Met (pioglitazone/metformin)	Tablet	Oral	Once or twice daily. Max dose: pioglitazone 45 mg and metformin IR 2550 mg.	Take with meals. Metformin doses > 2000 mg may be better tolerated when given 3 times a day. Avoid use in severe renal impairment (eGFR < 30 mL/min/1.73 m^2) and hepatic impairment. Initiating metformin in patients with eGFR between 30 to 45 mL/min/1.73 m^2 is not recommended; however, patients who develop this level of decreased renal function while taking metformin should have the risks

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				and benefits of continuing therapy assessed.
Actoplus Met XR (pioglitazone/metformin extended-release)	Tablet	Oral	Once or twice daily. Max dose: pioglitazone 45 mg and metformin ER 2000 mg.	Take with meals.
Duetact (pioglitazone/glimepiride)	Tablet	Oral	Once daily. Max dose: pioglitazone 45 mg and glimepiride 8 mg.	Take with first main meal. Max dose is 15 mg daily when used in combination with gemfibrozil or other strong CYP2C8 inhibitors. Do not initiate if the patient has active liver disease and discontinue if ALT is > 3x the upper limit of normal (ULN).
Avandia (rosiglitazone)	Tablet	Oral	Once or twice daily. Max dose: rosiglitazone 8 mg.	Do not initiate if the patient has active liver disease and discontinue if ALT is > 3x the ULN.
Avandamet (rosiglitazone/metformin)	Tablet	Oral	Once or twice daily. Max dose: rosiglitazone 8 mg and metformin 2000 mg.	Take with meals. Titrate gradually to reduce gastrointestinal (GI) side effects. Avoid use in severe renal impairment (eGFR < 30 mL/min/1.73 m^2) and hepatic impairment. Initiating metformin in patients with eGFR between 30 to 45 mL/min/1.73 m^2 is not recommended; however, patients who develop this level of decreased renal function while taking metformin should have the risks and benefits of continuing therapy assessed.
Avandaryl (rosiglitazone/glimepiride)	Tablet	Oral	Once daily. Max dose: rosiglitazone 8 mg and glimepiride 4 mg.	Take with first main meal. Do not initiate if the patient has active liver disease and discontinue if ALT is > 3x the ULN.

See the current prescribing information for full details

CONCLUSION

- The TZDs, pioglitazone and rosiglitazone, improve glycemic control by improving insulin sensitivity. Pioglitazone and rosiglitazone are available as single-entity agents and in fixed-dose combinations with metformin or glimepiride. However, at this time there is no commercially available rosiglitazone/metformin or rosiglitazone/glimepiride combination product. Pioglitazone is also available in combination with alogliptin, which is reviewed with the DPP-4 inhibitor class of drugs.
- As monotherapy, TZDs decrease A1C by approximately 1.5%. Additional A1C-lowering can be achieved by combining a TZD with another glucose-lowering agent, such as metformin or a sulfonylurea.
- Both TZDs are associated with weight gain, and both are associated with fluid retention that can lead to or exacerbate heart failure.
- Pioglitazone and rosiglitazone have comparable effects on A1C, FPG, and body weight.

- In several studies, pioglitazone had more favorable effects on lipid parameters compared to rosiglitazone. Rosiglitazone has been associated with significant increases in total cholesterol, LDL-C, triglycerides, and apo B, while pioglitazone has usually been associated with neutral or favorable effects on lipid parameters (*Derosa et al 2004, Derosa et al 2006, Goldberg et al 2005, Khan et al 2002*).
- To further evaluate the issue of increased risk of myocardial infarction with rosiglitazone, an FDA Advisory Committee met in June of 2013 to review the readjudicated results from the RECORD trial. The readjudication of the RECORD safety trial performed by the DCRI confirmed the initial finding of the trial that rosiglitazone was not associated with an increased risk for CV events. However, all parties agreed that the underlying design flaws of RECORD, in particular, its open-label, non-inferiority design, mean that data from the trial will never provide definitive assurance about the safety of rosiglitazone. Previously, rosiglitazone-containing medications were available only through a restricted distribution program due to the concerns of a potential increased risk of myocardial infarction. However, changes to the REMS program based on a re-analysis of data by the FDA eliminated the access restrictions that had been in place since 2011 (*GSK press release 2014*). As of December 2015, a REMS program is no longer required for rosiglitazone-containing products (*FDA press release 2015*).
- A large RCT and an MA demonstrated that pioglitazone is not associated with an increased risk of myocardial infarction (*Dormandy et al 2005, Lincoff et al 2007*). However, both of these trials did show an increased incidence of congestive heart failure in patients taking pioglitazone.
- Two MAs concluded that pioglitazone confers a modest but clinically significant increased risk of bladder cancer, and the risk is higher with increased cumulative dose or duration of exposure (*Turner et al 2014, Ferwana et al 2013*). A third MA could not exclude an association between pioglitazone exposure and bladder cancer (*Monami et al 2014*). More recently, results from cohort and nested case-control analyses revealed that pioglitazone use was not associated with a statistically significant increased risk of bladder cancer, although an increased risk, as previously observed, could not be excluded (*Lewis et al 2015*). The results from this analysis led the authors of the 2019 AACE guidelines to state that "a possible association with bladder cancer has largely been refuted" (*Garber et al 2019*). Despite this statement from the AACE guideline, the FDA states that discrepant study findings, combined with limitations in study design and the inherent difficulty of investigating moderate effect sizes in long latency endpoints, render the totality of the evidence regarding pioglitazone and bladder cancer risk inconclusive (*Hampp et al 2017*). Therefore, the urinary bladder tumor warning remains in the pioglitazone labeling.
- One MA and an observational trial indicated a potential for a significantly increased risk of fracture among women treated with TZDs (*Loke et al 2009, Schwartz et al 2015*).
- Guidelines recommend metformin as first-line oral therapy for T2DM. TZDs are one of several classes of oral agents that may be used with caution in selected patients as an alternative to, or in combination with, metformin (*ADA 2019, Garber et al 2018, Qaseem et al 2017, Davies et al* 2018).

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Therapeutic Class Overview
Calcitonin gene related peptide (CGRP) inhibitors

INTRODUCTION

- Migraine is a common, recurrent, incapacitating disorder characterized by moderate to severe headaches and disabling features, including nausea, vomiting, neurologic symptoms, photophobia, and phonophobia. Cluster headache is less prevalent than migraine and characterized by attacks of severe, unilateral pain with ipsilateral autonomic symptoms, which occur every other day to multiple times daily during a cluster period (*International Headache Society [IHS] 2018, Starling et al 2015).*
- The pathophysiology of migraines is assumed to involve the activation of trigeminal sensory nerves. CGRP is involved in pathophysiology through nociceptive mechanisms in the trigeminovascular system. CGRP is a vasodilator and is found at higher concentrations during a migraine attack. Vasodilation of dural blood vessels may occur with extravasation of dural plasma, resulting in inflammation *(Goadsby et al 2017, Starling et al 2015, Silberstein et al 2012)*.
- The International Classification of Headache Disorders (ICHD) includes both cluster headache and migraine as part of a group of primary headache disorders (*IHS 2018*):
  - Chronic migraine is defined as ≥ 15 headache days per month for > 3 months with the features of migraine headache for at least 8 migraine days per month (MMD). The most common cause of symptoms suggestive of chronic migraine is medication overuse. According to the ICHD, around 50% of patients apparently with chronic migraine revert to an episodic migraine type after drug withdrawal; such patients are in a sense wrongly diagnosed with chronic migraine. In most clinical trials, migraine that is not chronic (ie, < 15 headache days per month) is considered to be episodic migraine, although the condition is not clearly defined in the ICHD.
  - Cluster headache is defined as ≥ 5 attacks lasting 15 to 180 minutes every other day to 8 times a day with severe unilateral orbital, supraorbital, and/or temporal pain. Episodic cluster headache attacks occur for a period of 7 days to 1 year and are separated by pain-free periods lasting at least 3 months. Common symptoms include nasal congestion, rhinorrhea, conjunctival injection and/or lacrimation, eyelid edema, sweating (forehead or face), miosis, ptosis, and/or a sense of restlessness or agitation.
- Cluster headache is more likely to occur in men, whereas migraines are more likely to occur in women. Migraines have a global prevalence of 15 to 18% and are a leading cause of disability worldwide. Chronic migraine is estimated to occur in 2 to 8% of patients with migraine, whereas episodic migraine occurs in more than 90% of patients. Cluster headache is rare compared to other primary headache disorders. It is estimated to have a prevalence of 0.1% within the general population (*Global Burden of Disease Study [GBD] 2016, Hoffman et al 2018, Lipton et al 2016, Ljubisavljevic et al 2019, Manack et al 2011*).
- Treatments for migraines and cluster headache are divided into acute and preventive therapies. Evidence and reputable guidelines clearly delineate appropriate therapies for episodic migraine treatment and prophylaxis; options stretch across a wide variety of therapeutic classes and are usually oral therapies. For the prevention of migraines, treatment options include oral prophylactic therapies, injectable prophylactic therapies, and neuromodulator devices. Oral prophylactic migraine therapies have modest efficacy, and certain oral therapies may not be appropriate for individual patients due to intolerability or eventual lack of efficacy. For the treatment of cluster headache, subcutaneous sumatriptan, zolmitriptan nasal spray, and oxygen have the most positive evidence for acute therapy, and suboccipital steroid injections are most effective for prevention (*American Migraine Foundation [AMF] 2017, Robbins et al 2016, Silberstein et al 2012, Simpson et al 2016)*.
- The CGRP pathway is important in pain modulation. Erenumab-aooe is a fully human monoclonal antibody, which potently binds to the CGRP receptor in a competitive and reversible manner with greater selectivity than to other human calcitonin family receptors. Fremanezumab-vfrm and galcanezumab-gnlm are 2 humanized monoclonal antibodies that target and potently bind the CGRP ligand, in most cases both the α and β isoforms (*Dodick et al 2018[b], Edvinsson 2017, Goadsby et al 2017, Silberstein et al 2017, Sun et al 2016, Tepper et al 2017*).
  - All 3 of the available CGRP inhibitors are indicated for the preventive treatment of migraine in adults. Additionally, galcanezumab-glnm is indicated for the treatment of episodic cluster headache in adults.
  - In April 2019, Teva announced that fremanezumab-vfrm would not pursue development of episodic cluster headache due to results from the ENFORCE trial (*Teva Pharmaceuticals press release 2019*). Erenumab-aooe is not currently in early phase studies for the indication of cluster headache (*Clinicaltrials.gov 2019*).

- Medispan class: Migraine products – monoclonal antibodies; Calcitonin gene−related peptide (CGRP) receptor antagonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Aimovig (erenumab−aooe)	−
Ajovy (fremanezumab-vfrm)	−
Emgality (galcanezumab-gnlm)	−

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Aimovig (erenumab−aooe)	Ajovy (fremanezumab-vfrm)	Emgality (galcanezumab-gnlm)
Preventive treatment of migraine in adults	✔	✔	✔
Treatment of episodic cluster headache in adults	-	-	✔

(*Prescribing information: Aimovig 2019, Ajovy 2018, Emgality 2019*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Erenumab-aooe has been studied in approximately 2500 patients across 4 trials in patients with episodic or chronic migraine subtypes and 1 open-label extension (OLE) trial with data from interim analyses in published and unpublished formats.
- Fremanezumab-vfrm has been studied in approximately 2005 patients across 3 trials in patients with episodic or chronic migraine subtypes, with data in published formats. In fremanezumab-vfrm trials, the definition of a headache or migraine day for the primary endpoint required a consecutive 2 hour (episodic) or 4 hour (chronic) duration of pain, compared to other CGRP inhibitor trials which required a duration of ≥ 30 minutes.
- Galcanezumab-gnlm has been studied in approximately 2886 patients across 3 trials in patients with episodic or chronic migraine subtypes and 1 long-term safety trial with unpublished data to 1 year. The efficacy and safety of galcanezumab-gnlm was evaluated in one 8-week study with 106 adults with episodic cluster headache (maximum of 8 attacks/day).
- The definition of the primary and secondary endpoints differed in the prevention of episodic and chronic migraine trials. Additional differences included, but were not limited to, co-morbid conditions, concomitant medications, a requirement of stable doses of migraine prevention medication (if co-administered) for certain durations, the definition of headache, migraine headache, and migraine day. Some CGRP inhibitor trials allowed patients to receive concomitant preventive migraine medication during treatment. Also, some chronic migraine trials allowed for the inclusion of patients with medication overuse headache.

Prevention of episodic migraine

Erenumab-aooe

- The STRIVE trial was a 6-month, double-blind (DB), placebo-controlled (PC), multi-center (MC), Phase 3 trial in which 955 patients with episodic migraine were randomized to placebo (n = 319), erenumab-aooe 70 mg (n = 317), or erenumab-aooe 140 mg (n = 319) once monthly. The primary endpoint was the change in mean MMD from baseline to months 4 to 6, which favored treatment with erenumab−aooe 70 mg (mean change vs placebo, −1.4; 95% confidence interval [CI], −1.9 to −0.9; p < 0.001) and erenumab−aooe 140 mg (mean change vs placebo, −1.9; 95% CI, −2.3 to −1.4; p < 0.001). Erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 70 mg vs placebo, 16.7%; odds ratio [OR], 2.13; difference for 140 mg vs placebo, 23.4%; OR, 2.81). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific

medication treatment days (difference for 70 mg vs placebo, −0.9; difference for 140 mg vs placebo, −1.4) (*Goadsby et al 2017*).

- The ARISE trial was a 12-week, DB, PC, MC, Phase 3 trial in which 577 patients with episodic migraine were randomized to placebo (n = 291) or erenumab-aooe 70 mg (n = 286) once monthly. The primary endpoint was the change in MMD from baseline to weeks 9 to 12, which favored treatment with erenumab−aooe 70 mg (mean change vs placebo, −1.0; 95% CI, −1.6 to −0.5; p < 0.001). Compared to placebo, erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference, 10.2%; OR, 1.59). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference, −0.6) (*Dodick et al 2018[a]*).
- The LIBERTY trial was a 12-week, DB, PC, MC, Phase 3b trial in which 246 patients with episodic migraine who failed 2 to 4 prior preventive migraine treatments were randomized to placebo (n = 125) or erenumab-aooe 140 mg (n = 121) once monthly. The primary endpoint was the proportion of patients with ≥ 50% reduction in MMD from baseline to the last 4 weeks of DB treatment (weeks 9 to 12), which erenumab−aooe significantly increased over placebo (difference, 16.6%; OR, 2.73; 95% CI, 1.43 to 5.19; p = 0.002). Compared to placebo, a total of 5.9% more patients treated with erenumab−aooe 140 mg reported a 100% reduction in MMD, or migraine cessation. Erenumab 140 mg/month compared with placebo significantly reduced the MMD (difference, −1.61; 95% CI, −2.70 to −0.52; p = 0.004). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference, −1.73) (*Reuter et al 2018*).

Fremanezumab-vfrm

- The HALO-EM trial was a 12-week, DB, PC, MC, Phase 3 trial in which 875 patients with episodic migraine were randomized to placebo (n = 294), fremanezumab-vfrm 225 mg once monthly (n = 290), or fremanezumab-vfrm 675 mg once quarterly (n = 291). The primary endpoint was the change in mean MMD, which favored treatment with fremanezumab-vfrm 225 mg (mean change vs placebo, −1.5; 95% CI, −2.0 to −0.9; p < 0.001) and fremanezumab-vfrm 675 mg (mean change vs placebo, −1.3; 95% CI, −1.8 to −0.7; p < 0.001). Of note, HALO-EM was powered to detect a 1.6-day difference in the MMD between the fremanezumab-vfrm and placebo groups, but effect sizes resulted in a 1.5-day reduction for the fremanezumab-vfrm monthly dosing group and a 1.3-day reduction for the fremanezumab-vfrm quarterly dosing group. Although the threshold was not reached, a minimal clinically important difference has not been established for this particular outcome. Compared to placebo, greater MMD reductions were also observed in patients who were prescribed fremanezumab-vfrm 225 mg (mean change vs placebo, −1.3) and 675 mg (mean change vs placebo, −1.1) as monotherapy. Fremanezumab-vfrm significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 225 mg vs placebo, 19.8%; OR, 2.36; difference for 675 mg vs placebo, 16.5%; OR, 2.06). Additionally, fremanezumab-vfrm was associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 225 mg vs placebo, −1.4; difference for 675 mg vs placebo, −1.3) (*Dodick et al 2018[b]*).

Galcanezumab-gnlm

- The EVOLVE-1 and EVOLVE-2 trials were 6-month, DB, PC, MC, Phase 3 trials in 858 and 915 patients with episodic migraine, respectively. Patients were randomized to placebo (EVOLVE-1, n = 433; EVOLVE-2, n = 461), galcanezumab-gnlm 120 mg once monthly (EVOLVE-1, n = 213; EVOLVE-2, n = 231), or galcanezumab-gnlm 240 mg once monthly (EVOLVE-1, n = 212; EVOLVE-2, n = 223). Patients in the galcanezumab-gnlm 120 mg group received a loading dose of 240 mg at the first injection only. The EVOLVE-1 trial included a North American population and the EVOLVE-2 trial included a global population. The primary endpoint was the change in mean monthly migraine headache days (MMHD) (*Stauffer et al 2018, Skljarevski et al 2018*).
  - In EVOLVE-1, the primary endpoint outcome favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −1.9; 95% CI, −2.5 to −1.4; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.8; 95% CI, −2.3 to −1.2; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 23.7%; OR, 2.64; difference for 240 mg vs placebo, 22.3%; OR, 2.50). Compared to placebo, a total of 9.4% more patients treated with galcanezumab-gnlm 120 mg and 9.4% more treated with galcanezumab-gnlm 240 mg reported a 100% reduction in MMHD, or migraine cessation. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −1.8; difference for 240 mg vs placebo, −1.6) (*Stauffer et al 2018*).
  - In EVOLVE-2, the primary endpoint outcome favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −2.0; 95% CI, −2.6 to −1.5; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.9;

95% CI, −2.4 to −1.4; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 23.0%; OR, 2.54; difference for 240 mg vs placebo, 21.0%; OR, 2.34). Compared to placebo, a total of 5.8% more patients treated with galcanezumab-gnlm 120 mg and 8.1% more treated with galcanezumab-gnlm 240 mg reported migraine cessation. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −1.8; difference for 240 mg vs placebo, −1.7) (*Skljarevski et al 2018*).

- In an analysis of persistence for patients with episodic migraine, a total of 41.5 and 41.1% of galcanezumab-gnlm-treated patients (120 mg and 240 mg, respectively) had a ≥ 50% response for ≥ 3 months, which was greater than placebo (21.4%; p < 0.001). Approximately 6% of galcanezumab-gnlm-treated patients maintained ≥ 75% response all 6 months vs 2% of placebo-treated patients. Few galcanezumab-gnlm-treated patients maintained 100% response for all 6 months (< 1.5%) (*Förderreuther et al 2018*).

Prevention of chronic migraine

Erenumab-aooe

- Erenumab-aooe was studied in a 12−week, DB, PC, MC, Phase 2 trial in which 667 patients with chronic migraine were randomized to placebo (n = 286), erenumab−aooe 70 mg (n = 191), or erenumab−aooe 140 mg (n = 190) once monthly. The primary endpoint was the change in MMD from baseline to weeks 9 to 12, which favored treatment with erenumab−aooe 70 mg and erenumab−aooe 140 mg (mean change for both doses vs placebo, −2.5; 95% CI, −3.5 to −1.4; p < 0.0001). Erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 70 mg vs placebo, 17%; OR, 2.2; difference for 140 mg vs placebo, 18%; OR, 2.3). Both erenumab−aooe 70 mg (difference, −1.9) and erenumab−aooe 140 mg (difference, −2.6) significantly reduced the mean acute migraine−specific medication days; however, the higher 140 mg dose had a greater reduction numerically over placebo and reductions may be dose−dependent (*Tepper et al 2017*).

Fremanezumab-vfrm

- Fremanezumab-vfrm was studied in a 12-week, DB, PC, MC, Phase 3 trial, HALO-CM, in which 1130 patients with chronic migraine were randomized to placebo (n = 375), fremanezumab-vfrm 225 mg once monthly (n = 379), or fremanezumab-vfrm 675 mg once quarterly (n = 376). Patients in the fremanezumab-vfrm 225 mg group received a loading dose of 675 mg at the first injection only. The primary endpoint was the change in mean headache days (MHD), which favored treatment with fremanezumab-vfrm 225 mg (mean change vs placebo, −2.1; standard error [SE], ± 0.3; p < 0.001) and fremanezumab-vfrm 675 mg (mean change vs placebo, −1.8; SE, ± 0.3; p < 0.001). Fremanezumab-vfrm significantly increased the proportion of patients achieving ≥ 50% reduction in MHD (difference for 225 mg vs placebo, 22.7%; OR, 2.73; difference for 675 mg vs placebo, 19.5%; OR, 3.13). Additionally, fremanezumab-vfrm was associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 225 mg vs placebo, −2.3; difference for 675 mg vs placebo, −1.8) (*Silberstein et al 2017*).

Galcanezumab-gnlm

- Galcanezumab-gnlm was evaluated in a 12-week, DB, PC, MC, Phase 3 trial, REGAIN, in which 1113 patients with chronic migraine were randomized to placebo (n = 558), galcanezumab-gnlm 120 mg once monthly (n = 278), or galcanezumab-gnlm 240 mg once monthly (n = 277). Patients in the galcanezumab-gnlm 120 mg group received a loading dose of 240 mg at the first injection only. The primary endpoint was the change in MMHD, which favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −2.1; 95% CI, −2.9 to −1.3; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.9; 95% CI, −2.7 to −1.1; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 12.2%; OR, 2.10; difference for 240 mg vs placebo, 12.1%; OR, 2.10). Compared to placebo, a total of 0.2% more patients treated with galcanezumab-gnlm 120 mg and 0.8% more treated with galcanezumab-gnlm 240 mg reported migraine cessation; this was not statistically different for either dose group. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −2.5; difference for 240 mg vs placebo, −2.1) (*Detke et al 2018*).
  - In an analysis of persistence for patients with chronic migraine, 29% of galcanezumab-gnlm-treated patients maintained ≥ 30% response all 3 months compared to 16% of placebo-treated patients. A total of 16.8 and 14.6% of galcanezumab-gnlm-treated patients (120 mg and 240 mg, respectively) had a ≥ 50% response for ≥ 3 months, which was greater than placebo (6.3%; p < 0.001). Few patients maintained ≥ 75% response (< 3%) (*Förderreuther et al 2018*).

Treatment of episodic cluster headache

Galcanezumab-gnlm

- Galcanezumab-gnlm was evaluated in an 8-week, unpublished, DB trial, in which 106 patients with episodic cluster headache were randomized to placebo (n = 57) or galcanezumab-gnlm 300 mg once monthly (n = 49). A total of 90 (85%) patients completed the DB phase. Patients were allowed to use certain specified acute/abortive cluster headache treatments, including triptans, oxygen, acetaminophen, and NSAIDs during the study. At baseline, patients had a mean of 17.5 headache attacks/week, maximum of 8 attacks/day, minimum of 1 attack every other day, and at least 4 attacks during the prospective 7-day baseline period. For the primary endpoint, galcanezumab-gnlm significantly decreased the mean change from baseline in weekly cluster headache attack frequency during weeks 1 to 3 vs placebo (-8.7 vs -5.2 attacks; p = 0.036). Galcanezumab-gnlm was also associated with a significantly greater proportion of responders (≥ 50% reduction in weekly cluster headache attack frequency) at week 3 (71.4 vs 52.6%; p = 0.046) (*Clinicaltrials.gov [NCT02397473] 2019, Emgality prescribing information 2019*).

Open-label extensions (OLE) and long-term safety studies

- One published OLE with data to 1 year and 1 unpublished abstract with data to ≥ 3 years evaluated erenumab-aooe 70 mg (protocol amended to include 140 mg doses) in patients with episodic migraine. Of 472 patients in the parent study, a total of 308 patients completed 1 year of open-label (OL) treatment. For the ≥ 3 year assessment, of the 383 patients enrolled in the OLE, 250 continued into the 140 mg once monthly dosing. At the time of interim analysis, 236 patients remained in the OLE (*Amgen [data on file] 2018, Ashina et al 2017, Ashina et al 2018*).
  - There may be greater improvements with sustained therapy based on a 1-year OLE interim analysis of episodic migraine patients treated with erenumab-aooe 70 mg once monthly. Patients had a mean value of 8.8 MMDs at parent study baseline. After 3 months of treatment in the parent study, the number of MMDs was reduced to 6.3 days (mean change of 2.5 days). After a total of 16 months of treatment, the number of MMDs was reduced to 3.7 days (mean change of 5.1 days). After 64 weeks, a total of 65% (n = 184) of episodic migraine patients achieved a ≥ 50% reduction in MMDs and 26% (n = 73) had achieved a migraine-free status. The most frequently reported adverse events (≥ 4.0 per 100 patient-years) were viral upper respiratory tract infection, upper respiratory tract infection, sinusitis, influenza, and back pain.
- One unpublished OLE evaluated erenumab-aooe 70 mg (protocol amended to include 140 mg doses) with data to 1 year in patients with chronic migraine. A total of 609 patients with chronic migraine enrolled in the OLE. A total of 199 increased their dose from 70 mg to 140 mg by week 28 (*Amgen [data on file] 2018, Tepper et al 2018*).
  - Patients with chronic migraine had a mean value of 18.8 MMDs at parent study baseline. After a total of 1 year of treatment, the number of MMDs was reduced to 8.5 in the erenumab-aooe 70 mg group and 10.5 in the erenumab-aooe 140 mg group. After 1 year of erenumab-aooe 70 mg and 140 mg monthly dosing, a total of 53% and 67% of chronic migraine patients achieved a ≥ 50% reduction in MMDs and 6% and 13% had achieved a migraine-free status, respectively. The most frequently reported adverse events (≥ 2.0 per 100 patient-years) were viral upper respiratory tract infection, upper respiratory tract infection, sinusitis, and arthralgia.
- Another unpublished safety study, the CGAJ study, evaluated galcanezumab-gnlm 120 mg (plus 240 mg loading dose) and 240 mg monthly dosing to 1 year in patients with episodic or chronic migraine. At baseline, 80.7% of patients in the galcanezumab-gnlm 120 mg arm and 77.0% in the galcanezumab-gnlm 240 mg arm had episodic migraine. A total of 270 patients who had a history of ≥ 4 MMHDs and ≥ 1 headache-free day/month for the past 3 months continued galcanezumab-gnlm treatment (*Eli Lilly and Company [data on file] 2018, Emgality [dossier] 2018, Stauffer et al 2017*).
  - At baseline, patients had a mean value of 9.7 to 11.4 (standard deviation [SD], 6.0 to 6.6) MMHDs. After a total of 1 year of treatment, the number of MMHDs was reduced to 5.6 days in the galcanezumab-gnlm 120 mg group and 6.5 days in the galcanezumab-gnlm 240 mg group. After ≥ 12 consecutive months of treatment, 24.2% of patients treated with galcanezumab-gnlm 120 mg and 34.8% of patients treated with galcanezumab-gnlm 240 mg maintained response. The most frequently reported adverse events (incidence ≥ 15.0%) were injection site pain, nasopharyngitis, and upper respiratory tract infections. One patient discontinued due to suicidal ideation in the galcanezumab-gnlm 120 mg group. There were no overall concerns regarding safety or tolerability.
- Caution should be exercised in applying results from extension trials. The OL design may contribute to biased reports. Extension trials may have biased outcomes because those experiencing benefit are included in extension trials; results are useful for reporting trends in treatment. Additionally, there is no comparator to account for placebo effects.

CLINICAL GUIDELINES

Prevention of migraine

- According to the American Academy of Neurology and American Headache Society (AAN/AHS) evidence−based guideline update on the pharmacologic treatment for episodic migraine prevention in adults (*Silberstein et al 2012*), the following medications are effective preventive treatment options (see Appendix A for a definition of classifications):
  - Level A (established efficacy and > 2 Class I trials):
    - Antiepileptic drugs: divalproex sodium, sodium valproate, and topiramate
    - Beta blockers: metoprolol, propranolol, and timolol
    - Triptans (for menstrual related migraine [MRM]): for short−term prophylaxis, frovatriptan
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Antidepressants: amitriptyline and venlafaxine
    - Beta blockers: atenolol and nadolol
    - Triptans (for MRM): for short−term prophylaxis, naratriptan and zolmitriptan
  - Level C (possibly effective and 1 Class II trial):
    - Angiotensin−converting enzyme (ACE) inhibitors: lisinopril
    - Angiotensin II receptor blockers (ARBs): candesartan
    - Alpha agonists: clonidine and guanfacine
    - Antiepileptic drugs: carbamazepine
    - Beta blockers: nebivolol and pindolol
    - Antihistamines: cyproheptadine
- The AAN recommends onabotulinumtoxin A as an effective treatment option that should be offered for chronic migraine. However, onabotulinumtoxin A is considered ineffective for the treatment of episodic migraines and should not be offered. There is insufficient evidence to compare the effectiveness of botulinum neurotoxin A with that of oral prophylactic topiramate (*Simpson et al 2016*).

Cluster headache

- According to the AHS evidence-based guidelines for the treatment of cluster headache (*Robbins et al 2016*), there are a number of effective treatment options (AAN classifications were used for grading; see Appendix A for definitions).
- For acute therapy of cluster headache, the following therapy options have positive evidence:
  - Level A (established efficacy and ≥ 2 Class I trials):
    - Certain triptans: sumatriptan subcutaneous and zolmitriptan nasal spray
    - Oxygen
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Certain triptans: sumatriptan nasal spray and zolmitriptan oral
    - Sphenopalatine ganglion stimulation
  - Level C (possibly effective and 1 Class II trial):
    - Cocaine/lidocaine nasal spray
    - Octreotide subcutaneous
- For preventive therapy of cluster headache, the following therapy options have positive evidence:
  - Level A (established efficacy and ≥ 2 Class I trials):
    - Suboccipital steroid injection
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Civamide nasal spray (not marketed in the US)
  - Level C (possibly effective and 1 Class II trial):
    - Lithium
    - Verapamil
    - Warfarin
    - Melatonin

SAFETY SUMMARY

- All CGRP inhibitors are contraindicated in patients with serious hypersensitivity to the active ingredient or any of the excipients. Mild to moderate hypersensitivity reactions (eg, rash, pruritus, urticaria) were reported in trials. Reactions to erenumab-aooe have also included anaphylaxis and angioedema. In cases of serious or severe reactions, treatment should be discontinued.
- For the prevention of migraine, the CGRP inhibitors generally have a similar incidence of adverse events as placebo. Very few severe adverse events and treatment discontinuations due to adverse events were reported. The most common adverse reactions observed in CGRP inhibitor studies included injection site reactions (all agents) and constipation (erenumab-aooe only). For the treatment of episodic cluster headache, galcanezumab−gnlm was evaluated for 2 months in trials and the safety profile was similar to those adverse events observed in migraine prevention trials. Two patients discontinued DB treatment due to adverse events.
- Caution should be exercised as long-term safety is unknown. CGRP is a vasodilator and is found at higher concentrations during a migraine attack. In the 1-year interim analysis of an OLE study with erenumab-aooe, 2 patients had severe adverse events (an arteriosclerosis event and a myocardial ischemia event), of which 1 was fatal and 1 was confounded by sumatriptan administration. No additional concerns were raised within the OLE at ≥ 3 years, including any cardiovascular events. In a long-term safety study of patients treated with galcanezumab-gnlm for 1 year, 1 patient discontinued due to suicidal ideation in the galcanezumab-gnlm 120 mg group. The long-term implications of prolonged CGRP inhibition are not fully established and safety has not been fully characterized *(Amgen [data on file] 2018, Ashina et al 2017, Ashina et al 2018, Eli Lilly and Company [data on file] 2018, Stauffer et al 2017, Tepper et al 2018)*.
- There are no adequate data on the risks associated in patients who are pregnant or nursing, or in adolescent or pediatric populations.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Aimovig (erenumab−aooe)	Auto-injector (70 mg/mL or 140 mg/mL)	SC	Once monthly (70 or 140 mg)	May be self−administered by patients in the abdomen, thigh, or back of upper arm. Latex−sensitive patients may have an allergic reaction to the needle shield within the white cap and the gray needle cap of the syringe. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, erenumab-aooe has a limited stability of 7 days.
Ajovy (fremanezumab−vfrm)	Prefilled syringe (225 mg/1.5 mL)	SC	Once monthly (225 mg) or once every 3 months (675 mg)	May be self−administered by patients in the abdomen, thigh, or back of upper arm. The prefilled syringe cap is not made with natural rubber latex. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator,

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				fremanezumab-vfrm has a limited stability of 24 hours.
Emgality (galcanezumab−gnlm)	Auto-injector (120 mg/mL) Prefilled syringe (100 mg/mL or 120 mg/mL)	SC	*Prevention of migraine*: 2 consecutive injections (120 mg each) as a loading dose, then once monthly *Episodic cluster headache*: 3 consecutive injections (100 mg each) at onset, and then once monthly until the end of the cluster period	May be self−administered by patients in the abdomen, thigh, back of upper arm or buttocks. The cap is not made with natural rubber latex. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, galcanezumab-gnlm has a limited stability of 7 days.

See the current prescribing information for full details

Note: With all of the CGRP inhibitors, there are no data in pregnant women or breastfed infants. A benefit/risk assessment should be taken into consideration prior to administering.

CONCLUSION

- Migraine is a common, recurrent, incapacitating disorder characterized by moderate to severe headaches and disabling features, including nausea, vomiting, neurologic symptoms, photophobia, and phonophobia. Migraines have a spectrum of frequency and severity that can significantly affect the quality of life of patients. Cluster headache is less prevalent than migraine and characterized by attacks of severe, unilateral pain with ipsilateral autonomic symptoms, which occur every other day to multiple times daily during a cluster period. Cluster headache is more likely to occur in men, whereas migraines are more likely to occur in women.
- All CGRP inhibitors are indicated for the prevention of migraine. Galcanezumab−gnlm has an additional indication for the treatment of episodic cluster headache.
- Guidelines have not been updated to include the CGRP inhibitors.
  - Current evidence−based prophylactic migraine treatment options and guidance are limited for chronic migraine, and oral prophylactic medications prescribed for episodic migraine are often used for the preventive treatment of chronic migraine. Prophylactic migraine treatment options include oral agents (mainly anti−seizure agents, antidepressants, and beta blockers), injectable agents (onabotulinumtoxin A for chronic subtypes only), or neuromodulation devices for migraine or headache attacks. Certain oral therapies may not be appropriate for individual patients due to intolerability or eventual lack of efficacy. There is no optimal prophylactic migraine therapy and head-to-head trials are lacking.
  - For the treatment of cluster headache, subcutaneous sumatriptan, zolmitriptan nasal spray, and oxygen have the most positive evidence for acute therapy according to the AHS guidelines. To date, only subcutaneous sumatriptan is FDA-approved for the acute treatment of cluster headache. Additionally, sumatriptan nasal spray, zolmitriptan oral formulations, and sphenopalatine ganglion stimulation are probably effective for acute treatment per guidelines. For prevention of cluster headaches, suboccipital steroid injections are most effective according to the guidelines; however, there is no preventive medication currently FDA-approved for cluster headache.
- The CGRP inhibitors (erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm) are novel agents developed as alternatives for patients who do not tolerate, or do not have an adequate response to, currently marketed preventive migraine therapies. Galcanezumab-gnlm has an additional indication for the treatment of episodic cluster headaches.
  - Like other preventive medications for migraine, the CGRP inhibitors are not likely to render patients migraine-free. Based on 3 to 6 month data, primary endpoint reductions are similar to many oral prophylactic therapies; however, comparisons are limited as endpoints have been inconsistently defined. There are limited analyses and trials examining efficacy in patients who failed ≥ 2 prior preventive therapies; however, available data suggest that these patients may achieve greater reductions in migraine/headache frequency. Further research is warranted.
  - For the treatment of cluster headaches, galcanezumab-gnlm demonstrated efficacy compared to placebo in an unpublished 8-week trial, which allowed for acute/abortive treatments during therapy. Galcanezumab-gnlm significantly decreased the mean change from baseline in weekly cluster headache attack frequency by 3.5 during

weeks 1 to 3 vs placebo. Additionally, 18.8% more patients were classified as responders (≥ 50% reduction in weekly cluster headache attack frequency) with galcanezumab-gnlm at week 3 vs placebo (p = 0.046).

- There are no head-to-head studies with the CGRP inhibitors and no prophylactic migraine agent is clearly superior to others.
  - Compared to placebo, the CGRP inhibitors consistently demonstrated modest but statistically significant reductions in primary endpoint measures (eg, MMD, MMH, or MMHD) ranging from 1.0 to 2.5 days after 3 to 6 months of treatment. Overall, the odds for a 50% reduction in MM(H)D were approximately 1.6 to 3.1 times higher with the CGRP inhibitors than placebo with numbers-needed to treat (NNTs) ranging from 3 to 10.
- Lack of information during pregnancy and breastfeeding is a consideration as many migraine patients are women of childbearing potential. The unknown risks of monoclonal antibodies and the effects on certain conditions are not fully characterized. Important co-morbid populations were excluded from trials (eg, anxiety, depression, hypertension, and fibromyalgia), which also limits the generalizability to broader groups. There are no data in adolescents and children. Based on current data, the safety profiles of the CGRP inhibitors are generally mild with the most common adverse effects observed being injection site reactions.
- Overall, the CGRP inhibitors represent another therapy option in the prevention of episodic or chronic migraine. Fremanezumab-vfrm is the only agent in the class that may be administered quarterly, which may fulfill a niche in patients who are non-adherent with treatment. Galcanezumab-gnlm is the only CGRP inhibitor indicated for the treatment of episodic cluster headaches and frequency of administration (and dose) vary by indication. Further long-term study is warranted.

APPENDIX

- **Appendix A. AAN levels of evidence classification** *(Gronseth et al 2011)*

Rating of recommendation	
A	Established as effective, ineffective, or harmful for the given condition in the specified population
B	Probably effective, ineffective, or harmful for the given condition in the specified population
C	Possibly effective, ineffective, or harmful for the given condition in the specified population
U	Data inadequate or conflicting; given current knowledge, treatment is unproven.
Rating of therapeutic article	
Class I	RCT in representative population with masked outcome assessment. The following are required: a) concealed allocation; b) primary outcome(s) is/are clearly defined; c) exclusion/inclusion criteria are clearly defined; d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias; e) certain requirements are needed for noninferiority or equivalence trials claiming to prove efficacy for 1 or both drugs.
Class II	Cohort study that meets a–e (Class I) or RCT that lacks 1 criterion from above (b−e).
Class III	Controlled trials (including well−defined natural history controls or patients serving as own controls), a description of major confounding differences between groups, and where outcome assessment is independent of patient treatment.
Class IV	Does not include patients with the disease, different interventions, undefined/unaccepted interventions or outcomes measures, and/or no measures of effectiveness or statistical precision presented or calculable.

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Therapeutic Class Overview
Anti-migraine Agents (triptans)

INTRODUCTION

- Migraine is a common disabling primary headache disorder that can be divided into 2 major subtypes: without aura (the most common subtype and is associated with a higher average attack frequency) and with aura. According to the International Classification of Headache Disorder (IHS), migraine is a common primary headache disorder manifesting in attacks lasting 4 to 72 hours in adults and 1 to 72 hours in children. Migraines range from moderate to very severe and are sometimes debilitating. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia. When attacks occur ≥15 days/month for >3 months, patients are considered to have chronic migraines (Cutrer et al, 2018; Snow et al, 2002; IHS, 2018[a], IHS, 2018[b]).
- The migraine 1-year prevalence rate in Americans is approximately 12% (17% of women and 6% of men) (Cutrer et al, 2018; Lipton et al, 2001).
- The Food and Drug Administration (FDA) Industry Guidance recommendations and the IHS recommend 2 co-primary endpoints for trials measuring efficacy of acute treatment of migraines. One is the proportion of patients who are pain-free at 2 hours and the other is the reduction of the most bothersome migraine-associated symptom at 2 hours (FDA Industry Guidance [migraine], 2018; Tfelt-Hansen et al, 2012).
- The serotonin (5-HT1) receptor agonists, also referred to as triptans, work in the management of migraine via the promotion of vasoconstriction, inhibition of dural vasodilation and inflammation, and blockade of pain pathways in the brainstem (Clinical Pharmacology, 2019). In contrast to analgesics, the triptans are considered to be “specific” migraine therapies because they act at the pathophysiologic mechanisms of headaches (Bajwa et al, 2019).
- In adults, all triptans are FDA-approved for the acute treatment of migraines with or without aura. In addition to the acute treatment of migraines, subcutaneous sumatriptan is also approved for cluster headaches. The agents FDA-approved in pediatric patients include almotriptan, sumatriptan/naproxen, zolmitriptan nasal spray (for ≥12 years of age), and rizatriptan (for ≥6 years of age).
- There is well-established evidence demonstrating the triptans to be an effective option for acute treatment of migraine; however, there is inconsistent head-to-head data demonstrating the superiority of any triptan, making it difficult to recommend the use of 1 over another (Bajwa et al, 2019). The American Headache Society (AHS) published updated treatment guidelines for migraine in 2018 (AHS, 2019). They recommend the use of acetaminophen, nonsteroidal anti-inflammatory drugs, nonopioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans or dihydroergotamine (DHE) are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics. These guidelines do not differentiate the triptans but recommend that nonoral routes are used when severe nausea or vomiting is present. There are a number of older guidelines/treatment recommendations for the treatment of migraine but, similar to the 2018 guidelines, they do not state a preference for a particular triptan (Evers et al, 2009; Francis et al, 2010; Marmura et al, 2015; Matchar et al, 2000; Silberstein, 2000; Silberstein et al, 2012 [guideline reaffirmed in 2015]). For the treatment of cluster headaches, the 2016 AHS guidelines recommend subcutaneous sumatriptan and zolmitriptan nasal spray (Robbins et al, 2016). In pediatric patients, the Child Neurology Society recommends ibuprofen, followed by acetaminophen, and sumatriptan nasal spray when all other analgesics fail (Lewis et al, 2004). An update of the 2004 Child Neurology Society guideline is currently in progress.
- FDA-approved triptans are available as an oral tablet (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, sumatriptan/naproxen combination, zolmitriptan), orally disintegrating tablet (rizatriptan, zolmitriptan), nasal spray (sumatriptan, zolmitriptan), nasal powder (sumatriptan), and subcutaneous injection (sumatriptan) (DRUGS@FDA, 2019). Branded products are outlined in Table 1.
- According to DRUGS@FDA, the marketing status of ALSUMA and SUMAVEL DOSEPRO is discontinued; therefore, these products have been removed from the therapeutic class overview (DRUGS@FDA, 2019).
- In October 2017, the FDA announced Teva’s voluntary discontinuation of ZECUITY (sumatriptan iontophoretic transdermal system) due to post-marketing reports of application site reactions, including severe redness, cracked

skin, blistering/welts, and burns/scars associated with the product (FDA Drug Shortages and Discontinuations, 2017). Therefore, this product has been removed from the therapeutic class overview.
- Medispan class: Migraine Products – Selective Serotonin Agonists 5-HT(1); Selective Serotonin Agonist-NSAID Combinations

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
AMERGE (naratriptan hydrochloride tablet)	various	02/10/1998	✔
AXERT (almotriptan malate tablet)	various	05/07/2001	✔
FROVA (frovatriptan succinate tablet)	various	11/08/2001	✔
IMITREX (sumatriptan tablet, nasal spray, injection)	various	12/28/1992	✔
IMITREX STATDOSE (sumatriptan cartridges for injection)	various	12/23/1996	✔
MAXALT (rizatriptan benzoate tablet)	various	06/29/1998	✔
MAXALT MLT (rizatriptan benzoate orally disintegrating tablet)	various	06/29/1998	✔
MIGRANOW KIT* (sumatriptan tablet + camphor/menthol gel)	PureTek	-	-
ONZETRA XSAIL (sumatriptan nasal powder)	Merck & Co., Inc.	01/27/2016	-
RELPAX (eletriptan hydrobromide tablet)	Pfizer	12/26/2002	✔
TOSYMRA (sumatriptan nasal spray)	Dr. Reddy's Labs	1/25/2019	-
TREXIMET (sumatriptan/naproxen sodium tablet)	various	04/15/2008	✔
ZEMBRACE SYMTOUCH (sumatriptan injection)	Nupathe Inc.	01/28/2016	-
ZOMIG (zolmitriptan nasal spray, tablet)	various	09/30/2003	✔ (tablets only)
ZOMIG-ZMT (zolmitriptan orally disintegrating tablet)	various	02/13/2001	✔

*This product is not approved by the FDA.

(DRUGS@FDA, 2019; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2019)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

	AMERGE (naratriptan tablet)	AXERT (almotriptan tablet)	FROVA (frovatriptan tablet)	IMITREX (sumatriptan tablets, nasal spray, injection)	IMITREX STATDOSE (sumatriptan cartridges for injection)	MAXALT (rizatriptan tablet)	MAXALT MLT (rizatriptan ODT)	MIGRANOW KIT (sumatriptan tablet + camphor/menthol gel)	ONZETRA XSAIL (sumatriptan nasal powder)	RELPAX (eletriptan tablet)	TOSYMRA (sumatriptan nasal spray)	ZEMBRACE SYMTOUCH (sumatriptan injection)	ZOMIG (zolmitriptan nasal spray, tablet)	ZOMIG ZMT (zolmitriptan ODT)	TREXIMET (sumatriptan/naproxen tablet)
Acute treatment of migraine with or without aura	✔	✔	✔	✔	✔	✔	✔	✔ ‖	✔	✔	✔	✔	✔ ‡	✔	✔
Acute treatment of cluster headache				✔ *	✔										
Acute treatment of migraine with or without aura (aged ≥ 6 years)						✔	✔								
Acute treatment of migraine headache pain in adolescents with a history of migraine with or without aura, and who have migraine attacks usually lasting ≥ 4 hours when untreated (aged ≥ 12 years)		✔ §													
Acute treatment of migraine with or without aura (aged ≥ 12 years)													✔ †‡		✔

Abbrv: ODT = orally disintegrating tablet
Class Limitations of Use: All agents in class are not intended to be used as prophylactic migraine therapy. Use is recommended only after a clear diagnosis of migraine (or cluster headache, if FDA-approved for use) has been established. Agents are not indicated for the treatment of cluster headache unless FDA-approved.
Additional Limitations of Use:
*Indication applies only to the injection formulation
†Indication applies only to the nasal spray formulation
‡Nasal spray is not recommended in patients with moderate to severe hepatic impairment
§For adolescents aged 12 to 17 years, efficacy on migraine-associated symptoms was not established
‖ Indication applies only to the sumatriptan component

(Prescribing information: AMERGE, 2016; AXERT, 2017; FROVA, 2018; IMITREX injection, 2018; IMITREX nasal spray, 2017; IMITREX tablets, 2017; MAXALT, 2015; MAXALT MLT, 2015; MIGRANOW, 2019; ONZETRA XSAIL, 2016; RELPAX, 2013; TOSYMRA, 2019; TREXIMET, 2016; ZEMBRACE SYMTOUCH, 2017; ZOMIG nasal spray, 2018; ZOMIG tablets, 2018; ZOMIG ZMT, 2018)

Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- In general, clinical trial data consistently demonstrate the superiority of the triptans over placebo in achieving headache pain relief and freedom from pain at 2 hours and sustained pain-free response, reducing rescue medication use and improving migraine-associated symptoms such as nausea, photophobia and phonophobia (Bird et al, 2014; Brandes et al, 2007; Cady et al, 2015; Derry et al, 2012 [a]; Derry et al, 2012[b]; Derry et al, 2012[c]; Derry et al, 2014; Ferrari et al, 2002; Law et al, 2016; Oldman et al, 2002; Pascual et al, 2007; Poolsup et al, 2005; Prescribing information: IMITREX, 2018; ZEMBRACE SYMTOUCH, 2017; Richer et al, 2016).
- While there appear to be differences in the relative efficacies among the triptans, direct head-to-head trials do not consistently support the use of 1 over another, suggesting that individual variations in response to different triptans exist. 5-HT_1 receptor agonists have been evaluated in numerous meta-analyses and comparative trials with sumatriptan often used as the benchmark standard as it has the most clinical experience available. All 5-HT_1 receptor agonists are effective at treating migraines and are well tolerated; however, there are some notable differences between the different agents and formulations. Based on older evidence and reviews, the following conclusions were drawn (Derry et al, 2012[a]; Derry et al, 2012[b]; Derry et al, 2012[c]; Derry et al, 2014; Ferrari et al, 2002; Oldman et al, 2002; Pascual et al, 2007):
  - o Rizatriptan 10 mg has the fastest onset of action and the highest efficacy rates of pain-free and headache relief at 2 hours post-dose for oral agents (Oldman et al, 2002); however, the rate of recurrence at 24 hours appears to be higher with rizatriptan (Ferrari et al, 2002; Pascual et al, 2007). Naratriptan 2.5 mg has lower efficacy rates of pain-free and headache relief at 2 hours (Pascual et al, 2007) while eletriptan has a lower rate of recurrence (Ferrari et al, 2002).
  - o Subcutaneous sumatriptan is the most effective for migraine treatment but is associated with more adverse events (AEs) relative to the other 5-HT_1 receptor agonist formulations (Oldman et al, 2002; Derry et al, 2012[c]).
  - o Frovatriptan has the least number of head-to-head trials with active comparators. A recent pooled analysis of 3 studies showed similar efficacy at 2 hours post-dose with pain-free and pain relief responses between frovatriptan and the comparator group (consisting of almotriptan, rizatriptan, and zolmitriptan); however, frovatriptan had less recurrent episodes at 48 hours post-dose than the comparator group (P<0.001) (Cortelli et al, 2011).
  - o Sumatriptan/naproxen fixed-dose combination is more effective for migraine treatment than monotherapy or placebo when measuring headache relief at 2 hours and associated symptoms of migraine, with a similar AE profile to sumatriptan monotherapy (Brandes et al, 2007).
  - o Most 5-HT_1 receptor agonists are well tolerated; however, naratriptan 2.5 mg and almotriptan 12.5 mg appear to have the lowest risk of causing an AE (Ferrari et al, 2002).
- Recent evidence is summarized below:
  - o Recently, 2 novel sumatriptan nasal formulations have been studied in placebo-controlled clinical trials. ONZETRA XSAIL was evaluated in 2 double-blind (DB), randomized trials in 498 patients with moderate to severe migraines through the TARGET and COMPASS studies. The TARGET study (n=230) resulted in significantly more patients who experienced headache relief at 2 hours post-dose among those who received nasal powder sumatriptan 22 mg compared to placebo (68% vs. 45%, respectively; P=0.002). At 30 minutes post-dose, a significant difference in relief was maintained between treatment groups (42% vs. 27%; P=0.03) (Cady et al, 2015). The COMPASS study was a cross-over study with a high drop-out rate, which compared nasal powder sumatriptan 22 mg to oral sumatriptan 100 mg (n=275; 1,531 migraines assessed) in patients with 2 to 8 migraines/month at baseline. Primary endpoint results demonstrated a significant reduction in the adjusted mean difference in pain intensity scores (P<0.001). At 2 hours, the rates of pain relief (freedom) were comparable (Tepper et al, 2015). A phase 2 trial of TOSYMRA in 107 patients with 2 to 8 migraines/month found improved response (freedom from headache pain at 2 hours post-dose) with TOSYMRA compared with placebo (43.8% vs 22.5%; P=0.044). TOSYMRA was also significantly better than placebo at alleviating bothersome symptoms such as nausea, photophobia, and phonophobia 2 hours post-dose (70.7% vs 39.5%; p = 0.004) (Lipton et al, 2018).
  - o Data to support the approval of ZEMBRACE SYMTOUCH were based on subcutaneous sumatriptan succinate bioequivalence studies. The safety and efficacy of subcutaneous sumatriptan succinate were evaluated in 3 controlled, unpublished studies in over 1,000 patients with moderate to severe migraines. Studies demonstrated that the onset of relief began as early as 10 minutes following a 6 mg sumatriptan injection. Within 2 hours,

headache relief was achieved in 82% of patients treated with a sumatriptan 6 mg injection, and 65% were pain free (Prescribing Information: ZEMBRACE SYMTOUCH, 2017; IMITREX, 2018).
- In a randomized, double-blind, crossover study, the efficacy and tolerability of 3 mg subcutaneous sumatriptan (ZEMBRACE SYMTOUCH) and 6 mg subcutaneous sumatriptan (SUMAVEL DOSEPRO – now discontinued) were compared in 20 patients with rapidly-escalating migraine attacks. The proportion of patients who were pain-free at 1-hour post-dose was similar following treatment with 3 mg and 6 mg subcutaneous sumatriptan (50% vs 52.6%, respectively; P=0.87). Tolerability was also similar for both doses; although, sumatriptan 3 mg was associated with fewer triptan sensations (ie, paresthesia, neck pain, flushing, and involuntary muscle contractions of the neck) when compared to the the 6-mg dose (1 patient vs 4 patients) (Cady et al, 2017).
- A summary of Cochrane Reviews evaluating the various routes of administration for sumatriptan demonstrated that the injectable (particularly the 6 mg subcutaneous dose) routes of administration were most effective in reducing pain within the first 2 hours of treatment compared to placebo (number needed to treat [NNT], 2.3) and sustained pain-free after 24 hours (NNT, 6.1). Efficacy was dose-related with the oral sumatriptan 50 mg dose demonstrating the highest NNT for most endpoints. Compared to other triptans, only rizatriptan 5 mg (vs. sumatriptan 25 mg), rizatriptan 10 mg (vs. sumatriptan 25 to 100 mg), and eletriptan 40 to 80 mg (vs. sumatriptan 50 to 100 mg) were superior to sumatriptan for various endpoints. No differences in the incidence AEs were found (Derry et al, 2014).
- A Cochrane Review of zolmitriptan trials concluded that zolmitriptan 2.5 to 5 mg benefited the same proportion of patients as sumatriptan 50 mg for headache relief at 2 hours (range 66 to 68%) with no significant difference in safety (Bird et al, 2014).
- The TEENZ study assessed the efficacy and safety of zolmitriptan nasal spray for the acute treatment of a single migraine headache in 798 adolescents aged 12 to 17 years. The DB, 4-arm parallel study randomized patients in a ratio of 5:3:3:5 to placebo or zolmitriptan nasal spray in doses of 0.5 mg, 2.5 mg, or 5 mg, respectively. Zolmitriptan 5 mg nasal spray was statistically superior to placebo for the primary endpoint of pain-free status after 2 hours of administration (29.7% vs. 16.6%, respectively; P<0.001). Dysgeusia was the most frequently reported AE with zolmitriptan 5 mg nasal spray (occurring in 11.4% more of patients) (Winner et al, 2016).
- In pediatric patients, 1 Cochrane review concluded that triptans (moderate quality of evidence) and ibuprofen (low quality evidence) are effective at providing pain freedom in children and adolescents. There are limited safety data available for AEs associated with ibuprofen use, and there may be with higher rates of minor AEs associated with triptan use. Further studies are needed in this population to validate conclusions (Richer et al, 2016).

SAFETY SUMMARY

- All triptans are contraindicated in patients with significant underlying cardiovascular (CV) disease (eg, angina pectoris, history of myocardial infarction, documented silent ischemia, or coronary artery vasospasm); peripheral vascular disease; ischemic bowel disease; uncontrolled hypertension; a history of stroke, transient ischemic attack or history of hemiplegic or basilar migraine because these patients are at a higher risk of stroke; and recent use (ie, within 24 hours) of ergotamine-containing medication, ergot-type medication (such as DHE or methysergide) or another 5-HT_1 receptor agonist. Additional contraindications include:
  - Naratriptan, sumatriptan and sumatriptan/naproxen are contraindicated in severe hepatic impairment. Naratriptan is also contraindicated in severe renal impairment (creatinine clearance [CrCL] < 15 mL/min).
  - Frovatriptan, naratriptan, eletriptan, sumatriptan, sumatriptan/naproxen, or zolmitriptan are contraindicated in patients with Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders.
  - Concurrent administration of rizatriptan, sumatriptan, sumatriptan/naproxen, or zolmitriptan with a monoamine oxidase (MAO)-A inhibitor or recent (within 2 weeks) use of an MAO-A inhibitor.
  - Eletriptan is contraindicated in patients with recent use (within at least 72 hours) of potent cytochrome P450 (CYP) 3A4 inhibitors including ketoconazole, itraconazole, nefazodone, clarithromycin, ritonavir, or nelfinavir.
  - Sumatriptan/naproxen is contraindicated in the setting of coronary artery bypass graft (CABG) surgery; use during the third trimester of pregnancy; and in asthma, rhinitis, and in those patients with a history of asthma, urticaria, or allergic-type reactions after taking aspirin (ASA) or NSAIDs.
- Sumatriptan/naproxen has a boxed warning of potentially fatal CV and gastrointestinal (GI) risks associated with NSAID-use. NSAIDs can increase CV thrombotic events (eg, myocardial infarction and stroke); use is

contraindicated in the setting of CABG; and increased reports of GI events such as bleeding, ulceration, and perforation of the stomach or intestines have been reported, including fatal events.

- The following warnings and precautions are associated with medications in class:
  - o Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, sumatriptan/naproxen, and zolmitriptan have a higher risk of myocardial ischemia, infarction, Prinzmetal angina, arrhythmias, and other adverse cardiac events in certain patients; cerebrovascular events and associated fatalities in certain patients; other vaso-spasm-related events (ie, GI ischemic and peripheral vasospastic); chest, throat, neck, and jaw pain, tightness and pressure; exacerbation of headache with medication overuse; and serotonin syndrome.
  - o Almotriptan has additional warnings of corneal opacities and possible accumulation and subsequent toxicity due to the binding of melanin-containing tissues in certain patients. Almotriptan should be used with caution in patients with hypersensitivity to sulfonamides. Almotriptan, rizatriptan, and zolmitriptan, have had reports of significant elevations of blood pressure.
  - o All sumatriptan-containing products have reports of seizures reported following administration. Sumatriptan/naproxen also has warnings associated with NSAID use, which include: increased exacerbations of asthma, nasal polyps, or fatal bronchospasm due to ASA-sensitivity or cross-reactivity; increases in fluid retention and edema may worsen heart failure or cause hyperkalemia and renal toxicity; serious skin reactions (eg, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis); the potential to mask inflammation and fever; and elevated liver enzymes have been reported with use.
  - o Injectable sumatriptan (IMITREX and IMITREX STATDOSE) has a warning for hypersensitivity reactions, including anaphylaxis and angioedema. In addition, the needle shield of the prefilled syringe contains a latex derivative that has the potential to cause allergic reactions in patients sensitive to latex.
  - o Zolmitriptan ODTs contain phenylalanine, in which the labeling warns of use in patients with phenylketonuria.
- Triptan-containing medications have a large number of potential AEs, but the incidence of most individual reactions is relatively low and often dose-related. Among the oral preparations, no triptan is clearly safer than the others. In general, the injectable triptans are associated with more AEs compared with the oral/topical dosage forms. Triptans are often associated with atypical sensations, including numbness tingling, flushing, heaviness/tightness of the chest and throat, heat, burning, cold, or pressure.
  - o Generally, the most common AEs associated with 5-HT_1 receptor agonists are dizziness, numbness, tingling, flushing, sleepiness, and fatigue.
  - o Serious cardiac events, including myocardial infarction and coronary artery vasospasm, have occurred following use of 5-HT_1 receptor agonists. These events are extremely rare and have been reported in patients with risk factors predictive of coronary artery disease. Other events reported in association with drugs in this class have included ventricular tachycardia and fibrillation.
- A 2017 meta-analysis including 141 trials compared the tolerability of 14 oral treatments for acute migraine. In indirect comparisons of PC trials utilizing triptans, naratriptan had the lowest odds of any AE (odds ratio [OR]=1.11; 95% confidence interval [CI], 0.84 to 1.43) and treatment-related AE (OR=0.86, 95% CI, 0.51 to 1.55); zolmitriptan had the highest odds of any AE (OR, 2.22; 95% CI, 1.83 to 2.70) and sumatriptan had the highest odds of treatment-related AE (OR=2.23, 95% CI, 1.83 to 2.73). Results from the meta-regression reported that the dose of triptans had a significant effect on the occurrence of any AE and treatment-related AE, with higher doses yielding a higher probability of AE occurrence and lower doses lessening the risk (Thorlund, 2017).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
Oral agents			
AMERGE (naratriptan)	Tablet: 1 mg 2.5 mg	Adult: 1 mg or 2.5 mg orally as a single dose; may repeat administration in 4 hours. Max daily dose: 5 mg.	Safety of treating > 4 migraines in 1 month has not been established.

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
AXERT (almotriptan)	Tablet: 6.25 mg 12.5 mg	Adult and adolescent (≥12 years): 6.25 mg or 12.5 mg orally as a single dose; may repeat administration in 2 hours. Max daily dose for adults: 25 mg.	Safety of treating >4 migraines in 1 month has not been established. In adults, 12.5 mg dose is more effective.
FROVA (frovatriptan)	Tablet: 2.5 mg	Adult: 2.5 mg orally as a single dose; may repeat administration in 2 hours. Max daily dose: 7.5 mg.	Safety of treating >4 migraines in 1 month has not been established.
IMITREX (sumatriptan)	Tablet: 25 mg 50 mg 100 mg	Adult: 25, 50, or 100 mg orally as a single dose; may repeat administration in 2 hours. Max daily dose: 200 mg.	Safety of treating >4 migraines in 1 month has not been established. Doses of 100 mg may not provide a greater effect than the 50 mg dose.
MAXALT, MAXALT MLT (rizatriptan)	Tablet; Orally disintegrating tablet: 5 mg 10 mg	Adult: 5 mg or 10 mg orally as a single dose. Max daily dose: 30 mg. Pediatric (≥6 years): Weight based dosing of 5 mg for <40 kg and 10 mg for ≥40 kg. May repeat administration in 2 hours in adults and 24 hours in pediatric patients. Dose adjustments are needed for patients taking propranolol concomitantly.	Safety of treating >4 migraines/month in adults or children, and >1 dose within 24 hours in patients 6 to 12 years of age have not been established.
MIGRANOW KIT (sumatriptan + camphor/ menthol)	Tablet (sumatriptan): 25 mg 50 mg 100 mg Gel roll-on applicator: 4% camphor/10% menthol	Adult: Sumatriptan: 25, 50, or 100 mg orally as a single dose; may repeat administration in 2 hours. Max daily dose: 200 mg. Camphor/menthol: Apply gel to affected area up to 3 or 4 times daily.	Safety of treating >4 migraines in 1 month has not been established. Doses of 100 mg may not provide a greater effect than the 50 mg dose. Do not apply the gel to wounds, damaged skin, mucous membranes, or eyes.
RELPAX (eletriptan)	Tablet: 20 mg 40 mg	Adult: 20 or 40 mg orally as a single dose; may repeat administration in 2 hours. Max daily dose: 80 mg. Max single dose: 40 mg.	Safety of treating >3 migraines in 1 month has not been established.
TREXIMET (sumatriptan/ naproxen)	Tablet: 10/60 mg 85/500 mg	Adult and adolescent (≥12 years): 1 tablet (85/500 mg for adults and 10/60 mg for adolescents) orally as a single dose. Max daily dose: 2 tablets in 24 hours, taken at least 2 hours apart for adults and 1 tablet in a 24 hour period for adolescents.	Safety of treating >5 migraines in adults and >2 migraines in pediatric patients over the span of 1 month has not been established.
ZOMIG, ZOMIG-ZMT (zolmitriptan)	Orally disintegrating tablet; Tablet: 2.5 mg	Adult: starting dose is 1.25 or 2.5 mg dose; may repeat administration in 2 hours. Max daily dose: 10 mg. Max single dose: 5 mg.	Safety of treating >3 migraines in 1 month has not been established.

Drug	Dosage Form: Strength	Usual Recommended Dose	Administration Considerations
	5 mg		
Intranasal agents			
IMITREX nasal spray (sumatriptan)	Nasal spray: 5 or 20 mg/actuator unit-of-use inhaler	Adult: 5, 10, or 20 mg administered as a single dose intranasally; may repeat administration in 2 hours. Max daily dose: 40 mg. Max single dose: 20 mg.	Safety of treating >4 migraines in 1 month has not been established.
ONZETRA XSAIL (sumatriptan)	Nasal powder: 2 breath-powered delivery systems containing 11 mg sumatriptan per each nosepiece	Adult: 22 mg (2 nosepieces) administered using the breath-powered delivery device; may repeat administration in 2 hours. Max daily dose: 2 doses (44 mg/4 nosepieces).	Safety of treating >4 migraines in 1 month has not been established. Breath-powered powder delivery requiring a forceful blow into each nostril.
TOSYMRA (sumatriptan)	Nasal spray: 10 mg/spray single-use unit	Adult: 10 mg as a single dose intranasally; may repeat after 1 hour. Max daily dose: 30 mg.	Administered as a single spray to 1 nostril.
ZOMIG (zolmitriptan)	Nasal spray: 2.5 or 5 mg/spray single-use nasal spray units	Adult and adolescent (≥12 years): 2.5 mg administered as a single dose intranasally; may repeat administration in 2 hours. Max daily dose: 10 mg. Max single dose: 5 mg.	Safety of treating >4 migraines in 1 month has not been established.
Subcutaneous agents			
IMITREX (sumatriptan)	Subcutaneous injection: 6 mg single dose vial	Adult: 6 mg administered subcutaneously; may repeat administration in 1 hour. Max daily dose: 12 mg. Max single dose: 6 mg, particularly for cluster headaches; however, lower doses (1 to 5 mg) may be administered for the treatment of migraine.	Administer the needle only to the skin; intramuscular (IM) or intravascular (IV) delivery should be avoided.
IMITREX STATDOSE (sumatriptan)	Subcutaneous injection: 4 and 6 mg single dose, prefilled cartridges for pen use	Adult: 6 mg administered subcutaneously; may repeat administration in 1 hour. Max daily dose: 12 mg. Max single dose: 6 mg, particularly for cluster headaches; however, lower doses (1 to 5 mg) may be administered for the treatment of migraine.	Administer where the needle penetrates ¼ inch of skin; IM or IV delivery should be avoided.
ZEMBRACE SYMTOUCH (sumatriptan)	Subcutaneous injection: 3 mg single dose, prefilled autoinjector	Adult: 3 mg injected subcutaneously; each dose should be separated by at least 1 hour. May administer up to 4 times per day. Max daily dose: 12 mg. Max single dose: 3 mg.	Administer where the needle penetrates ¼ inch of skin; IM or IV delivery should be avoided. Administer dose to the upper arm or thigh. May be administered at least 1 hour following a dose of another sumatriptan agent.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
AXERT (almotriptan)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established in children <12 years of age.	For CrCL ≤30 mL/minute, an initial dose of 6.25 mg and a max dose of 12.5 mg/day are recommended.	Dosage adjustment required for moderate to severe impairment, reduce dose to 6.25 mg and a max dose of 12.5 mg/day.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.
RELPAX (eletriptan)	No overall difference in safety or efficacy between elderly and younger patients. BP was increased to a greater extent in elderly patients. Additionally, a statistically significant increased half-life (from 4.4 hours to 5.7 hours) was observed between elderly and younger patients. No dose adjustments are recommended.	Safety and efficacy have not been established.	No significant change in clearance for patients with mild, moderate, or severe impairment; although, BP elevations were observed in this population. No dosage adjustment required.	Use in severe impairment is not recommended.	Pregnancy Category C* Excreted in breast milk. AAP classifies drug as compatible with breastfeeding. Drug would not be expected to cause any adverse effects in breastfed infants, especially if the infant is >2 months; use with caution.
FROVA (frovatriptan)	Mean blood concentrations were 1.5 to 2 times higher in elderly patients versus younger patients. No dose adjustments are recommended.	Safety and efficacy have not been established.	No dosage adjustment is required.	An estimated 2-fold increase in AUC is predicted with severe impairment; use with caution. No dosage adjustment is required for mild to moderate impairment.	†Unclassified There are no adequate data on the developmental risk associated with the use of frovatriptan in pregnant women. Several studies have suggested women with migraine may be at increased risk of preeclampsia. Use with caution.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
					Unknown whether excreted in breast milk; use with caution.
AMERGE (naratriptan)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established.	For mild to moderate impairment, reduce initial dose to 1 mg and a max dose of 2.5 mg/day. Use in severe impairment (CrCL ≤15 mL/min) is contraindicated.	For mild to moderate impairment, reduce initial dose to 1 mg and a max dose of 2.5 mg/day. Use in severe impairment (Child-Pugh C) is contraindicated.	†Unclassified Several studies have suggested women with migraine may be at increased risk of preeclampsia. Post-marketing reports of naratriptan included mainly first trimester exposures. The incidence of major birth defects with naratriptan was similar to the incidence of the general US population (2.2% vs. 2.2 to 2.9%, respectively). Use with caution. Unknown whether excreted in breast milk; use with caution.
MAXALT, MAXALT MLT (rizatriptan)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established in children <6 years of age.	No dosage adjustment is required.	Drug plasma concentrations are 30% greater with moderate impairment. No dosage adjustment is required for mild to moderate impairment.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.

IMITREX, IMITREX STATDOSE, MIGRANOW, ONZETRA XSAIL, TOSYMRA, ZEMBRACE SYMTOUCH (sumatriptan)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established.	Not studied.	The maximum single oral dose should not exceed 50 mg. Use in severe impairment is contraindicated.	Pregnancy Category C* (MIGRANOW, ONZENTRA XSAIL, ZEMBRACE SYMTOUCH) †Unclassified (IMITREX, IMITREX STATDOSE, TOSYMRA) Overall, data from a pregnancy exposure registry have not detected an increased frequency of birth defects or a consistent pattern of birth defects associated with sumatriptan exposure during pregnancy. Several studies have suggested women with migraine may be at increased risk of preeclampsia. A registry study reported a 4.2% occurrence of major birth defects during first-trimester exposure and during any trimester of exposure, which is numerically higher than the 2.2% to 2.9% rate of major birth defects among deliveries to women with migraine. ALL FORMULATIONS: Excreted in breast milk after subcutaneous administration. Unknown excretion after oral administration. Withhold breastfeeding for 12 hours after oral, nasal, or

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
					subcutaneous administration to minimize infant exposure.
TREXIMET (sumatriptan/ naproxen)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established in children <12 years of age.	No renal dosage adjustment required for mild to moderate impairment. Not recommended for severe impairment (CrCL ≤30 mL/min). Renal effects of the drug may hasten progression of renal dysfunction in pre-existing renal disease.	Administer 1 10/60 mg tablet in a 24 hour period for mild to moderate impairment. Use in severe impairment is contraindicated.	Pregnancy Category C during the first 2 trimesters; Pregnancy Category X during the third trimester* Both agents are excreted in breast milk. Limited information indicates that levels are low and adverse effects in breastfed infants are apparently uncommon. However, because of naproxen's long half-life and reported serious adverse reaction in a breastfed neonate, other agents may be preferred while nursing a newborn or preterm infant; use with caution.
ZOMIG, ZOMIG-ZMT (zolmitriptan)	Safety and efficacy have not been established. In general, start at the low end of the dosing range. A CV evaluation is recommended for geriatric patients who have other CV risk factors.	Safety and efficacy have not been established for the nasal spray in children <12 years of age and <18 years of age for oral formulations.	Clearance was reduced by 25% in patients with severe impairment (CrCL ≤25 mL/min); no significant change in clearance was observed in moderate impairment (CrCL 26 to 50 mL/min). No dosage adjustment required.	Dosage adjustment required for moderate to severe impairment, reduce dose to 1.25 mg and a max dose of 5 mg/day.	Pregnancy Category C* Unknown whether excreted in breast milk; use with caution.

Abbrv: AAP = American Academy of Pediatrics; AUC = area under the curve; BP = blood pressure; CrCL = creatinine clearance; CV = cardiovascular; ODT = orally disintegrating tablet

*Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus, and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Pregnancy Category X = Contraindicated in pregnant women due to evidence of fetal abnormalities from adverse effects data from investigational or marketing experience. Risks of use of the drug in pregnant women clearly outweigh potential benefits.
†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

(American Academy of Pediatrics, 2001; LactMed, 2018)

CONCLUSION

- The 5-HT_1 receptor agonists, commonly referred to as triptans, are a well-established therapy for the acute treatment of migraine attacks with or without aura. These agents work via the promotion of vasoconstriction, inhibition of dural vasodilation and inflammation and blockade of pain pathways in the brainstem. In contrast to analgesics, the triptans are considered to be specific migraine therapies because they act at the pathophysiologic mechanisms of headaches (Bajwa et al, 2019; Clinical Pharmacology, 2019).
- Currently, there are 7 single-entity triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) and 1 fixed-dose triptan/nonsteroidal anti-inflammatory combination product (sumatriptan/naproxen) available. All triptans are available as a tablet; however, some are available in a variety of other dosage formulations. Specifically, sumatriptan (nasal spray, nasal powder, subcutaneous injection, and tablet) and zolmitriptan (nasal spray, orally disintegrating tablet, and tablet) are available in the greatest number of dosage formulations. While it is noted that the subcutaneous sumatriptan injection has the fastest onset of action, there is no evidence to suggest that different oral triptan formulations have a faster onset of action than others (Francis et al, 2010). Almotriptan, eletriptan, naratriptan, rizatriptan, sumatriptan, sumatriptan/naproxen and zolmitriptan are available generically in at least 1 dosage form or strength (DRUGS@FDA, 2019).
- Triptan selection is based on the characteristics of the headache, dosing convenience, and patient preference. All available triptans are FDA-approved for the acute treatment of migraine with or without aura. The subcutaneous sumatriptan injections (with the exception of ZEMBRACE SYMTOUCH) are also FDA-approved for the acute treatment of cluster headache episodes. In pediatric patients, almotriptan, zolmitriptan nasal spray (fastest onset), and sumatriptan/naproxen are approved for use in children 12 years of age and older, while rizatriptan is approved for use in children as young as 6 years of age.
- While there are data to suggest that the available triptans differ in comparative efficacy, because of the lack of consistent superiority of 1 triptan over another in direct head-to-head comparisons, it appears that individual variations in response to the different triptans exist. There are no pediatric comparative effectiveness data and studies are sparse. Based on pharmacokinetic and –dynamic data, subcutaneous and intranasal formulations generally have a quicker onset of action and subcutaneous formulations generally have a lower NNT but more AEs. Frovatriptan and naratriptan have the longest onset of action, which may be responsible for lower incidences of AE. Meta-analyses and systematic reviews point to a potential for lower efficacy with naratriptan and frovatriptan; however, more studies are needed to validate findings.
- Triptan-containing medications have a large number of potential AEs, but the incidence of most individual reactions is relatively low and often dose-related. Among the oral preparations, no triptan is clearly safer than the others. A 2017 meta-analysis including 141 trials compared the tolerability of 14 oral treatments for acute migraine. In indirect comparisons of placebo-controlled trials utilizing triptans, naratriptan had the lowest odds of any AE (odds ratio [OR]=1.11; 95% confidence interval [CI], 0.84 to 1.43) and treatment-related AE (OR=0.86, 95% CI, 0.51 to 1.55); zolmitriptan had the highest odds of any AE (OR, 2.22; 95% CI, 1.83 to 2.70) and sumatriptan had the highest odds of treatment-related AE (OR=2.23, 95% CI, 1.83 to 2.73). Results from the meta-regression reported that the dose of triptans had a significant effect on the occurrence of any AE and treatment-related AE, with higher doses yielding a higher probability of AE occurrence and lower doses lessening the risk (Thorlund, 2017).
- In general, the injectable triptans are associated with more AEs compared with the oral dosage forms. Triptans are often associated with atypical sensations, including numbness, tingling, flushing, heaviness/tightness in the chest and throat, heat, burning, cold, or pressure.
- The American Headache Society (AHS) published updated treatment guidelines for migraine in 2018 (AHS, 2019). They recommend the triptans or dihydroergotamine (DHE) for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics. These guidelines do not differentiate the triptans but recommend that non-oral routes be used when severe nausea or vomiting is present. There are a number of older

guidelines/treatment recommendations for the treatment of migraine but, similar to the 2018 guidelines, they do not state a preference for a particular triptan (Evers et al, 2009; Francis et al, 2010; Marmura et al, 2015; Matchar et al, 2000; Silberstein, 2000; Silberstein et al, 2012 [guideline reaffirmed in 2015]).

- For the treatment of cluster headaches, the 2016 AHS guideline provides an update to the 2010 AAN guidelines (Francis et al, 2010; Robbins et al, 2016). For acute treatment, subcutaneous sumatriptan and zolmitriptan nasal spray are recommended with a higher level of evidence; although zolmitriptan nasal spray is not FDA-approved for use (Robbins et al, 2016). In pediatric patients, older guidelines published by the Child Neurology Society recommend ibuprofen as first-line therapy for the treatment of migraines, followed by acetaminophen, and sumatriptan nasal spray when all other analgesics fail (Lewis et al, 2004). An update of the 2004 Child Neurological Society guideline is currently in progress.
- All 5-HT_1 receptor agonists are generally effective for the acute treatment of migraine attacks and are well tolerated with a similar safety profile. Although some 5-HT_1 receptor agonists have been shown to be significantly superior to other 5-HT_1 receptor agonists in direct comparator studies, these results may not translate to significant differences within meta-analyses and systematic reviews. Additionally, the clinical superiority cannot be determined as an individual patient's response to a particular drug may vary. In general, injection treatments have been associated with the fastest onset of action; therefore, they are amenable to quick relief. However, injectable triptans are associated with more AEs compared to oral or topical dosage forms. Treatment guidelines do not recommend 1 agent over another; rather, choice of treatment should be individualized based on patient needs, response, and preference, migraine severity, and tolerability.

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INTRODUCTION

- Antipsychotic medications have been used for over 50 years to treat schizophrenia and a variety of other psychiatric disorders (*Miyamato et al 2005*).
- Antipsychotic medications generally exert their effect in part by blocking dopamine (D)-2 receptors (*Jibson et al 2017*).
- Antipsychotics are divided into 2 distinct classes based on their affinity for D2 and other neuroreceptors: typical antipsychotics, also called first-generation antipsychotics (FGAs), and atypical antipsychotics, also called second-generation antipsychotics (SGAs) (*Miyamato et al 2005)*.
- Atypical antipsychotics do not have a uniform pharmacology or mechanism of action; these differences likely account for the different safety and tolerability profiles of these agents (*Clinical Pharmacology 2019, Jibson et al 2017*). The atypical antipsychotics differ from the early antipsychotics in that they have affinity for the serotonin 5-HT2 receptor in addition to D2.
  - Clozapine is an antagonist at all dopamine receptors (D1-5), with lower affinity for D1 and D2 receptors and high affinity for D4 receptors. Aripiprazole and brexpiprazole act as partial agonists at the D2 receptor, functioning as an agonist when synaptic dopamine levels are low and as an antagonist when they are high. Cariprazine is a partial agonist at D2 and D3. Pimavanserin does not have dopamine blocking activity and is primarily an inverse agonist at 5-HT2A receptors. The remaining atypical antipsychotics share the similarity of D2 and 5-HT2A antagonism, but differ in activity at other central nervous system (CNS) receptor classes.
- There are a number of atypical antipsychotic formulations available as both branded and generic products. Food and Drug Administration (FDA)-approved indications for the atypical antipsychotics include irritability associated with autistic disorder, bipolar disorder, Tourette's disorder, major depressive disorder (MDD), schizophrenia, schizoaffective disorder, and hallucinations and delusions associated with Parkinson's disease (PD) psychosis.
- Autism
  - Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by impairment in socialization, communication, and behavior (*Weissman et al 2018*).
  - ASD are more common in males than females and estimates of prevalence vary based on populations studied.
  - Data from the Autism and Developmental Disabilities Monitoring Network in the U.S. reported a prevalence of 14.6 per 1000 children at age 8 in 2012 (*Morbidity and Mortality Weekly Report [MMWR] 2016*).
  - The pathogenesis of ASD is not completely understood but is believed to have a genetic component, which alters brain development (*Augustyn 2017*).
  - Overall treatment goals include maximization of functioning, improvement in quality of life, and helping the patient achieve and maintain independence.
  - Specific treatment goals include improving social, communication, and adaptation skills, improving academic functioning, and decreasing nonfunctional behaviors.
  - Treatments include educational and behavioral therapies and pharmacologic interventions to treat targeted symptoms including aggression, impulsivity, hyperactivity, anxiety, sleep disturbances, and depression (*Weissman et al 2018*).
- Bipolar disorder
  - Bipolar disorder is characterized by discrete mood instability. The lifetime prevalence of bipolar disorder is reported to be between 1 and 3%, although the true prevalence is uncertain (*Stovall 2018[a]*).
  - Genetics, in addition to environmental factors, appear to play an important role in the pathogenesis of bipolar disorder.
  - Drugs commonly used to treat acute mania or hypomanias include lithium, anticonvulsants, and antipsychotics. Benzodiazepines may be helpful when adjunctive treatment is needed for insomnia, agitation, or anxiety (*Stovall 2018[b]*).
- Major depressive disorder (MDD)
  - MDD manifests with symptoms of depressed mood, loss of interest or pleasure in almost all activities, altered sleep, change in appetite or weight, poor energy and/or concentration, thoughts of worthlessness, and potentially thoughts of death or suicide (*Gelenberg et al 2010*).

- For the diagnosis of MDD, patients must have ≥ 5 symptoms that have been present during the same 2-week period or represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. The goal of treatment is full remission (*Diagnostic and Statistical Manual of Mental Disorders [DSM] V 2013*).
- Based on data from 2013 to 2016, approximately 8.1% of individuals aged ≥20 years in the United States (U.S.) meet the criteria for depression. Women are more likely to experience symptoms of depression in their lifetime as compared to men (10.4% vs 5.5%) (*Centers for Disease Control and Prevention [CDC] Web site*).

- Schizophrenia
  - Schizophrenia is a disorder involving chronic or recurrent psychosis and is associated with significant functional impairment. Schizophrenia is believed to be caused by an increase in the cerebral activity of dopamine in the mesolimbic and/or mesocortical regions of the brain (*Lehman et al 2004*).
  - The disease includes positive symptoms such as hallucinations, delusions, and disorganized speech, as well as negative symptoms including flat affect, cognitive impairment, and impairment in executive functioning (*DSM V 2013*, *Lehman et al 2004*).
  - For the diagnosis of schizophrenia, patients must have ≥ 2 symptoms that have been present for a significant portion of time during a 1-month period and continuous signs of the disturbance persist for at least 6 months. Symptoms must include 1 of the following: delusions, hallucinations, and disorganized speech, but may also include grossly disorganized or catatonic behavior, and negative symptoms (*DSM V 2013*).
  - The prevalence of schizophrenia is approximately 0.25 to 0.64%, and the lifetime incidence is 10.2 to 22 per 100,000 person-years (*McGrath et al 2008*, *National Institute of Mental Health Web site*, *van Os et al 2009*).
- Tourette's disorder
  - Tourette's disorder ranges greatly in terms of symptom severity and is often associated with comorbidities (*Murphy et al 2013*).
  - Tourette's disorder is characterized by persistent and repetitive motor and/or vocal tics, and onset is typically observed in childhood. For diagnosis, tics need to be present for at least 1 year. The pathophysiology of chronic tic disorders is not known but believed to be due to motor issues at both cortical and subcortical levels that are not properly modulated at the cortico-striatal-thalamo-cortical circuits.
  - Other comorbidities often observed with Tourette's disorder include attention-deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD).
  - The prevalence of chronic tic disorders has been estimated as 0.5 to 3%, with approximately 7% of school-age children having had tics in the previous year.
- Parkinson's disease psychosis
  - Parkinson's disease is characterized by motor symptoms, which include tremor, bradykinesia, rigidity, and postural instability *(Bozymski et al 2017).*
  - Nonmotor symptoms can also occur in PD, which include autonomic dysfunction, sensory disturbances, and neuropsychiatric manifestations such as hallucinations, delusions, cognitive impairment, sleep disturbances, depression, and anxiety.
  - Approximately 60% of patients with PD develop psychosis.
  - For the diagnosis of PD psychosis, patients must meet the following criteria: primary diagnosis of PD; present with at least delusions, hallucinations, illusions, or false sense of presence; symptoms recurrent or continuous for at least 1 month; and exclusion of dementia-related psychosis or psychotic disorders.
- The agents included in this review are listed in Table 1 by brand name. Those drugs excluded from this review include Equetro (carbamazepine ER) capsule. Since there are multiple branded agents that contain the same generic component, the remaining tables in the review are organized by generic name. This review is restricted to the atypical antipsychotic agents and their respective FDA-approved indications.
  - Aripiprazole lauroxil is the prodrug of aripiprazole, and paliperidone is the active metabolite of risperidone.
- Medispan class: Antipsychotics/Antimanic agents; Antipsychotics – Misc., Quinolinone derivatives, Dibenzo-oxepino Pyrroles, Dibenzodiazepines.

Table 1. Medications included within class review

Drug	Generic
Single Entity Agents	
Abilify (aripiprazole)	✔ *
Abilify Discmelt (aripiprazole)	✔ *
Abilify MyCite (aripiprazole)	-†
Clozaril (clozapine)	✔
Fanapt (iloperidone)	-‡
Fazaclo (clozapine)	✔
Geodon (ziprasidone hydrochloride [HCl])	✔
Geodon (ziprasidone mesylate)	-
Invega (paliperidone extended-release [ER])	✔
Latuda (lurasidone)	-‖
Nuplazid (pimavanserin)	-
Rexulti (brexpiprazole)	-
Risperdal (risperidone)	✔
Risperdal M-Tab (risperidone)	✔
Saphris (asenapine)	-§
Seroquel (quetiapine)	✔
Seroquel XR (quetiapine ER)	✔
Versacloz (clozapine)	-
Vraylar (cariprazine)	-
Zyprexa (olanzapine)	✔
Zyprexa Zydis (olanzapine)	✔
Long-Acting Injectable Products	
Abilify Maintena (aripiprazole ER)	-
Aristada (aripiprazole lauroxil ER)	-
Aristada Initio (aripiprazole lauroxil ER)	-
Invega Sustenna (paliperidone palmitate)	-
Invega Trinza (paliperidone palmitate)	-
Risperdal Consta (risperidone microspheres)	-
Perseris (risperidone ER)	-
Zyprexa Relprevv (olanzapine pamoate)	-
Combination Products	
Symbyax (olanzapine/fluoxetine)	✔

*Brand Abilify oral solution and orally disintegrating tablets have been discontinued; generic products are available.
† Abilify MyCite is the only drug-device combination product, comprised of a tablet with an embedded sensor, a wearable sensor patch, a smartphone application, and a web-based portal.
‡ Vanda filed a patent infringement lawsuit against Inventia for Fanapt generic products. In December 2016, Vanda and Inventia entered into a confidential stipulation regarding any potential launch date of the generic products (*ME staff press release, 2016*). Alembic was granted tentative approval of a generic formulation in July 2018, but it is not yet marketed.
§ A generic formulation was approved in July 2018 but is not yet marketed.
‖ Generic formulations were approved in January 2019 but none are currently available.

(*Drugs@FDA 2019*, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

- The following summarizes all FDA-approved indications:
  - Autism: Aripiprazole and risperidone are the only agents indicated for the treatment of irritability associated with autistic disorder in pediatric patients (aged 6 to 17 years, and 5 to 17 years, respectively).
  - Bipolar disorder: All oral agents in this class review are indicated for use in bipolar disorder, except clozapine, iloperidone, paliperidone, brexpiprazole, pimavanserin, and ziprasidone mesylate. Aripiprazole ER (Abilify Maintena only) and Risperdal Consta are the only long-acting injectables indicated for the treatment of bipolar disorder.
    - Oral aripiprazole, olanzapine/fluoxetine, risperidone, quetiapine, asenapine, and lurasidone are approved for use in pediatric patients ≥ 10 years of age with bipolar disorder. Oral olanzapine is approved for use in patients ≥ 13 years of age with bipolar disorder.
  - Depression: Aripiprazole, brexpiprazole, and quetiapine ER are indicated as adjunctive treatment for MDD in patients already taking an antidepressant. Olanzapine/fluoxetine is indicated for treatment-resistant depression.
  - Schizophrenia: All agents in this class review are indicated for use in schizophrenia with the exception of pimavanserin, and the combination agent, Symbyax (olanzapine/fluoxetine). Clozapine and paliperidone products, excluding Invega Trinza, are indicated for the treatment of schizoaffective disorder. Clozapine is the only agent in this class that is FDA-approved for treatment-resistant schizophrenia.
    - Oral aripiprazole (with the exception of tablets with sensor), lurasidone, olanzapine, quetiapine, and risperidone are approved for use in patients ≥ 13 years of age and paliperidone oral products are approved for patients ≥ 12 years of age with schizophrenia.
  - Tourette's Disorder: Aripiprazole is the only agent indicated for the treatment of Tourette's disorder in pediatric patients, aged 6 to 18 years.
  - Parkinson's disease psychosis: Pimavanserin is the first atypical antipsychotic FDA-approved for use in patients with PD psychosis.
  - Prescribing considerations: The labeling for iloperidone and ziprasidone state that when deciding among the alternative treatments, the prescriber should consider that these drugs are associated with prolongation of the QTc interval. In addition, patients must be titrated to an effective dose of iloperidone; thus control of symptoms may be delayed during the first 1 to 2 weeks of treatment compared to other antipsychotics that do not require similar titration.
- Table 2 highlights FDA-approved indications at a high level.

Table 2. Food and Drug Administration approved indications

Agent	Autism	Bipolar disorder: manic/mixed	Bipolar disorder: depressive	Depression – treatment-resistant	MDD: adjunct	Schizoaffective disorder	Schizophrenia	Schizophrenia: treatment-resistant	Tourette's Disorder	Parkinson's disease psychosis
Single Entity Products										
aripiprazole	✔ *	✔ *¶	-	-	✔ ¶	-	✔ *¶	-	✔ *	-
asenapine	-	✔ *	-	-	-	-	✔	-	-	-
brexpiprazole	-	-	-	-	✔	-	✔	-	-	-
cariprazine	-	✔	-	-	-	-	✔	-	-	-
clozapine	-	-	-	-	-	✔	-	✔	-	-
iloperidone	-	-	-	-	-	-	✔	-	-	-
lurasidone	-	-	✔ *	-	-	-	✔ *	-	-	-
olanzapine	-	✔ *	-	-	-	-	✔ *‖	-	-	-
paliperidone	-	-	-	-	-	✔	✔ *	-	-	-
pimavanserin	-	-	-	-	-	-	-	-	-	✔
quetiapine	-	✔ *	✔	-	✔ †	-	✔ *	-	-	-
risperidone	✔ *	✔ *	-	-	-	-	✔ *	-	-	-
ziprasidone HCl	-	✔	-	-	-	-	✔	-	-	-
ziprasidone mesylate	-	-	-	-	-	-	✔ §	-	-	-
Long-Acting Injectable Products										
aripiprazole ER (Abilify Maintena)	-	✔	-	-	-	-	✔	-	-	-
aripiprazole lauroxil ER (Aristada, Aristada Initio)	-	-	-	-	-	-	✔	-	-	-
paliperidone palmitate (Invega Sustenna)	-	-	-	-	-	✔	✔	-	-	-
paliperidone palmitate (Invega Trinza)	-	-	-	-	-	-	✔	-	-	-
risperidone microspheres	-	✔	-	-	-	-	✔	-	-	-

Agent	Autism	Bipolar disorder: manic/mixed	Bipolar disorder: depressive	Depression – treatment-resistant	MDD: adjunct	Schizoaffective disorder	Schizophrenia	Schizophrenia: treatment-resistant	Tourette's Disorder	Parkinson's disease psychosis
(Risperdal Consta)										
risperidone ER (Perseris)	-	-	-	-	-	-	✔	-	-	-
olanzapine pamoate ER (Zyprexa Relprevv)	-	-	-	-	-	-	✔ ‡	-	-	-
Combination Products										
olanzapine/ fluoxetine	-	-	✔ *	✔	-	-	-	-	-	-

Abbreviations: ER = extended release, IM = intramuscular, ODT = orally disintegrating tablet
*FDA-approved indications for pediatric patients.
† Indicated for the ER formulation.
‡ Patients must be observed by a health care professional for 3 hours post-dose administration with Zyprexa Relprevv.
§ IM injection indicated for acute agitation associated with schizophrenia.
‖ IM injection indicated for acute agitation associated with schizophrenia and bipolar mania.
¶ Indicated for the drug-device combination with tablet and sensor. The ability to improve patient compliance or modify aripiprazole dosage has not been established. The ability to track drug ingestion in "real-time" or during an emergency is not recommended because detection may be delayed or not occur.

(*Prescribing information: Abilify 2018, Abilify Maintena 2018, Abilify MyCite 2017, Aristada 2018, Aristada Initio 2018, Clozaril 2017, Fanapt 2017, Fazaclo 2017, Geodon 2018, Invega 2017, Invega Sustenna 2018, Invega Trinza 2017, Latuda 2018, Nuplazid 2018, Perseris 2018, Rexulti 2018, Risperdal 2019, Risperdal Consta 2019, Saphris 2017, Seroquel 2018, Seroquel XR 2018, Symbyax 2018, Versacloz 2018, Vraylar 2018, Zyprexa 2018, Zyprexa Relprevv 2018, Zyprexa Zydis 2018*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The goal of this review is to evaluate key published literature regarding atypical antipsychotics for FDA-approved indications in children, adolescents, and adults. Numerous studies evaluating the efficacy of antipsychotic medications have been conducted. In clinical practice, the role of the atypical antipsychotics has been clearly established for the treatment of bipolar disorder and schizophrenia. In general, clinical consensus guidelines do not differentiate one agent from another, supporting the concept that all patients will require an individualized approach to treatment selection, taking into account the agent's safety profile and patient's individual risk factors.
- Key clinical studies evaluating the roles of atypical antipsychotic agents in the treatment of FDA-approved indications are included in the review. However, in recognition of the vast number of published studies of older atypical antipsychotics in adults, only a selection of randomized controlled studies (RCTs), systematic reviews (SRs), and meta-analyses (MAs) are included in this review.

CHILDREN/ADOLESCENTS

- The Agency for Healthcare Research and Quality (AHRQ) conducted an SR evaluating the safety and efficacy of antipsychotics in children and adolescents. The review included 135 studies of atypical antipsychotics (aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone), conducted in patients 24 years of age or younger, and used for various psychiatric conditions including schizophrenia and related disorders, autism spectrum disorders, bipolar disorder, and tic disorder, among others. Overall, indications associated with moderate strength evidence for the use of atypical antipsychotics included schizophrenia and related psychoses, bipolar disorder, autism spectrum disorders, and ADHD. The risk of weight gain was highest for olanzapine, clozapine, and lurasidone. It was found that atypical antipsychotics probably increase short-term risk for high triglyceride levels, extrapyramidal symptoms, sedation, and somnolence vs placebo (*Pillay et al 2017*).

Autism Spectrum Disorder

- For the treatment of irritability associated with autistic disorder, risperidone has been approved in pediatric patients aged 5 to 17 years and aripiprazole has been approved in patients aged 6 to 17 years. Very few RCTs have been conducted evaluating safety and efficacy, and only 1 low-quality study has been conducted evaluating comparative effectiveness. The primary outcome measure in trials was the change from baseline to endpoint in the Aberrant Behavior Checklist-Irritability subscale of the ABC (ABC-I), which measured symptoms of irritability in autistic disorder. One risperidone trial measured the Clinical Global Impression-Change (CGI-C) scores as a co-primary outcome measure.
- The safety and efficacy of aripiprazole was evaluated in 2 placebo-controlled (PC), 8-week trials. Over 75% of these subjects were under 13 years of age. In one of these trials, children and adolescents with autistic disorder (N = 98) received daily doses of placebo or aripiprazole 2 to 15 mg/day. The mean daily dose of aripiprazole at the end of 8-week period was 8.6 mg/day. Aripiprazole significantly improved ABC-I subscale scores, including emotional and behavioral symptoms of irritability, aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods (*Owen et al 2009*). In the second of these trials in children and adolescents with autistic disorder (N = 218), 3 fixed doses of aripiprazole (5, 10, or 15 mg/day) were compared to placebo. ABC-I subscale scores were significantly decreased by 12.4 points with 5 mg/day, 13.2 with 10 mg/day, and 14.4 with 15 mg/day compared with 8.4 with placebo. Clinical Global Impressions (CGI)-Improvement scores were significantly improved: 2.6 points with 5 mg/day, 2.5 with 10 mg/day, and 2.5 with 15 mg/day compared with 3.3 with placebo. At the higher doses, ABC stereotypy, hyperactivity, CGI-S (Severity of Illness) scores, and other secondary measures were also improved (*Marcus et al 2009*).
- In one MA of 3 trials evaluating pediatric patients (N = 316) treated with aripiprazole, results demonstrated a greater increase in weight vs placebo (weight gain,1.13 kg; 95% confidence interval [CI], 0.71 to 1.54; p < 0.00001), and had a higher relative risk (RR) for sedation (RR, 4.28; 95% CI, 1.58 to 11.6; p = 0.004) and tremor (RR, 10.26; 95% CI, 1.37 to 76.63; p = 0.02) (*Hirsch et al 2016*).
- A 2018 MA evaluated the efficacy of aripiprazole in patients with autism spectrum disorder (N = 408) and found aripiprazole significantly improved irritability, hyperactivity, and inappropriate speech but not social withdrawal compared with placebo. The RR for response rate was also improved with aripiprazole (RR, 2.08; 95% CI, 1.24 to 3.46) (*Maneeton et al 2018*).

- The safety and efficacy of risperidone was evaluated in two 8-week and one 6-week, PC pivotal trials (*McCracken et al 2002, Shea et al 2004*). Approximately 90% of these subjects were under 12 years of age. In the two 8-week trials, the efficacy and safety of risperidone were measured in patients aged 5 to 16 years (N = 101) in weight-based, twice-daily doses of 0.5 to 3.5 mg/day (the RUPP trial) and in patients aged 5 to 12 years (N = 79) who received 0.02 to 0.06 mg/kg/day given once or twice daily (*McCracken et al 2002, Shea et al 2004*). The 6-week trial measured efficacy and safety in patients using lower than FDA-approved recommended dosing, and outcomes did not demonstrate efficacy (*Risperdal prescribing information 2017*). In the RUPP trial, risperidone-treated patients exhibited a 56.9% reduction in the mean ABC-I score from baseline, compared to a 14.1% reduction observed in the placebo group ($p < 0.001$) (*McCracken et al 2002*). Risperidone was generally well tolerated, and most adverse events were mild and transient. Due to the uncertainty of a clear benefit with regard to the core symptoms of autism, the authors recommend that risperidone be reserved for the treatment of moderate-to-severe behavioral problems accompanying autism. In the second 8-week trial, risperidone patients demonstrated a 64% improvement in ABC-I subscale vs 31% improvement with placebo, which was a significant positive finding for hyperactivity (*Shea et al 2004*). Somnolence was the most frequently reported adverse event (72.5% vs 7.7%), and risperidone-treated subjects experienced statistically greater increases in weight (2.7 kg vs 1 kg), pulse rate, and systolic blood pressure.
- In an extension of the RUPP trial, 63 responders received open-label (OL) risperidone for another 16 weeks. Risperidone dose adjustments were allowed up to a maximum total daily dose of 3.5 mg/day. At the end of the 4-month extension, an intention-to-treat analysis revealed a minor, but clinically insignificant increase in ABC-I score. There was also a significant time effect on the ABC-I scale at the end of the 4-month extension phase ($p = 0.02$) (*McDougle et al 2005*).
- Additional trials have been conducted measuring effects of risperidone; however, most trials included less than 50 patients. The outcomes of these trials are more sensitive to variability within the trials due to the small effect size (*Aman et al 2008, Capone et al 2008, Gagliano et al 2004, Gencer et al 2008, Luby et al 2006, Miral et al 2008, Nagaraj et al 2006*).
- One head-to-head, prospective, 8-week trial was conducted comparing the effects of aripiprazole ≤ 10 mg/day (mean dose, 5.5 mg/day) to risperidone ≤ 3 mg/day (mean dose, 1.12 mg/day) in patients (N = 59) aged 4 to 18 years of age. Approximately 65% of patients were diagnosed with autism, and additional diagnoses included Asperger syndrome, pervasive developmental disorder, and disruptive behavior disorder. Study authors stated double-blind (DB) techniques were not enforced for all patients. At the end of the trial, the mean change from baseline in ABC-I subscale score was not statistically different ($p = 0.06$), but numerically favored risperidone. No differences were detected between groups for each adverse event or in the rate of discontinuations due to adverse events. Study authors concluded the safety and efficacy of both agents were comparable (*Ghanizadeh et al 2014*).
- A network MA evaluated 8 clinical trials (N = 878) with risperidone, aripiprazole, lurasidone, and placebo in pediatric autism spectrum disorder. Both risperidone and aripiprazole significantly reduced irritability compared with placebo with similar safety profiles. Lurasidone was not significantly different from placebo (*Fallah et al 2019*).

Bipolar Disorder

Manic/Mixed Episodes

- Aripiprazole, olanzapine, olanzapine/fluoxetine, risperidone, quetiapine and asenapine have FDA-approved indications for the treatment of pediatric patients diagnosed with bipolar disorder. All agents are approved for ages ≥ 10 years, except olanzapine which is approved in patients aged ≥ 13 years. In pediatric patients with bipolar disorder, evidence is extremely limited.
- In an AHRQ SR of 135 trials evaluating typical and atypical antipsychotics, a total of 19 trials measured efficacy and safety in adolescents with bipolar disorder. Compared with placebo, atypical antipsychotics decrease mania and depression symptoms slightly, and improve symptom severity and global functioning to a small extent. In addition, they probably increase response and remission rates vs placebo for manic/mixed phases (*Pillay et al 2017*).
- In a 21-day, DB, PC trial, 403 patients aged 10 to 17 years with bipolar I disorder were randomized to placebo or asenapine 2.5 mg, 5 mg, or 10 mg twice daily. The primary endpoint, change from baseline in Young Mania Rating Scale (YMRS) score, demonstrated a statistically significant and dose-dependent mean difference in YMRS scores at 21 days for all asenapine groups vs placebo (2.5 mg, -3.2; $p = 0.0008$ vs 5 mg, -5.3; $p < 0.001$ vs 10 mg, -6.2; $p < 0.001$). Weight gain was higher across the asenapine groups, with 8 to 12% of patients experiencing ≥ 7% weight gain vs 1.1% of patients in the placebo group ($p < 0.05$). Fasting glucose, insulin and cholesterol changes were also numerically higher in the asenapine groups vs placebo (p = not reported). Overall, asenapine was well tolerated and

showed efficacy in the treatment of this pediatric population, although the duration of the study period was brief (*Findling et al 2015*).

Depressive Episodes

- Clinical trials measuring the safety and efficacy of atypical antipsychotics in depressive episodes in pediatric patients diagnosed with bipolar disorder are limited. Two trials examined efficacy of quetiapine in this population. In a small trial, a total of 32 patients aged 12 to 18 years were randomized to quetiapine 300 to 600 mg/day or placebo and followed over a period of 8 weeks. The primary endpoint was change in the Children's Depression Rating Scale, Revised Version (CDRS-R) score, in which both quetiapine and placebo groups exhibited statistically significant reductions in the CDRS-R scores from baseline ($p < 0.001$), with no difference between groups (19 vs 20; $p = 0.89$). All other efficacy measures were not statistically different from placebo (*DelBello et al 2009*). A similar 8-week trial enrolled 193 patients aged 10 to 17 years with acute bipolar depression. Patients were randomized to placebo or quetiapine XR 150 to 300 mg/day. The primary endpoint was change in CDRS-R score from baseline, with mean CDRS-R scores decreasing from baseline in both placebo (-29.6) and treatment (-27.3) groups. The difference between groups was not statistically significant (95% CI, -6.22 to 1.65; $p = 0.25$). Triglyceride levels were elevated in 9.3% of the quetiapine XR group vs 1.4% of the placebo group. Mean weight gain was 1.3 kg in the quetiapine XR group vs 0.6 kg in the placebo group (p = not reported) (*Findling et al 2014*).
- In a DB, PC trial, 291 patients aged 10 to 17 with bipolar I disorder and depressive episodes were randomized 2:1 to olanzapine/fluoxetine or placebo for 8 weeks. Doses of olanzapine/fluoxetine were titrated to 12/50 mg daily over 2 weeks. The olanzapine/fluoxetine group had a 5-point greater mean decrease in CDRS-R score from baseline vs placebo (-28.4 vs -23.4; $p = 0.003$). A total of 78.2% olanzapine/fluoxetine patients achieved response (defined as ≥ 50% reduction of CDRS-R score from baseline and a YMRS item 1 score ≤ 2) vs 59.2% of placebo group patients ($p = 0.003$). Weight gain was more common in the olanzapine/fluoxetine group vs placebo (4.4 vs 0.5 kg; $p < 0.001$), as well as increase in fasting total cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides (all $p < 0.001$). Mean prolactin increase was higher in the olanzapine/fluoxetine group vs placebo ($p < 0.001$) and increase in heart rate was also statistically significantly higher in the treatment group ($p = 0.013$). This trial demonstrated efficacy in pediatric patients, but also demonstrated serious adverse effects (*Detke et al 2015*).
- In a DB, PC trial, 347 patients aged 10 to 17 years were assigned to flexible doses of lurasidone 20 to 80 mg/day or placebo. The primary endpoint was change from baseline to week 6 in the CDRS-R total score. At week 6 of therapy, treatment with lurasidone was associated with a significant improvement compared with placebo in CDRS-R total score (-21.0 versus -15.3; $p<0.0001$). Lurasidone also was associated with statistically significant improvements in the Clinical Global Impression-Bipolar Severity depression score (key secondary measure) and in measures of anxiety, quality of life, and global functioning (*DelBello et al* 2017).

Schizophrenia and/or Schizoaffective Disorder

- In pediatric patients diagnosed with schizophrenia, FDA-approved treatments include aripiprazole, lurasidone, olanzapine, quetiapine and risperidone for use in patients ≥ 13 years of age and paliperidone oral products in patients aged ≥ 12 years. Many trials include a small sample size of patients, or are not well-designed. However, efficacy has been demonstrated and results are similar to adult trials.
- An SR and network MA of 12 RCTs (N = 2158) evaluated 8 antipsychotics (aripiprazole, asenapine, paliperidone, risperidone, quetiapine, olanzapine, molindone, and ziprasidone) for treatment of children and adolescents with schizophrenia-spectrum disorders. Network MA found that change in Positive and Negative Syndrome Scale (PANSS) total, positive, and negative symptoms did not differ significantly between agents except for ziprasidone, which was inferior on PANSS total symptoms vs molindone, olanzapine, paliperidone, quetiapine, and risperidone, and inferior on PANSS negative symptoms vs molindone, olanzapine, and risperidone. All antipsychotics were superior to placebo on PANSS total symptom change except asenapine and ziprasidone. All antipsychotics, except ziprasidone, were superior to placebo on PANSS positive symptom change; additionally, all antipsychotics, except paliperidone, quetiapine, and ziprasidone, were superior to placebo on PANSS negative symptom change. Weight gain was primarily associated with olanzapine, while prolactin was increased with risperidone, paliperidone, and olanzapine (*Pagsberg et al 2017*).
- In an AHRQ SR of 135 trials evaluating typical and atypical antipsychotics, a total of 39 studies evaluated efficacy and safety in adolescents with schizophrenia. Compared with placebo, atypical antipsychotics as a class probably increase response rates; decrease slightly (not clinically significant for many patients) negative and positive symptoms; and

improve slightly global impressions of improvement, severity, and functioning. Six studies comparing risperidone vs olanzapine found little or no difference in their effects for negative and positive symptoms, response rates, and global impressions of severity (*Pillay et al 2017*).

- A Cochrane review compared atypical antipsychotic medications to placebo, typical antipsychotics, or another atypical antipsychotic in adolescents with psychosis. Compared to typical antipsychotics, there were no significant differences in Brief Psychiatric Rating Scale (BPRS) scores in an analysis of 5 trials with 236 patients. There was no evidence to suggest the superiority of atypical antipsychotics over typical antipsychotics; however, fewer adolescents dropped out due to adverse effects when administered an atypical antipsychotic (RR, 0.65; 95% CI, 0.36 to 1.15). Minimal evidence was available comparing one atypical antipsychotic to another. In terms of the number of patients who did not respond (defined as ≤ 30% reduction in BPRS score), results significantly favored clozapine, but increases in salivation, sweating, and glucose levels were observed vs olanzapine in 1 trial with 39 patients. Treatment with olanzapine, risperidone and clozapine was associated with weight gain. Aripiprazole was not associated with increased prolactin or dyslipidemia. Low-dose risperidone significantly decreased improvement in PANSS total score but also reduced the rate of extrapyramidal symptoms (EPS) vs standard-dose risperidone in 1 trial with 255 patients. Overall, efficacy between atypical and typical antipsychotics may be similar; however, safety benefits may favor treatment with atypical antipsychotics (*Kumar et al 2013*).
- A 6-week, randomized, PC trial evaluating the efficacy of lurasidone in acutely symptomatic adolescents with schizophrenia found that the least squares (LS) mean change in PANSS total score from baseline to week 6 was greater for the lurasidone 40 mg/day group (-18.6; $p < 0.001$; effect size = 0.51) and the lurasidone 80 mg/day group (-18.3; $p < 0.001$; effect size = 0.48) vs the placebo group (-10.5). The LS mean change from baseline to week 6 in CGI-S score was significantly greater for the lurasidone 40 mg/day group (-1.0; $p < 0.001$; effect size = 0.49) and the lurasidone 80 mg/day group (-0.9; $p = 0.0015$; effect size = 0.45) compared with the placebo group (-0.5). The most common adverse events in the lurasidone groups were nausea, anxiety, akathisia, somnolence, and vomiting (*Goldman et al 2017*).

Tourette's Disorder

- Aripiprazole is the only agent indicated for the treatment of Tourette's disorder. Efficacy and safety is based on low quality evidence in one fixed dose and one flexible-dose trial. There is minimal evidence of safety and efficacy in this population.
- In one published, DB, PC, 10-week trial, aripiprazole significantly reduced total tic score (Yale Global Tic Severity Scale [YGTSS-TTS]; -15 vs -9.6) and phonic tic score (YGTSS-PTS; -7.4 vs -4.2), but not motor tic score, compared with placebo in patients aged 6 to 18 years with Tourette's disorder. The response rate (score of 1 or 2 on the Tourette's syndrome CGI-Improvement scale) was 66% vs 45%, respectively (*Yoo et al 2013*).
- In another similarly designed, unpublished, 8-week trial in patients aged 7 to 17 years who received weight-based aripiprazole, significant improvements compared with placebo were seen on YGTSS-TTS with a change of -13.4 and -16.9 points with low- and high-dose aripiprazole compared to -7.1 with placebo (*Abilify prescribing information 2017*).
- Aripiprazole was associated with increased body weight compared to placebo (range, 0.4 to 1.5 kg). Additional adverse reactions (incidence ≥ 5% and at least twice that for placebo) were sedation, somnolence, nausea, headache, nasopharyngitis, fatigue, and increased appetite (*Abilify prescribing information 2017*). In one safety trial, aripiprazole had a safer cardiovascular profile vs pimozide, and was associated with a lower frequency of QT prolongation (*Gulisano et al 2011*).

ADULTS

- The AHRQ conducted an SR of literature on the safety and efficacy of antipsychotics in adults comparing typical and atypical antipsychotics. The review included studies of atypical antipsychotics (aripiprazole, asenapine, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone), conducted in patients 18 to 64 years of age, and used for the following FDA-approved indications: bipolar disorder, schizophrenia, and schizophrenia-related psychoses. The most frequent comparisons involved haloperidol, with 43 studies comparing haloperidol with risperidone and 37 studies comparing haloperidol with olanzapine. Nevertheless, the number of studies available for each comparison and outcome was often limited. Overall, indications associated with moderate to low strength evidence for the use of atypical antipsychotics included schizophrenia and schizophrenia-related psychoses. Bipolar disorder was associated with low strength of evidence. Few differences of clinical importance for outcomes of effectiveness were found. Patient-important outcomes were rarely assessed. Data were sparse for the 4 key adverse events deemed to be most

clinically important. In terms of efficacy, few differences were found between typical and atypical antipsychotic agents, specifically when compared to haloperidol and clinical significance (defined as ≥ 20% difference between interventions) was rarely found. The evidence regarding safety, particularly those adverse events of most interest (ie, diabetes, tardive dyskinesia, metabolic syndrome, and mortality) were insufficient to draw firm conclusions about the risks among treatment groups. No differences were found in mortality for chlorpromazine vs clozapine and haloperidol vs aripiprazole, or in metabolic syndrome for haloperidol vs olanzapine. The most frequently reported adverse events with significant differences were EPS; in most cases, the atypical antipsychotic had fewer EPS than haloperidol (*Abou-Setta et al 2012*).

Bipolar Disorder

Manic/Mixed Episodes

- All oral atypical antipsychotic agents in this class review are indicated for use in bipolar disorder, except clozapine, iloperidone, paliperidone, brexpiprazole, and pimavanserin. The following summarizes direct comparative evidence and recent MAs and SRs.
- A 2018 AHRQ SR of 156 trials concluded that symptoms of acute mania were modestly improved with asenapine, cariprazine, quetiapine, and olanzapine compared to placebo. Risperidone, ziprasidone, and paliperidone may also be effective for acute mania symptoms. Lithium was effective in the treatment of acute mania and prolonged the time to relapse compared to placebo, and this was the only agent that achieved a minimal clinically important difference in symptoms. All of these results were based on low-strength evidence because moderate and strong evidence was lacking (*Butler et al 2018*).
- In a 2012 AHRQ SR of 125 trials evaluating typical and atypical antipsychotics, a total of 12 measured efficacy and safety in adults with bipolar disorder. Compared to haloperidol, there was no difference in YMRS score for manic episodes for aripiprazole, olanzapine, and risperidone, and no difference in Montgomery-Asberg Depression Rating Scale (MADRS) score for aripiprazole in a total of 9 trials. In one trial of 350 patients, haloperidol was favored in terms of YMRS score over ziprasidone. Haloperidol produced lower relapse rates than aripiprazole in one trial with 347 patients and provided better response rates than ziprasidone in one trial of 350 patients. The most frequently reported adverse effects with significant differences were in the category of EPS and most often involved haloperidol. Haloperidol appears to be an equally effective treatment compared with the atypical antipsychotics; however, it is associated with more incidences of EPS compared to other agents (*Abou-Setta et al 2012*).
- A SR and MA of 15 RCTs and 1 observational study was conducted to evaluate the efficacy of maintenance treatment in bipolar disorder using atypical antipsychotics, either as monotherapy or as adjunctive therapy. As adjunctive therapy to lithium or valproate, MAs showed that treatment with aripiprazole (RR, 0.65; 95% CI, 0.50 to 0.85), quetiapine (RR, 0.38; 95% CI, 0.32 to 0.46), or ziprasidone (RR, 0.62; 95% CI, 0.40 to 0.96) reduced the overall risk of relapses in patients that had responded during the stabilization phase. Quetiapine was the only drug that reduced both manic and depressive episodes. Due to high risk of bias and low levels of evidence, no conclusions could be drawn for olanzapine or risperidone. For monotherapy, quetiapine was shown to be better than lithium/valproate for both manic and depressive relapses; no reliable conclusions could be made for olanzapine due to the low quality of evidence. Monotherapy with olanzapine, quetiapine, and risperidone were shown to be superior vs placebo in reducing the overall risk of relapse; no reliable conclusions could be made for aripiprazole due to the low quality of evidence (*Lindström et al 2017*).
- One SR of 9 RCTs (N = 1289) compared the effectiveness of atypical antipsychotics to placebo, either as monotherapy or as adjunctive treatment with a mood stabilizer. Atypical antipsychotics, either alone or in combination with mood stabilizers, had superior efficacy in treating manic symptoms of mixed episodes compared to placebo in short-term trials lasting 3 to 6 weeks ($p < 0.00001$). Atypical antipsychotics also had superior efficacy in treating depressive symptoms of mixed episodes ($p < 0.001$) (*Muralidharan et al 2013*).
- The efficacy and safety of asenapine in the treatment of manic or mixed bipolar I disorder were evaluated in 6 PC, and active-controlled (olanzapine) studies in adult patients, with or without psychotic features (*McIntyre et al 2009[a], McIntyre et al 2010[a], McIntyre et al 2009[b], McIntyre et al 2010[b], Szegedi et al 2011, Szegedi et al 2018*). In a pooled analysis of patients experiencing bipolar mania, asenapine and olanzapine were comparable in terms of reduction from baseline in YMRS scores at week 52 of therapy (*McIntyre et al 2010[b]*). A MA of various anti-manic therapy options found that asenapine was associated with a statistically significant improvement in YMRS scores from baseline compared to placebo (mean difference [MD], -0.3; 95% CI, -0.53 to -0.07), though it was less effective compared to olanzapine (0.22; 95% CI, 0.08 to 0.37) (*Cipriani et al 2011*). The most commonly reported adverse

events reported with asenapine included sedation, dizziness, somnolence and weight gain. Of note, it was calculated that for every 9 patients treated with olanzapine over asenapine, one would experience clinically significant weight gain with olanzapine (19 vs 31%) (*McIntyre et al 2009[b]*).

- The approval of the newest FDA-approved agent, cariprazine, was based on the efficacy and safety from 3 flexible-dose, DB, PC, 3-week trials (*Calabrese et al 2015, Durgam et al 2015[a], Sachs et al 2015*). A total of 1047 adult patients with acute manic or mixed episodes were administered placebo or cariprazine 3 to 12 mg per day based on tolerability. Across trials, the mean daily dose was 8.8 mg per day and the mean final dose was 10.4 mg per day (*FDA/CBER summary review 2015*). All doses were superior to placebo in reducing YMRS and CGI-S scores and a significant reduction in YMRS was observed as early as 4 days in some studies and persisted until week 3. The proportion of YMRS remitters was significantly higher in the cariprazine group than placebo (difference range, 15 to 19%) (*Calabrese et al 2015, Durgam et al 2015[a], Sachs et al 2015*). Of note, doses higher than 6 mg had similar efficacy, but adverse events were less tolerable. Due to the long half-life and pharmacokinetics of the active metabolite, DDCAR, drug steady state was not achieved in trials (*FDA/CBER summary review 2015*). It is anticipated that late-onset of adverse reactions would be observed if assessed for a longer period. In bipolar studies, 4% of patients with normal hemoglobin A1c developed elevated levels (≥ 6.5%). According to a pooled analysis (n = 1940 cariprazine-treated patients) within the FDA summary review, the most frequently observed adverse events include akathisia (14.2%), EPS (20.8%), constipation (7.6%), and nausea/vomiting (6 to 8%). The proportion of patients with weight increase ≥ 7% from baseline ranged from 1 to 3% across cariprazine doses.
- The efficacy and safety of risperidone 1 to 6 mg/day compared to olanzapine 5 to 20 mg/day were evaluated in a 3-week, DB, RCT in patients hospitalized for bipolar I disorder, manic or mixed episode, without psychotic features. Olanzapine and risperidone mean doses were 14.7 mg/day and 3.9 mg/day, respectively. There was no difference between groups in many outcome measures in remission or response in YMRS, 21-item Hamilton Rating Scale for Depression (HAM-D-21), or MADRS scales. More patients given olanzapine completed the trial compared with patients given risperidone (78.7% vs 67%, respectively). In total, 62.1% of patients in the olanzapine group and 59.5% of patients in the risperidone group were categorized as responders (defined as ≥ 50% reduction in the YMRS score at endpoint). Olanzapine-treated patients experienced significantly greater elevations in liver function enzymes and weight gain (2.5 kg vs 1.6 kg). Risperidone-treated patients experienced significantly more prolactin elevations and sexual dysfunction (*Perlis et al 2006[a]*).

Depressive Episodes

- Placebo-controlled trials measuring effects for the treatment of bipolar depression have demonstrated efficacy with lurasidone, quetiapine (immediate- and extended-release [ER]), and olanzapine/fluoxetine as monotherapy and adjunctive treatment (*Calabrese et al 2005, Corya et al 2006, McElvoy et al 2010, Loebel et al 2014[a], Loebel et al 2014[b], Shelton et al 2005, Suppes et al 2010, Thase et al 2007, Young et al 2010*).
- Treatment with olanzapine/fluoxetine was superior to monotherapy with olanzapine and lamotrigine in achieving greater improvements in MADRS and CGI-BP (bipolar version) (*Tohen et al 2003, Brown et al 2009*). Patients treated with olanzapine/fluoxetine had significantly greater rates of treatment response and remission compared to those receiving olanzapine monotherapy (*Tohen et al 2003*). It is not clear if quetiapine outperforms lithium in terms of treatment of bipolar depression, as various studies have produced different results (*Chiesa et al 2012, Young et al 2010*).
- Meta-analyses have found that combination treatment with olanzapine/fluoxetine may be the optimal treatment for bipolar depression compared to other treatment options. However, the overall evidence quality was considered low, trials had limited durations, and a high placebo effect was observed. Olanzapine, quetiapine, lurasidone, valproate, selective-serotonin reuptake inhibitors (SSRIs), lithium, and tricyclic antidepressants (TCAs) also appeared to be effective, but with varied acceptability (*Fornaro et al 2016, Ostacher 2017*, *Silva et al 2013, Taylor et al 2014, Vieta et al 2010*). No notable efficacy differences were identified between atypical antipsychotics, suggesting that lurasidone, quetiapine, and olanzapine/fluoxetine may be reasonable choices.

Major Depressive Disorder (MDD)

Key MDD Meta-Analyses

- A number of MAs and SRs have been conducted evaluating the safety and efficacy of atypical antipsychotics to augment treatment for MDD. Aripiprazole, brexpiprazole, and quetiapine ER are indicated for the treatment of MDD as

adjunctive treatment; and olanzapine, in combination with fluoxetine, is indicated for the treatment of treatment-resistant depression. The most recent, well-designed MAs have been summarized for efficacy and safety evaluations.

- One MA, which followed Cochrane methodologies, evaluated 17 trials of short-term duration ranging from 4 to 12 weeks. The analysis compared adjunctive atypical antipsychotics in combination with an SSRI/serotonin-norepinephrine reuptake inhibitor (SNRI) to SSRI or SNRI monotherapy in patients with refractory or treatment-resistant MDD. Results demonstrated that the augmentation of antidepressants with atypical antipsychotics (olanzapine, quetiapine, aripiprazole, and risperidone [Note: risperidone is not FDA-approved for this indication]) was more effective than antidepressant monotherapy in improving response and remission rates. However, adjunctive atypical antipsychotic therapy was associated with a higher discontinuation rate due to adverse effects (9.1% vs 2.6%). The attributable risk for the discontinuation rate due to adverse effects was 0.07 (number needed to harm [NNH], 16; 95% CI, 12 to 20) (*Wen et al 2014*).
- Another MA evaluated 14 trials in patients with current MDD and an inadequate response to at least 1 course of antidepressant medication treatment. Compared to placebo, the atypical antipsychotics significantly improved remission rates: aripiprazole (odds ratio [OR], 2.01; 95% CI, 1.48 to 2.73), olanzapine/fluoxetine (OR, 1.42; 95% CI, 1.01 to 2), quetiapine (OR, 1.79; 95% CI, 1.33 to 2.42) and risperidone (OR, 2.37; 95% CI, 1.31 to 4.3). In terms of remission, all atypical antipsychotics were efficacious; however, olanzapine/fluoxetine had a higher number needed to treat (NNT) compared to other agents (NNT for olanzapine/fluoxetine, 19 vs NNT for aripiprazole, quetiapine, risperidone, 9). Treatment was associated with several adverse events, including akathisia (aripiprazole), sedation (quetiapine, olanzapine/fluoxetine and aripiprazole), abnormal metabolic laboratory results (quetiapine and olanzapine/fluoxetine), and weight gain (all 4 drugs, especially olanzapine/fluoxetine). However, little to no information was provided in detail regarding the adverse events (*Spielmans et al 2013*).

Adjunctive treatment for MDD

- Aripiprazole, brexpiprazole, and quetiapine ER are indicated for the treatment of MDD as adjunctive treatment. The following information describes the pivotal trials used for FDA-approval.
- The FDA-approval of aripiprazole for the adjunctive treatment of MDD was based on 2 PC, 6-week trials in adult patients (N = 381; N = 362) who had failed 1 to 3 courses of antidepressant therapy, including an inadequate response to 8 weeks of antidepressant treatment. Aripiprazole was superior to placebo in reducing the mean MADRS total scores and remission rates. The NNT to reduce remission rates (defined as MADRS total score ≤ 10 and ≥ 50% reduction in MADRS) was 10 (*Berman et al 2007, Marcus et al 2008*). Increased incidences of akathisia were seen across trials with one trial reporting a NNH of 4 (*Marcus et al 2008*). One pooled analysis of 3 similarly designed trials (N = 409) measured the effects of aripiprazole in older vs younger patients. Results demonstrated adjunctive aripiprazole was effective in improving depressive symptoms in older patients (50 to 67 years), and akathisia was the most commonly reported adverse event in both the older (17.1%) and younger (26%) patient groups (*Steffens et al 2011*). Other trials have demonstrated similar results (*Kamijima et al 2013, Papakostas et al 2005*). In a 12-week, randomized, DB, PC trial evaluating the safety and efficacy of aripiprazole for adjunctive MDD treatment in patients over the age of 60 years (N = 181), a higher percentage of patients achieved remission (defined as a MADRS score of ≤ 10) in the aripiprazole group as compared to placebo (44% vs 29%; p = 0.03; NNT 6.6). Similar to other studies, akathisia was the most common side effect in the aripiprazole group (26% vs 12%), and Parkinsonism was also more often reported (17% vs 2%) (*Lenze et al 2015*).
  The safety and efficacy of brexpiprazole was evaluated in 2 DB, PC, pivotal, 6-week trials in adult patients as an adjunct to antidepressant therapy for MDD. In the pivotal studies, brexpiprazole 2 mg daily doses significantly reduced the mean MADRS score, the primary endpoint, compared with placebo (Study 1 [N = 353], -8.4 points with brexpiprazole 2 mg vs -5.2 points with placebo) (*Thase et al 2015[a]*). In an FDA analysis, the brexpiprazole 1 mg and 3 mg dose did not reduce the mean MADRS score; however, an FDA analysis found evidence of efficacy based on phase 2 data, and per protocol and intention-to-treat analyses of Study 2 (*Thase et al 2015[b], FDA briefing document 2015*). The most common adverse reactions in MDD trials were akathisia (NNH, 15), increased weight (NNH, 20) and somnolence (NNH, 22); and in schizophrenia trials were increased weight (NNH, 48) and tremor (NNH, 51) (*Correll et al 2015, Kane et al 2015[a], Thase et al 2015[b]*). An SR and MA of 4 DB, randomized, PC trials evaluating the efficacy and safety of brexpiprazole for adjunctive treatment of MDD found that it was superior to placebo for MADRS (MD, -1.76; 95% CI, -2.45 to -1.07; p < 0.00001) and the HAM-D-17 (MD, -1.21; 95% CI, -1.71 to -0.72; p < 0.00001). The RRs for response and remission were 1.57 (95% CI, 1.29 to 1.91) and 1.55 (95% CI, 1.22 to 1.96), respectively (*Yoon et al 2017*).

- The FDA-approval of quetiapine fumarate ER as an adjunct to antidepressant therapy for the treatment of MDD was based on two 6-week, PC, fixed dose trials (N = 939) in doses of 150 mg or 300 mg/day. A pooled analysis of the 2 RCTs demonstrated that quetiapine fumarate 300 mg/day (58.3%; p < 0.01; NNT, 9) significantly improved the MADRS response (defined as ≥ 50% decrease in MADRS total score), but quetiapine fumarate 150 mg/day (53.7%; p = 0.06) did not compared to placebo (46.2%). However, MADRS remission was significantly improved for both the quetiapine fumarate 300 mg/day (36.5%; p < 0.001; NNT, 8) and 150 mg/day doses (35.6%; p < 0.01; NNT, 9) vs placebo (24.1%). The most common adverse events leading to discontinuation were somnolence and sedation. For the quetiapine fumarate 300 mg/day, 150 mg/day, and placebo groups, the mean weight gain was 1.3, 0.9, and 0.2 kg, and the incidence of EPS was 6.4, 3.8, and 4.2%, respectively (*Bauer et al 2010*).

Treatment-resistant depression

- Olanzapine, combined with fluoxetine, is the only agent in this class review that is indicated for treatment-resistant depression. Approval of olanzapine/fluoxetine for the acute treatment of treatment-resistant depression was based on 3 clinical trials of 8- (2 trials) and 12-week duration. Treatment with olanzapine/fluoxetine was generally more effective than monotherapy with either olanzapine or fluoxetine in improving MADRS scores; however, results in trials have been mixed (*Corya et al 2006, Shelton et al 2005, Thase et al 2007*). In one 12-week, DB trial, olanzapine/fluoxetine was compared to olanzapine, fluoxetine, or venlafaxine monotherapy. Olanzapine/fluoxetine demonstrated a statistical MADRS advantage over all monotherapy agents after week 1 which was maintained up to week 6; however, this effect was only sustainable over olanzapine monotherapy at week 12 (*Corya et al 2006*). Other trial data demonstrated that olanzapine/fluoxetine was not significantly different compared to other antidepressants such as nortriptyline and fluoxetine monotherapy in improving MADRS scores (*Corya et al 2006, Shelton et al 2005*).
- Treatment with olanzapine/fluoxetine has consistently demonstrated increases in the incidence (≥ 10%) of weight gain, increased appetite, somnolence, and dry mouth. Additional adverse events have varied in trials. Compared to fluoxetine and olanzapine monotherapy, the most common adverse events for olanzapine/fluoxetine (incidence ≥ 10%) included peripheral edema and hypersomnia, which were significantly higher than that of fluoxetine monotherapy (p < 0.001) (*Thase et al 2007*). Compared to olanzapine, fluoxetine or venlafaxine monotherapy, the most common adverse events for olanzapine/fluoxetine (incidence ≥ 10%) included dizziness, asthenia, peripheral edema, and headache. More patients in the combination therapy group discontinued due to weight gain (*Corya et al 2006*). Compared to fluoxetine, olanzapine, and nortriptyline monotherapy, the most common adverse events for olanzapine/fluoxetine combination therapy (incidence ≥ 10%) were asthenia, headache, anxiety, tremor, nervousness, insomnia, and nausea (*Shelton et al 2005*).

Schizophrenia and/or Schizoaffective Disorder

- All oral atypical antipsychotic agents in this class review are indicated for use in schizophrenia with the exception of combination agent olanzapine/fluoxetine. Clozapine is the only agent indicated for treatment-resistant schizophrenia. Clozapine and paliperidone products, excluding Invega Trinza, are indicated for the treatment of schizoaffective disorder. The following is a summary of recent MAs and SRs, landmark trials in schizophrenia, and study evidence related to newer atypical antipsychotic agents (ie, asenapine, brexpiprazole, cariprazine, iloperidone, and lurasidone) that do not have extensive trial evidence.
- Based on a 2012 AHRQ SR of 125 trials evaluating typical and atypical antipsychotics, a total of 113 measured efficacy and safety in adults with schizophrenia or schizophrenia-related psychoses. Compared to haloperidol, there was no difference in PANSS (and/or Scale for the Assessment of Positive Symptoms [SAPS]) score for positive symptoms for aripiprazole, clozapine, olanzapine, quetiapine, and risperidone. Outcomes measuring negative symptoms demonstrated a significant difference in PANSS scores favoring aripiprazole for 1701 patients in 3 trials, risperidone for 4043 patients in 20 trials, and olanzapine-treatment for 3742 patients in 14 trials. When compared with haloperidol, risperidone yielded lower relapse rates for 1405 patients in 6 trials and olanzapine provided better response rates for 4099 patients in 14 trials and remission rates for 582 patients in 3 trials. The most common adverse effects with significant differences were in the category of EPS and most often involved haloperidol. Haloperidol appears to be equally effective to treatment with the atypical antipsychotics in terms of positive symptoms; however, for negative symptom scores aripiprazole, risperidone, and olanzapine may be better options for treatment. Olanzapine and risperidone may be better options when remission/relapse rates are considered (*Abou-Setta et al 2012*).

- One large, recent Bayesian MA of 212 RCTs compared 15 antipsychotic medications for efficacy and safety outcomes in patients with schizophrenia or related disorders in short-term trials. The primary endpoint was efficacy measured by mean overall change in symptoms after 6 weeks and all antipsychotics were significantly more effective than placebo. Clozapine had the greatest mean difference in the change in symptom scores and was significantly superior to all other antipsychotics, including olanzapine and risperidone which have demonstrated some efficacy in treatment-resistant patients. After clozapine, olanzapine, and risperidone were significantly more effective than the other antipsychotics apart from paliperidone. Overall, effect sizes were small and there were some inconsistencies between results, but the authors did not consider that this was substantial enough to change the results. Safety assessment for the FDA-approved agents indicated that EPS was lowest for clozapine and highest for haloperidol; sedation was lowest for risperidone and highest for clozapine; weight gain was lowest for haloperidol and highest for olanzapine; prolactin increase was lowest for aripiprazole and highest for paliperidone; and QT prolongation was lowest for lurasidone and highest for ziprasidone. The authors concluded that the properties of antipsychotic drugs differed greatly among agents and that treatment should be fit to individual patients' needs. As the MA had many limitations, including substantial differences between studies, and uncertainties surround indirect comparisons, generalizability of the findings and authors' conclusions are limited. This is similar to many large atypical antipsychotic MAs (*Leucht et al 2013*).
- One Cochrane SR evaluated aripiprazole vs other atypical antipsychotics for the treatment of schizophrenia. Differences in efficacy between aripiprazole and other atypical antipsychotics (olanzapine, risperidone, and ziprasidone) demonstrated no advantage in terms of overall global state (defined as MD in CGI-S score) or mental state (defined as MD total change in PANSS score). When compared with any one of several new generation antipsychotic drugs in one RCT (N = 523), the aripiprazole group showed improvement in energy, mood, negative symptoms, somnolence, and weight gain. More nausea was seen in patients given aripiprazole (N = 2881; RR, 3.13; 95% CI, 2.12 to 4.61). Weight gain with aripiprazole-treatment was less common (N = 330; RR, 0.35; 95% CI, 0.19 to 0.64). Attrition ranged from 30% to 40% (no differences between groups). Due to the high attrition rates validity is limited, thereby making it difficult to make strong conclusions. There are limited data on the safety and efficacy of aripiprazole. Based on current available evidence, efficacy of aripiprazole appears to be similar and there may be benefits in terms of weight gain, but there appears to be an increased incidence of nausea compared to other agents (*Khanna et al 2014*).
- One Cochrane SR evaluated quetiapine compared to other atypical antipsychotics for the treatment of schizophrenia. Efficacy and safety were evaluated in 5971 patients across 35 RCTs. For the primary efficacy endpoint, PANSS total score, the comparator drugs may be more effective than quetiapine, but the clinical meaning of these data is unclear. There were no significant differences in efficacy between quetiapine and clozapine, but quetiapine was associated with fewer adverse events. Quetiapine demonstrated fewer movement disorders compared to risperidone (RR, 0.5; 95% CI, 0.36 to 0.69), olanzapine (RR, 0.51; 95% CI, 0.32 to 0.81), and paliperidone (RR, 0.64; 95% CI, 0.45 to 0.91). There are limited studies; however, data provide evidence that quetiapine-treated patients may need to be hospitalized more frequently than those taking risperidone or olanzapine. Quetiapine may be slightly less effective than risperidone and olanzapine in reducing symptoms, and it may cause less weight gain and fewer side effects and associated problems (such as heart problems and diabetes) than olanzapine and paliperidone, but more than risperidone and ziprasidone (*Asmal et al 2013*).
- The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) was a large, multi-center study initiated by the National Institute of Mental Health to examine the effectiveness of SGAs compared to FGAs in patients with chronic schizophrenia. It was intended to include patients treated in typical clinical settings and to reflect typical clinical practice in which individuals with schizophrenia may require multiple medication trials before finding one that is adequately both efficacious and tolerable. The study design allowed for patients who discontinued one study antipsychotic drug to enter subsequent phases of the study to receive additional antipsychotic medications (*Lieberman et al 2005, Stroupe et al 2006, Stroupe et al 2009*). Among the unexpected outcomes was the finding that, with the exception of clozapine, the SGAs did not separate out robustly from the FGAs with respect to overall efficacy and times to treatment discontinuation. However, because of relatively high discontinuation rates across all treatment arms, potential biases regarding optimal dosing of individual drugs, and clear differences in treatment-emergent side effect profiles, the implications of CATIE are subject to interpretation which may preclude definitive guidance in developing pharmacotherapy guidelines for patients with schizophrenia as a whole.
- The efficacy of asenapine in the treatment of schizophrenia in adults was evaluated in 4 published, randomized, DB, PC, and active-controlled (haloperidol, risperidone, and olanzapine) trials, ranging in duration from 6 weeks to 1 year

(*Kane et al 2011, Kane et al 2010[a], Potkin et al 2007, Schoemaker et al 2010*). Asenapine was associated with statistically significant improvement in PANSS scores from baseline compared to placebo, starting from week 2 of therapy. CGI-I and CGI-S scores were also significantly improved with asenapine therapy compared to placebo. Moreover, an extension study demonstrated a reduced risk of relapse associated with continuation of asenapine therapy (*Kane et al 2011*). However, a direct-comparison study suggests that asenapine is less effective than olanzapine in terms of changes from baseline in PANSS and CGI-S scores. Furthermore, study discontinuation due to inadequate efficacy was noted in only 14% of patients receiving olanzapine compared to 25% of patients in the asenapine group. Mean weight gain was 0.9 kg with asenapine and 4.2 kg with olanzapine (*Shoemaker et al 2010*). In another study, while 17% of patients receiving risperidone experienced a weight gain of at least 7% from baseline, 9% of patients in the asenapine group were noted to exhibit clinically significant weight gain (*Potkin et al 2007*).

- The safety and efficacy of brexpiprazole was evaluated in 2 DB, PC, 6-week trials in adults with schizophrenia. In the pivotal studies, brexpiprazole 2 mg and 4 mg daily doses significantly reduced the PANSS score (-20.73 and -19.65 vs -12.01 points with placebo), the primary endpoint, compared with placebo; however, in the BEACON trial, only the brexpiprazole 4 mg dose significantly reduced the PANSS score (-20 vs -13.53 points with placebo) (*Correll et al 2015; Kane et al 2015[a]*). The most common adverse reactions in MDD trials were akathisia (NNH, 15), increased weight (NNH, 20) and somnolence (NNH, 22); in schizophrenia trials, the most common adverse effects were increased weight (NNH, 48) and tremor (NNH, 51) (*Correll et al 2015, Kane et al 2015[a], Thase et al 2015[b]*). The safety and efficacy of brexpiprazole for maintenance therapy of schizophrenia was evaluated in a randomized, DB, MC, PC trial. It enrolled 524 patients with an acute exacerbation of psychotic symptoms to be stabilized on brexpiprazole 1 to 4 mg daily. Patients who achieved stabilization (criteria including PANSS total score ≤ 70, CGI-S score ≤ 4 [moderately ill], no current suicidal behavior, or violent or aggressive behavior) for 12 weeks then entered a 52-week maintenance phase where they were randomized to their stabilization dose of brexpiprazole (N = 97) or placebo (N = 105). The co-primary endpoints were time to exacerbation of psychotic symptoms or impending relapse, defined as worsening of CGI-I and PANSS scores, hospitalization due to worsening of psychotic symptoms, suicidal behavior, or violent/aggressive behavior. In the maintenance phase, 13.5% of patients in the brexpiprazole group experienced impending relapse vs 38.5% of placebo patients ($p < 0.0001$) and time to impending relapse was statistically significantly lower (hazard ratio [HR], 0.34; $p = 0.0008$). However, based on results of an interim analysis, the trial was terminated early. Only a small number of patients were exposed to brexpiprazole for the prescribed 52 weeks and, therefore, conclusions cannot be drawn for long-term use (*Fleischhacker et al 2016*).
- The efficacy and safety of cariprazine in schizophrenia were demonstrated in 3 DB, randomized, PC, 6-week trials (*Durgam et al 2014, Durgam et al 2015[b], Kane et al 2015[b]*). A total of 1792 adult patients with acute exacerbation of schizophrenia were administered placebo or cariprazine 1.5 to 9 mg per day. Two trials were fixed-dose studies and included active comparators, risperidone 4 mg and aripiprazole 10 mg, to assess sensitivity; one study was a flexible-dose study with no active comparator. In the flexible-dose study, the mean daily dose ranged from 5 to 8 mg per day (*Kane et al 2015[b]*). All doses were superior to placebo in reducing PANSS and CGI-S scores and a significant PANSS reduction was observed as soon as 7 days for the higher doses and 2 to 3 weeks for the lower doses (*FDA/CBER summary review 2015*). Of note, higher doses do result in quicker control of symptoms; however, if high doses continue resulting in accumulation of the active metabolite DDCAR, it is not clear how this may influence safety results. Delayed incidences of akathisia occurred. According to pooled analysis (n = 1317 cariprazine-treated patients) within the FDA clinical summary, the most common adverse events reported in schizophrenia trials were EPS (28.5%) and akathisia (11.2%) (*FDA/CBER summary review 2015*). The akathisia observed at cariprazine doses ≤ 6 mg is comparable to those observed with aripiprazole, but accumulation of the DDCAR metabolite may result in later-onset effects. In schizophrenia studies, 4% of patients with normal hemoglobin A1c developed elevated levels (≥ 6.5%). The proportion of patients with weight increase ≥ 7% from baseline ranged from 8 to 17% across cariprazine doses. In an OL 48-week extension (N = 97) of a 6-week trial, safety and tolerability were found to be maintained. The most common adverse events were akathisia (14%), insomnia (14%), and weight gain (11.8%) (*Durgam et al 2014, Durgam et al 2017*). Another study evaluated cariprazine for maintenance therapy for schizophrenia relapse in 765 patients. A flexible-dose, OL, 8-week, run in phase was followed by a 12-week, fixed-dose, stabilization phase. Patients completing the OL phase (N = 264) entered a DB phase and received cariprazine (3 to 9 mg/day), or placebo for up to 72 weeks. During the DB phase, 24.8% of the cariprazine group experienced relapse vs 47.5% of the placebo group (HR, 0.45; 95% CI, 0.28 to 0.73). Time to relapse was statistically significantly longer for the cariprazine group vs placebo (25^{th} percentile time to relapse, 224 vs 92 days, respectively; $p < 0.001$). The long-term safety profile of cariprazine was found to be consistent with findings from previous trials (*Durgam et al 2016).*

- Iloperidone has been studied as monotherapy for the treatment of adults with an acute or subacute exacerbation of schizophrenia. Three 6-week, randomized, DB, placebo- and active comparator (risperidone and haloperidol)-controlled studies found iloperidone to be significantly more effective than placebo (*Potkin et al 2008*). Another 4-week, placebo- and active comparator- (ziprasidone) controlled study found a significant improvement in PANSS scores with iloperidone therapy compared to placebo (*Cutler et al 2008*). Two MAs of these 4 studies corroborated earlier data, finding iloperidone more effective than placebo in terms of improvement from baseline in various subscales of the PANSS scale and BPRS scores (*Citrome et al 2011, Citrome et al 2012*). The long-term efficacy and safety of iloperidone in the treatment of schizophrenia was evaluated in an MA that pooled the follow-up data (up to 52 weeks) from 3 prospective RCTs. The MA found the long-term efficacy of iloperidone, assessed via the time to relapse endpoint, to be comparable to haloperidol (p = 0.85), with a more favorable long-term safety profile (*Kane et al 2008*). Moreover, another MA designed to evaluate the short-term safety of iloperidone found the following dose-related adverse effects: dry mouth, dizziness, somnolence and dyspepsia. EPS was noted in association with iloperidone but was more common with haloperidol and risperidone therapies. Iloperidone was also associated with QTc prolongation and weight gain (1.5 to 2.1 kg) (*Weiden et al 2008*). The efficacy of iloperidone for relapse-prevention during maintenance phase of schizophrenia treatment was evaluated in a DB, PC, randomized withdrawal study. Patients were not blinded and were stabilized for 24 weeks. If clinically stable for 12 weeks, they were then randomized to iloperidone (8 to 24 mg/day) (N = 153) or placebo (N = 150) for 26 weeks. The primary endpoints were time to relapse and proportion of patients experiencing relapse (defined as hospitalization due to worsening schizophrenia, worsening of PANSS and CGI-I scores, suicidal or aggressive behavior, or treatment escalation [ie, dose increases or additional medications]). The trial was stopped early due to superior iloperidone relapse prevention. Time to relapse was statistically significantly longer with iloperidone vs placebo (140 vs 95 days, respectively; p < 0.0001). The relapse rate for placebo was 64% vs 17.9% for iloperidone (p < 0.0001). The safety was comparable to other trial results, with dizziness, insomnia, headache, dry mouth, and somnolence being the most common adverse events. Weight gain ≥ 7% occurred in 25.2% of iloperidone-treated patients in the relapse-prevention phase. Mean change in QTcF from baseline was 4.9 ms in the iloperidone group (vs 1 ms in placebo) during the relapse-prevention phase. Rates of EPS (2.5% in stabilization phase/1.3% in relapse-prevention phase) and akathisia (3.7% and 1%, respectively) were consistently low in iloperidone-treated patients as well (*Weiden et al 2016*).
- Lurasidone was investigated for the treatment of adult patients with acute and chronic symptoms of schizophrenia in 2 PC, 6-week studies and two 21-day studies directly comparing the safety and efficacy of lurasidone 120 mg once daily with ziprasidone 80 mg twice daily. In PC studies, lurasidone 40, 80, or 120 mg once daily was associated with significant improvements from baseline in PANSS and the BPRS scores, compared to placebo (*Meltzer et al 2011, Nakamura et al 2009*). The 2 direct-comparison studies demonstrated comparable improvements in the lurasidone and ziprasidone groups in terms of the reduction in total PANSS, PANSS positive symptom, PANSS general symptom, CGI-S scores, and several cognition scales. Likewise, the 2 groups were comparable in terms of rates of discontinuation for any reason and discontinuation due to adverse events (*Harvey et al 2011, Potkin et al 2011*). Of note, lurasidone was more effective in improving negative symptom PANSS scores compared to ziprasidone (p = 0.046). Both therapies were associated with a small weight loss from baseline and neither therapy was associated with a clinically significant electrocardiogram abnormality. Extrapyramidal adverse events were noted in 3.3% of patients in the ziprasidone group and in 3.3% of patients receiving lurasidone (*Potkin et al 2011*). The efficacy of lurasidone in maintenance treatment was evaluated in a DB, PC, RCT. Patients (N = 676) with schizophrenia experiencing an acute exacerbation entered into an OL stabilization phase for 12 to 24 weeks. Patients achieving stabilization for 12 weeks (N = 285) were randomized into a 28-week, DB phase to receive lurasidone (40 to 80 mg/day) or placebo. The probability of relapse at the 28-week point was 42.2% vs 51.2% in the lurasidone and placebo groups, respectively (NNT = 12). Lurasidone statistically significantly delayed the time to relapse vs placebo (p = 0.039). In patients receiving lurasidone in both the OL and DB phases, the most common adverse events were akathisia (16.7%), insomnia (12.5%), and headache (11.8%) (*Tandon et al 2016*).

Parkinson's Disorder Psychosis

- Pimavanserin is the only oral atypical antipsychotic FDA-approved for the treatment of hallucinations and delusions associated with PD psychosis. The FDA-approval of pimavanserin was based on a 6-week PC, DB, RCT of 199 patients evaluating the safety and efficacy of pimavanserin 40 mg once daily. Compared to placebo, the least-squares mean difference of total PD adapted SAPS (SAPS-PD) score change from baseline at day 43 favored pimavanserin 40 mg (-3.06; 95% CI, -4.91 to -1.20; p = 0.0014). The most common adverse events in the pimavanserin vs the

placebo group included urinary tract infection (13 vs 12%), falls (11 vs 9%), peripheral edema (7 vs 3%), hallucinations (7 vs 4%), nausea (6 vs 6%), confusion (6 vs 3%), and headache (1 vs 5%) *(Cummings et al 2014).*

- One MA of pimavanserin included 4 RCTs measuring the efficacy and safety compared to placebo in patients with PD psychosis. Pimavanserin was associated with a significant decrease in SAPS-hallucination and delusions score compared to placebo (weighted mean differences [WMD],-2.26; 95% CI, -3.86 to -0.67; p=0.005). Adverse effects were not significantly different from placebo, except pimavanserin was associated with a significantly lower incidence of orthostatic hypotension (RR, 0.33; 95% CI, 0.15 to 0.75; p = 0.008) *(Yasue et al 2016, Bozymski et al 2017)*.

Long-Acting Injectable Atypical Antipsychotics:

Bipolar Disorder

- Risperdal Consta (risperidone microspheres) and Abilify Maintena (aripiprazole ER) are the only long-acting injections FDA-approved for bipolar I disorder in adults.
  - Abilify Maintena (aripiprazole ER) long-acting injection is indicated as maintenance monotherapy treatment (*Calabrese et al 2017*).
  - Risperdal Consta (risperidone microspheres) long-acting injection is indicated as monotherapy or in combination with lithium or valproate for maintenance therapy. Compared to placebo, risperidone long-acting injection has demonstrated superior efficacy in acute and non-acute patients with similar safety effects to that of oral risperidone (*Macfadden et al 2009, Quiroz et al 2010, Vieta et al 2012, Yatham et al 2007*).
- In a DB, PC, 52-week randomized withdrawal study (N = 266), aripiprazole ER injection significantly delayed recurrence of any mood episode compared with placebo, with a 55% reduction in risk of experiencing a mood episode over 1 year (HR, 0.45; 95% CI, 0.3 to 0.68). The proportion of patients experiencing recurrence of a manic episode was significantly less with aripiprazole ER injection (9.1 vs 30.1%); however, the recurrence rate for either depressive or mixed episodes was not different between treatment groups. After acute treatment of a manic episode with oral aripiprazole and transition to monotherapy with aripiprazole ER 400 mg intramuscularly (IM) once every 4 weeks (reduction to 300 mg was allowed for adverse reactions) for a 12-week stabilization period, patients were randomized to continue aripiprazole IM or withdrawal to placebo for 52 weeks. Of note, a large proportion of patients did not complete the study. Of the 266 randomized patients, 48.1% (N = 64) of the aripiprazole group and 28.6% (N = 38) of the placebo group completed the study. Treatment-emergent adverse effects that lead to discontinuation more commonly occurred with placebo (25.6 vs 17.4%); those that occurred more often with aripiprazole included weight gain of 7% or greater (18 vs 12.9%), akathisia (21.2 vs 12.8%), and anxiety (6.8 vs 4.5%) (*Calabrese et al 2017, Micromedex 2018*).
- For maintenance therapy, risperidone long-acting injection monotherapy has demonstrated inconsistent results regarding the endpoint of delayed time to recurrence of any mood episode compared to placebo (*Quiroz et al 2010, Vieta et al 2012*). When risperidone long-acting injection was used in combination with mood stabilizers (eg, lithium and valproate), antidepressants, or anxiolytics, the time to relapse was significantly longer with fewer proportions of patients relapsing compared to placebo (*Macfadden et al 2009*). An exploratory post hoc analysis showed that the time to recurrence of any mood episode was also significantly longer with oral olanzapine compared with risperidone long-acting injection (p = 0.001) (*Vieta et al 2012*). The adverse effect profile of long-acting injection therapy is not fully understood; however, EPS, weight gain, hyperprolactinemia, and cardiovascular events were observed in risperidone long-acting injection therapy trials (*Macfadden et al 2009, Quiroz et al 2010, Vieta et al 2012, Yatham et al 2007*).

Schizophrenia

- All 8 long-acting injectable atypical antipsychotics are FDA-approved for the treatment of schizophrenia in adults. These agents include Abilify Maintena (aripiprazole ER), Aristada and Aristada Initio (aripiprazole lauroxil), Zyprexa Relprevv (olanzapine pamoate ER), Invega Sustenna (paliperidone palmitate once-a-month injection), Invega Trinza (paliperidone palmitate once-every-3-months injection), Risperdal Consta (risperidone microspheres), and Perseris (risperidone once-a-month injection). Invega Sustenna is the only agent FDA-approved for the treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers or antidepressants.
- A number of MAs and SRs have been conducted evaluating long-acting injection atypical antipsychotics compared to oral antipsychotics for the treatment of schizophrenia. Comparative effectiveness data between long-acting injectable atypical antipsychotics are lacking and there is insufficient evidence to draw firm conclusions. The most recent, well-designed MAs have been summarized for efficacy and safety evaluations.

- One MA of atypical antipsychotics included 13 RCTs measuring the efficacy and safety of long-acting injection atypical antipsychotics vs oral antipsychotics or placebo in patients with schizophrenia. Long-acting injectable atypical antipsychotics were not associated with a significant decrease in the PANSS total score from baseline from oral antipsychotics (p = 0.33); therefore, both formulations had similar efficacy. No additional significant differences were noted. The long-acting injectable atypical antipsychotics were associated with a higher incidence of EPS compared to placebo (p < 0.001) and oral antipsychotics (p = 0.048) (*Fusar-Poli et al 2013*).
- One SR and MA of long-acting antipsychotic injectable agents (including typical and atypical agents) measured the safety and efficacy of treatment compared to oral antipsychotics in 21 RCTs (11 trials measured atypical antipsychotic agents). Patients with schizophrenia, schizophreniform, or schizoaffective disorder were evaluated in longer duration trials of greater than or equal to 6 months. Long-acting injectable antipsychotics were similar to oral antipsychotics for relapse prevention in outpatient studies lasting ≥ 1 year (RR, 0.93; 95% CI, 0.71 to 1.07; p = 0.03). Among individual long-acting injectable antipsychotics, only fluphenazine was superior to oral antipsychotics in drug efficacy (p = 0.02) and in preventing hospitalization (p = 0.04). There was no difference between each individual long-acting injectable antipsychotic and pooled long-acting injectable antipsychotics compared to oral antipsychotics regarding discontinuation due to adverse events (p = 0.65) (*Kishimoto et al 2014*).
- One MA compared outcomes for once-monthly long-acting injections of paliperidone palmitate and risperidone across 7 RCTs. Paliperidone palmitate was less likely to show no improvement in global state (defined as reduction in PANSS scores) vs placebo (RR, 0.79; 95% CI, 0.74 to 0.85). When comparing both active treatments, one trial favored paliperidone palmitate and one trial favored risperidone long-acting injection; therefore, conclusions could not be made. In terms of safety, paliperidone palmitate and risperidone long-acting injection were similar. Compared to placebo, paliperidone palmitate led to significant elevations in serum prolactin, regardless of patient gender (*Nussbaum et al 2012*).
- One SR of 41 trials measuring safety concluded that long-acting injectable atypical antipsychotics are associated with similar adverse effects to that of oral formulations, and no clinically significant trends can be conclusively drawn. Data suggested that olanzapine pamoate was associated with dose-dependent weight gain, lipid and glucose metabolism issues, and may increase prolactin levels even at low doses. Post-injection syndrome, due to accidental intravascular injection of olanzapine pamoate, was characterized by delirium and/or excessive sedation (incidence, 1.2%). The risperidone long-acting injection may increase the risk of QT prolongation, although the clinical significance is unknown. Hyperprolactinemia, EPS, cardiovascular events (ie, tachycardia and orthostatic hypotension), and weight gain are known side effects of risperidone long-acting injection and paliperidone palmitate. The most common adverse event associated with paliperidone palmitate was worsening of psychotic symptoms (incidence, 3.5 to 16%) (*Gentile et al 2013*).
- Recently-approved long-acting injectable agents include Aristada and Aristada Initio (aripiprazole lauroxil), Invega Trinza (paliperidone palmitate once-every-3-months injection), and Perseris (risperidone once-a-month injection).
  - The safety and efficacy of aripiprazole lauroxil in adult patients with schizophrenia was established in one PC, DB, RCT of 622 patients over a period of 12 weeks. Oral aripiprazole was administered concomitantly for the first 3 weeks of treatment. The PANSS total score was significantly decreased at day 85 by 10.9 with monthly IM injections of aripiprazole lauroxil 441 mg and by 11.9 with 882 mg IM monthly compared with placebo (p < 0.001 for both). PANSS was significantly improved as early as day 8 and maintained throughout the study. In terms of safety, more than double the proportion of patients taking aripiprazole lauroxil experienced akathisia (441 mg, 11.6%; 882 mg, 11.5%) compared to placebo (4.3%). The majority of the akathisia (75%) was experienced before the second injection within the first 3 weeks. Additional treatment-emergent adverse effects (incidence ≥ 2%) included insomnia, headache, and anxiety (*Meltzer et al 2015*). In an indirect comparison of aripiprazole lauroxil (441 or 882 mg) and aripiprazole ER injection (400 mg), all treatment groups had similar reductions in symptoms of schizophrenia as measured by PANSS total score (*Cameron et al 2018*). The incidence of akathisia and changes in weight were also similar between treatments; although, the occurrence of treatment emergent adverse events was potentially lower with aripiprazole lauroxil 882 mg vs aripiprazole ER injection (OR, 0.46; 95% CI, 0.22 to 0.97).
    - Aristada Initio is indicated only to be used as a single dose in conjunction with oral aripiprazole for the initiation of Aristada, when used for the treatment of schizophrenia in adults. Effectiveness of Aristada Initio was established by adequate and well-controlled studies of oral aripiprazole and Aristada in adult patients with schizophrenia and a single pharmacokinetics bridging study (*Aristada Initio prescribing information 2018*).
  - The FDA-approval of Invega Trinza, the 3-month IM paliperidone palmitate injection, was based on one PC, OL, DB trial of 305 patients with schizophrenia experiencing acute symptoms. Prior to administration of paliperidone

palmitate once every 3 months injection, patients were administered flexible oral doses for 17 weeks, and then administered the paliperidone palmitate once monthly injection for 12 weeks. If stable, patients were then administered the once-every-3-months injection. Paliperidone palmitate once-every-3-months injection significantly lengthened the median time to first relapse vs placebo. The mean change in PANSS total scores showed greater improvement in the paliperidone group compared to placebo ($p < 0.001$). Due to the low percentage of relapse in treated patients (7.4%), the median time was not estimated; however, in the placebo group, 23% experienced relapse, with a median time of 274 days. The trial was stopped early due to demonstration of efficacy. Those adverse events noted more frequently in the group receiving paliperidone palmitate vs the placebo group included headache (9 vs 4%), increased weight (9 vs 3%), nasopharyngitis (6 vs 1%), and akathisia (4 vs 1%) (*Berwaerts et al 2015*).

- The efficacy of risperidone ER monthly injection (Perseris) was evaluated in an 8-week, DB, randomized, PC trial in 354 patients who were experiencing an acute schizophrenia exacerbation. Patients received risperidone 90 mg, 120 mg, or placebo subcutaneously on days 1 and 29. LS squares mean change from baseline in PANSS total score (the primary outcome) was significantly greater with risperidone 90 mg (-6.148, $p = 0.004$) and 120 mg (-7.237, $p < 0.001$) compared to placebo. Compared to placebo, CGI-S scores were also significantly decreased in both risperidone dose groups ($p = 0.0002$ and $p < 0.0001$, respectively). Adverse effects were similar between groups, with the exception of weight gain (13% in the risperidone 90 mg group, 12.8% in the risperidone 120 mg group, and 3.4% in the placebo group) (*Nasser et al 2016*).

CLINICAL GUIDELINES

- The use of these agents for the treatment of schizophrenia is recognized by national and international guidelines as a mainstay in therapy. Guidelines vary by indication and the following outlines use in children, adolescents, and adults:

Adults

- Bipolar disorders – Guidelines recommend the use of drugs such as lithium, anticonvulsants and/or antipsychotics for the treatment of bipolar disorders (*Hirschfeld et al 2002, Hirschfeld et al 2005, VA/DoD 2010 [this guideline has been retired]*).
  - Drugs likely to be beneficial for bipolar mania include lithium, anticonvulsants (eg, valproate, carbamazepine), and atypical antipsychotics. Lithium or valproate may be combined with an atypical antipsychotic.
  - Treatment options for bipolar depression include lithium, lamotrigine, and certain atypical antipsychotics (eg, quetiapine, olanzapine in combination with fluoxetine, and lurasidone).
- MDD – In general, guidelines state that no particular antidepressant agent is superior to another in efficacy or time to response. Choice can be guided by matching patient's symptoms to side effect profile, presence of medical and psychiatric comorbidity, and prior response (*VA/DoD 2016*; *Gelenberg et al 2010*).
  - For the majority of patients, an SSRI, SNRI, bupropion or mirtazapine is optimal for first-line treatment. Atypical antipsychotics may be useful to augment antidepressant therapy (*Gelenberg et al 2010*).
- Schizophrenia – Guidelines recommend that agents should be chosen based on clinical circumstances and side effects. Clozapine has the greatest efficacy on persistent hostility, aggressive behavior, and suicidal behavior, and should be considered in patients with suicidal ideation; recent evidence has also demonstrated there may be lower rates of overall mortality with clozapine use. Clozapine should be used to treat persistent psychotic symptoms or treatment-resistant patients. A minimum of 6 weeks is needed for an adequate trial to establish efficacy. If a patient is non-adherent to treatment or has chronic relapse, a long-acting injectable antipsychotic agent may be considered (*Dixon et al 2009; Lehman et al 2004; VA Pharmacy Benefits Management Services 2012*).
- Parkinson's disease psychosis – The American Academy of Neurology Practice Parameter on the treatment of depression, psychosis, and dementia in PD states that clozapine should be considered for the treatment for PD and psychosis, quetiapine may be considered, and olanzapine should not be routinely considered (*Miyasaki 2006*).

Children and Adolescents

- Use of atypical antipsychotics - According to guidelines from the American Academy of Child and Adolescent Psychiatry (AACAP), prior to the initiation of antipsychotic therapy patients should undergo a thorough diagnostic assessment and evaluation for comorbid medical conditions and concomitant medications. Furthermore, a multidisciplinary plan that includes education and psychotherapy should be established. The prescriber should also have a thorough discussion about the risks and benefits of psychotropic treatment (*Findling et al 2011*).
- Autism Spectrum Disorders (ASD) – AACAP guidelines state that pharmacotherapy may be considered in children with ASD when there is a specific target symptom or comorbid condition. Risperidone and aripiprazole are FDA-

approved for irritability associated with autism; other drugs that have been studied include: clonidine, olanzapine, valproic acid, lamotrigine, levetiracetam, clomipramine, amantadine, pentoxifylline (in combination with risperidone), and naltrexone (*Volkmar et al 2014*).
  - Bipolar disorder – According to AACAP guidelines for treatment of children and adolescents with bipolar disorder, pharmacotherapy is the primary treatment for bipolar mania. Standard therapy includes lithium, valproate, and/or atypical antipsychotic agents, with other adjunctive medications used as indicated (*McClellan et al 2007*).
  - Schizophrenia – According AACAP guidelines, antipsychotics are a primary treatment for schizophrenia spectrum disorders in children and adolescents. The choice of agent is typically based on factors such as FDA-approval status, side effect profile, patient and family preference, and cost (*McClellan et al 2013*).
  - Tourette's disorder – According to AACAP guidelines for the treatment of children and adolescents with tic disorders, pharmacotherapy should be considered for moderate to severe tics causing severe impairment in quality of life, or when psychiatric comorbidities are present that can also be targeted. Most clinicians use atypical antipsychotics before first-generation agents and some prefer α-agonists over antipsychotic medications due to the adverse effect profile. Commonly used drugs include risperidone, aripiprazole, and clonidine (*Murphy et al 2013*).

SAFETY SUMMARY

- Ziprasidone is contraindicated in patients with recent acute myocardial infarction (MI), uncompensated heart failure (HF), and history of QT prolongation, or those taking drugs that have demonstrated QT prolongation. Lurasidone is contraindicated for concomitant use with strong cytochrome (CYP) 3A4 inducers and/or inhibitors. Olanzapine/fluoxetine is contraindicated in patients taking concurrent pimozide or thioridazine due to the potential for QT prolongation, and in patients taking concurrent monoamine oxidase inhibitors due to the potential for serotonin syndrome. Lastly, asenapine is contraindicated in patients with severe hepatic impairment.
- All atypical antipsychotic agents, including pimavanserin, have a boxed warning for increased mortality in elderly patients with dementia-related psychosis. Those agents (ie, aripiprazole, lurasidone, brexpiprazole, quetiapine, quetiapine ER, olanzapine/fluoxetine) indicated for depressive episodes carry a boxed warning for an increased risk of suicidal thoughts and behaviors. Zyprexa Relprevv has a boxed warning for incidences of post-injection delirium and/or sedation syndrome; this agent should not be used in patients with dementia-related psychosis. Lastly, clozapine-containing agents (ie, Clozaril, Fazaclo, and Versacloz) have a boxed warning for severe neutropenia, orthostatic hypotension, bradycardia, syncope, seizures, myocarditis, and cardiomyopathy.
- The atypical antipsychotics have warnings relating to risks of neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes, falls, orthostatic hypotension, leukopenia/neutropenia/agranulocytosis, seizures, cognitive and motor impairment, body temperature dysregulation, suicide, and dysphagia. Additional warnings for various agents include:
  - Aripiprazole: Pathological gambling and other compulsive behaviors and cerebrovascular adverse events in elderly patients with dementia-related psychosis
  - Brexpiprazole: Pathological gambling and other compulsive behaviors.
  - Clozapine-containing products: Eosinophilia, hepatotoxicity, QT prolongation, pulmonary embolism, fever, and anticholinergic toxicity
  - Iloperidone: QT prolongation, hyperprolactinemia, and priapism
  - Ziprasidone: QT prolongation, severe cutaneous reactions (eg, Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS] and Stevens-Johnson syndrome), hyperprolactinemia, and priapism
  - Paliperidone: QT prolongation, hyperprolactinemia, priapism, and potential for gastrointestinal obstruction (due to non-deformable tablet)
  - Lurasidone: Hyperprolactinemia and activation of mania/hypomania
  - Risperidone: Priapism, hyperprolactinemia, thrombotic thrombocytopenic purpura, increased sensitivity in patients with PD or dementia with Lewy bodies, and recent myocardial infarction or unstable cardiac disease
  - Asenapine: QT prolongation, hyperprolactinemia, and hypersensitivity reactions
  - Quetiapine: QT prolongation, cataracts, hypothyroidism, hyperprolactinemia, increased blood pressure in children and adolescents, leukopenia, neutropenia and agranulocytosis, and anticholinergic effects
  - Olanzapine: DRESS and hyperprolactinemia
  - Pimavanserin: QT prolongation
- Clozapine-containing products and Zyprexa Relprevv are a part of the Risk Evaluation and Mitigation Strategies (REMS) program. Registry, training, and counseling are required as part of both programs (*REMS@FDA 2019*).

Clozapine products also require certain laboratory levels prior to prescribing. Zyprexa Relprevv requires patients to be observed in clinic for 3 hours after administration. In December 2016, the FDA announced that the full clozapine REMS program would not be implemented in 2016 due to technical and logistical challenges. The date of full launch is February 28, 2019 (*FDA safety communication [clozapine] 2019*).
    - In September 2015, the FDA made modifications to the clozapine REMS program. The absolute neutrophil count (ANC) requirements were modified to a lower ANC level. Benign ethnic neutropenia (BEN) patients were also included as now eligible for clozapine-treatment (*FDA safety communication [clozapine] 2015*).
- Post-marketing reports of intense urges, particularly for gambling, have been reported in patients taking aripiprazole and brexpiprazole. Other compulsive urges include: sexual urges, shopping, eating or binge eating, and other compulsive behaviors have been reported. Dose reductions or stopping aripiprazole and brexpiprazole should be considered.
- In 2018, the FDA completed an analysis of reported postmarketing deaths and serious adverse events with the use of pimavanserin, including those reported to the FDA Adverse Event Reporting System (FAERS). The FDA did not identify any new or unexpected safety findings, or findings inconsistent with the established safety labeling. The FDA's conclusion was that the benefits of pimavanserin outweighed its risks for patients with hallucinations and delusions of Parkinson's disease psychosis (*FDA Drug Safety and Availability 2018*).
    - In assessing the reports of deaths, FDA considered that patients with Parkinson's disease have psychosis, a higher mortality rate due to their older age, advanced Parkinson's disease, and other medical conditions. In FAERS reports that included a cause of death, there was no evident pattern to suggest a drug effect (*FDA Drug Safety and Availability 2018*).
- Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at an increased risk of extrapyramidal and/or withdrawal symptoms. Neonates exposed to fluoxetine, a component of Symbyax, late in the third trimester have developed complications arising immediately upon delivery requiring prolonged hospitalization, respiratory support, and tube feeding. These drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In general, a decision should be made whether to discontinue nursing or to discontinue the antipsychotic drug, taking into account the importance of the drug to the mother. It is recommended that women do not breastfeed during treatment with iloperidone, olanzapine, and ziprasidone.
- Many factors are taken into consideration when prescribing an atypical antipsychotic, including co-morbid conditions and safety risks. Common adverse events observed within the class include EPS, sedation, increased prolactin levels, autonomic effects, metabolic effects, and cardiac risks including the risk of ventricular arrhythmias (QT prolongation). Table 3 outlines the relative adverse event trends observed between the various atypical antipsychotic agents:

Table 3. Relative adverse event risk observed in trials for atypical antipsychotic agents

Adverse Event	Aripiprazole	Asenapine	Brexpiprazole	Cariprazine	Clozapine*	Iloperidone	Lurasidone	Olanzapine	Paliperidone	Quetiapine	Risperidone	Ziprasidone
Sedation – sleepiness	Low	Moderate	Low	Low	High	Low	Moderate	Moderate	Low	Moderate	Low	Low
Diabetes	Low	Moderate	Low	Low	Very high	Moderate	Negligible to low	High	High	High	High	Negligible to low
EPS – akathisia (motor restlessness), parkinsonism (tremor, rigidity, and slow movements), dystonia (continuous muscle spasms or contractions), and tardive dyskinesia (jerky movements).	Low	Moderate	Low	Moderate	Negligible to low	Negligible to low	Moderate	Low	High	Negligible to low	High	Low
Anticholinergic – blurred vision, constipation, dry mouth, drowsiness, memory impairment, etc.	Negligible	Negligible	Negligible to low	Negligible to low	High	Low	Negligible	Moderate	Negligible	Moderate	Low	Negligible
Orthostasis – low blood pressure resulting in dizziness when standing up.	Negligible	Low	Negligible to low	Negligible to low	High	High	Low	Low	Moderate	Moderate	Low	Low
Weight Gain	Low	Moderate	Low	Low	Very high	Moderate	Negligible to low	High	High	High	High	Negligible to low
Prolactin – high levels linked to gynecomastia, sexual dysfunction, menstrual disruption, acne, amenorrhea, hirsutism, osteoporosis, increased risk of hip fracture, etc.	Negligible	Moderate	Negligible to low	Negligible to low	Negligible to low	Negligible to low	Negligible to low	Low	High	Negligible to low	High	Low
QT prolongation	Negligible to low	Low	Negligible to low	Negligible to low	Low	Moderate	Negligible to low	Low	Low	Low	Low	Moderate
Hypercholesterolemia	Negligible	Negligible	Low	Negligible to low	Very high	Moderate	Negligible to low	Very high	Low	High	Low	Negligible to low

Abbreviation: EPS = extrapyramidal side effects
Note: Information is based on indirect comparisons and expert assessments; however, more head-to-head trials are warranted to substantiate observations
*Granulocytopenia or agranulocytosis has been reported in 1%. Clozapine associated with excess risk of myocarditis and venous thromboembolism (VTE), including fatal pulmonary embolism (PE).

(*Jibson et al 2017)*

DOSING AND ADMINISTRATION

Table 4. Dosing and administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Abilify (aripiprazole)	Tablet, tablet with sensor (drug/device), orally disintegrating tablet, oral solution	Oral	Daily Tablet with sensor has a patch which should be changed weekly or sooner, as needed.	Dose adjustments are recommended in known CYP2D6 poor metabolizers, or with concomitant CYP2D6 inhibitors, and/or CYP3A4 inhibitors/inducers. The MyCite (tablet with sensor) system is composed of an ingestible event marker (IEM) sensor, MyCite patch (wearable sensor), MyCite app, and a web-based portal for healthcare professionals and caregivers. Tablets with sensor may be administered with or without food. Most ingestions will be detected in 30 minutes to 2 hours. Patients should be instructed not to repeat doses if not detected.
Abilify Maintena (aripiprazole ER)	Injection	IM	Monthly	Must be administered by a healthcare professional. Dose adjustments are recommended in known CYP2D6 poor metabolizers, or with concomitant CYP2D6 inhibitors, and/or CYP3A4 inhibitors/inducers. Aripiprazole-naïve patients should establish tolerability with oral formulations prior to initiating long-acting injections.
Aristada (aripiprazole lauroxil)			Monthly (441 mg, 662 mg, or 882 mg) or every 6 weeks (882 mg) or every 2 months (1064 mg)	
Aristada Initio (aripiprazole lauroxil)			One dose of Aristada Initio 675 mg and aripiprazole 30 mg orally with the first Aristada injection	Must be administered by a healthcare professional. Avoid use in known CYP2D6 poor metabolizers, or with concomitant strong CYP2D6 inhibitors, and/or strong CYP3A4 inhibitors/inducers.
Saphris (asenapine)	Sublingual tablet	Oral	Twice daily	Sublingual tablets should be placed under the tongue and left to dissolve completely; they should not be swallowed. Eating and drinking should be avoided for 10 minutes after administration.
Rexulti (brexpiprazole)	Tablet	Oral	Daily	Dose adjustments are recommended in known CYP2D6 poor metabolizers, concomitant moderate to strong CYP2D6 and/or CYP3A4 inhibitors, and/or CYP3A4 inducers.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Dosage adjustments are recommended for hepatic and renal impairment.
Vraylar (cariprazine)	Capsule, therapy pack	Oral	Daily	Dose adjustments are recommended with concomitant CYP3A4 inhibitors. Concomitant use is not recommended with CYP3A4 inducers. Use of the drug is not recommended in severe hepatic or renal impairment since it has not been studied in these populations.
Clozaril (clozapine)	Tablet	Oral	Once or twice daily	Prior to initiating, a baseline ANC must be ≥ 1500/mcL (≥ 1000/mcL for patients with BEN). To continue treatment, ANC must be monitored regularly. Dose adjustments are recommended in patients with renal/hepatic impairment, CYP2D6 poor metabolizers, taking concomitant CYP2D6, CYP1A2, CYP3A4 inhibitors and/or CYP3A4, CYP1A2 inducers.
Fazaclo (clozapine)	Orally disintegrating tablet			
Versacloz (clozapine)	Suspension			
Fanapt (iloperidone)	Tablet	Oral	Twice daily	Dose adjustments are recommended in patients with hepatic impairment, CYP2D6 poor metabolizers, taking concomitant CYP2D6 and/or CYP3A4 inhibitors.
Latuda (lurasidone)	Tablet	Oral	Daily	Dose adjustment recommended with concomitant use with a moderate CYP3A4 inhibitor and renal/hepatic impairment. Should be administered with food (≥ 350 calories).
Zyprexa (olanzapine)	Tablet	Oral	Daily	
Zyprexa Zydis (olanzapine)	Orally disintegrating tablet			
Zyprexa IntraMuscular (olanzapine)	Injection	IM	As needed; max. 3 doses 2 to 4 hrs apart	
Zyprexa Relprevv (olanzapine ER)	Injection	IM	Every 2 weeks (initial: 210 mg or 300 mg; maintenance: 150mg, 210 mg, or 300 mg) or every 4 weeks (initial: 405 mg;	This product is available only through a restricted distribution program and must be administered by a healthcare professional; patient observation is required for at least 3 hours after injection due to the potential for Post-Injection Delirium/Sedation Syndrome.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			maintenance: 300 mg or 405 mg)	Tolerability with oral olanzapine must be established prior to initiating therapy with this long-acting injection.
Symbyax (olanzapine/fluoxetine)	Capsule	Oral	Daily	The safety of doses above 18 mg/75 mg has not been evaluated in clinical studies. The safety of doses above 12 mg of olanzapine and 50 mg of fluoxetine has not been evaluated in pediatric clinical studies. Start olanzapine/fluoxetine at 3 mg/25 mg or 6 mg/25 mg in patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of olanzapine/fluoxetine (female gender, geriatric age, nonsmoking status).
Invega (paliperidone ER)	Tablet	Oral	Daily	Tablets should be swallowed whole and should not be chewed, divided, or crushed.
Invega Sustenna (paliperidone ER)	Injection	IM	Monthly	Must be administered by a healthcare professional. Dosage adjustment for renal impairment. For patients naïve to oral paliperidone or oral or injectable risperidone, tolerability with oral paliperidone or oral risperidone must be established prior to initiating therapy with this long-acting injection.
Invega Trinza (paliperidone ER)	Injection	IM	Every 3 months	Must be administered by a healthcare professional. Prior to initiation, patients must have been adequately treated with Invega Sustenna for at least 4 months. Dosage adjustment for renal impairment.
Nuplazid (pimavanserin)	Tablet, capsule	Oral	One 34 mg capsule once daily; or one 10 mg tablet with strong CYP3A4 inhibitors	No initial dosage titration. Dosage adjustment is required with concomitant use with strong CYP3A4 inhibitors and/or inducers.
Seroquel (quetiapine)	Tablet	Oral	Daily to twice daily	Dosage adjustment for hepatic impairment, geriatric use, and with concomitant CYP3A4 inhibitors and/or inducers.
Seroquel XR (quetiapine ER)	Tablet	Oral	Daily	Tablets should be swallowed whole and not split, chewed, or crushed.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Dosage adjustment for hepatic impairment, geriatric use, and with concomitant CYP3A4 inhibitors and/or inducers
Risperdal (risperidone)	Tablet, oral solution	Oral	Daily to twice daily	Dosage adjustment for renal/hepatic impairment.
Risperdal M-Tabs (risperidone)	Orally disintegrating tablet			
Risperdal Consta (risperidone microspheres)	Injection	IM	Every 2 weeks	Must be administered by a healthcare professional. Tolerability to oral risperidone must be established prior to initiating therapy with this long-acting injection.
Perseris (risperidone ER)		SC	Monthly	
Geodon (ziprasidone)	Capsule	Oral	Twice daily	Give capsules with food. IM ziprasidone should be administered with caution to patients with impaired renal function as the cyclodextrin excipient is cleared by renal filtration.
	Injection	IM	As needed; 10 mg every 2 hrs or 20 mg every 4 hrs up to a maximum of 40 mg/day	

See the current prescribing information for full details.

CONCLUSION

- The antipsychotics are divided into 2 distinct classes: typical antipsychotics, also called FGAs, and atypical antipsychotics, also called SGAs (*Miyamato et al 2005*).
- There are a number of atypical antipsychotic formulations available as both branded and generic products. These agents are available in various dosage forms including capsules, tablets, injections, oral solutions, sublingual tablets, and orally disintegrating tablets.
- FDA-approved indications for the atypical antipsychotics include irritability associated with autistic disorder, bipolar disorder, Tourette's disorder, MDD, schizophrenia, schizoaffective disorder, and PD psychosis. The indications vary by diagnosis, age, or by use as mono- or adjunctive-therapy. All agents in this class are indicated for use in schizophrenia with the exception of combination agent Symbyax (olanzapine/fluoxetine) and pimvanserin. Clozapine and paliperidone products, excluding Invega Trinza, are indicated for the treatment of schizoaffective disorder, and clozapine is the only agent in this class FDA-approved for treatment-resistant schizophrenia. Aripiprazole, lurasidone, olanzapine, quetiapine and risperidone are approved for use in patients ≥ 13 years of age and paliperidone oral products are approved for patients ≥ 12 years of age with schizophrenia. All oral agents in this class are indicated for use in bipolar disorder, except clozapine, iloperidone, paliperidone, pimavanserin, and brexpiprazole. Risperdal Consta and Abilify Maintena are the only long-acting injectables indicated for the treatment of bipolar disorder. Aripiprazole, olanzapine/fluoxetine, risperidone, quetiapine, lurasidone, and asenapine are approved for use in pediatric patients ≥ 10 years of age with bipolar disorder. Olanzapine is approved for use in patients ≥ 13 years of age with bipolar disorder. Aripiprazole and risperidone are the only agents indicated for the treatment of irritability associated with autistic disorder in pediatric patients (aged 6 to 17 years, and 5 to 17 years, respectively). Aripiprazole is the only agent indicated for the treatment of Tourette's disorder in pediatric patients, aged ≥ 6 years. Aripiprazole, brexpiprazole, and quetiapine ER are indicated as adjunctive treatment for MDD in patients already taking an antidepressant. Olanzapine, when prescribed in combination with fluoxetine, is indicated for treatment-resistant depression. Pimavanserin is the only agent in the class FDA-approved for treatment of PD psychosis.

- Comparative effectiveness data are most available for the treatment of schizophrenia and schizophrenia-like psychosis in adults; however, outcomes are often inconsistent. Study evidence demonstrates that there are no consistent differences in the efficacy between the atypical antipsychotics in acute or short-term trials, although clozapine has often been touted as significantly more effective for patients with treatment-resistant schizophrenia compared to all other atypical antipsychotics (*Leucht et al 2013, Lieberman et al 2005, Stroupe et al 2006, Stroupe et al 2009*). In general, clozapine is often followed by olanzapine and risperidone in terms of improved efficacy (*Lehman et al 2004, Leucht et al 2013*). There is also very little evidence evaluating the long-acting injection agents and newer agents brexpiprazole, cariprazine, iloperidone, and lurasidone. Challenges associated with comparative effectiveness reviews are mainly due to high attrition rates, internal validity study concerns, and small sample sizes within trials.
- Each atypical antipsychotic has a distinctive chemical structure, mechanism of action, and neuropharmacologic and adverse event profile. It should be noted that paliperidone is an active metabolite of risperidone and therefore carries some similarity in chemical structure and pharmacologic effects with the parent drug. Plasma levels of cariprazine and its metabolite accumulate over time; adverse reactions may not appear until after several weeks of drug administration.
- Safety profiles vary between agents and are often an important component of treatment selection. The long-acting injection antipsychotics are often prescribed for patients who demonstrate adherence issues with oral formulations. Common adverse events observed within the class include EPS, increased prolactin levels, autonomic effects, metabolic effects, and cardiac risks including risk of ventricular arrhythmias (QT prolongation). When compared to the typical antipsychotics, the atypical antipsychotics are associated with a lower risk of EPS and tardive dyskinesia, making them a generally better-tolerated treatment option (*Abou-Setta et al 2012, Lehman et al 2004, VA Pharmacy Benefits Management Services 2012, Clinical Pharmacology 2019*). However, certain atypical antipsychotic agents appear to have varying levels of risk according to the side effect profile (*Jibson et al 2017; Micromedex 2019*). The following factors may be considered when selecting certain agents in patients:
  - Metabolic syndrome – Metabolic effects influencing weight gain, glycemic effects, and lipid profiles have been reported to fluctuate with all atypical antipsychotics. Clozapine and olanzapine have been associated with the highest risks; aripiprazole, lurasidone, and ziprasidone have been associated with lower risks. Despite the stratified risks, routine monitoring of metabolic measures is recommended for patients on all antipsychotics.
  - EPS or tardive dyskinesia – Atypical antipsychotics have a lower risk of these side effects compared to typical antipsychotic agents. Tardive dyskinesia risks have been reported to be similar to the prevalence of EPS. Risperidone has been associated with a higher risk of EPS (up to 25% in adults); clozapine and quetiapine carry the lowest risk.
  - Anticholinergic effects – Anticholinergic side effects include dry mouth, constipation, blurred vision, and urinary retention. Clozapine has the strongest affinity for muscarinic receptors among the agents in this class review; therefore, anticholinergic side effects are reported most often. This is followed by olanzapine and quetiapine.
  - QT prolongation – QT prolongation has been reported with a number of atypical antipsychotic agents, but to a lesser degree than other classes of medications. Iloperidone and ziprasidone have been reported to prolong the QT interval (average increase in QTc of 9 to 10 msec) most often, and should be avoided in high risk patients. Those less likely to cause cardiac arrhythmias include aripiprazole, lurasidone, and cariprazine; however, very few studies have been conducted with lurasidone and cariprazine.
  - Myocarditis and cardiomyopathy – Clozapine has been associated with fatal cases, often within the first few months of treatment.
  - Orthostatic hypotension and tachycardia – Changes in heart rate and blood pressure are most frequently observed with clozapine (9% to 25%) and iloperidone (3% to 12%). In pediatric patients, quetiapine has been associated with increased systolic/diastolic pressure in 15% to 41% of patients, but in adults orthostatic hypotension and tachycardia have been reported in up to 7% of patients. Tachycardia has been reported in up to 16% of paliperidone-treated adult patients. Hypotension has been reported less frequently with aripiprazole, asenapine, brexpiprazole, cariprazine, lurasidone, and pimavanserin. However, fewer studies have been conducted with the newer agents.
  - Seizure – All atypical antipsychotics carry a risk for seizures; however, this appears to be associated with lowering the seizure threshold vs new-onset seizures. Incidences of seizure are most often reported with clozapine (3% to 5%), and to a lesser degree risperidone (0.3%).
  - Prolactin levels and sexual side effects – Elevations of prolactin have been most associated with risperidone and paliperidone. This is particularly concerning in pediatric patients as it is associated with changes in estrogen and testosterone levels and may result in gynecomastia and menstrual disturbances. In pediatric patients administered risperidone, hyperprolactinemia has been reported in 49% to 87% of patients versus adults in which incidences range from 1% to 4% depending on formulation (IM or oral routes). Abnormal prolactin levels have also been associated

with sexual dysfunction, infertility and galactorrhea. Of the atypical antipsychotics that are well studied, prolactin abnormalities are less frequently reported with olanzapine and ziprasidone. For patients in which sexual dysfunction is a concern, a number of MAs have referred to aripiprazole as the drug of choice (*Serretti et al 2011*).
  - Sedation – Clozapine is most associated with sedation (46%), followed by olanzapine (20% to 52%) and quetiapine (18% to 57%). In this class, aripiprazole is unique as insomnia was reported in ≥ 10% of adult patients, but somnolence/fatigue and insomnia were reported in ≥ 10% of pediatric patients.
  - Agranulocytosis – Agranulocytosis, leukopenia, and neutropenia are associated with use of clozapine. Within the first few months of treatment, this is particularly evident in patients with pre-existing low blood counts or those who had prior drug-induced blood dyscrasias.
  - Hypersensitivity – Olanzapine and ziprasidone have a specific warning for a fatal drug reaction with eosinophilia and systemic symptoms or DRESS. Asenapine has a warning for hypersensitivity reactions.
- Cariprazine, has demonstrated safe and effective use in doses ≤ 6 mg/day for the treatment of bipolar disorder or schizophrenia in short-term adult trials (*Calabrese et al 2015, Durgam et al 2015[a], Durgam et al 2014, Durgam et al 2015[b], FDA/CBER summary review 2015, Kane et al 2015[b], Sachs et al 2015*). The most common adverse events with treatment are EPS and akathisia. The clinical implications of the long half-life have not been well characterized and some experts have cited safety concerns associated with the accumulating active metabolite. One 72-week (N = 264) and one 48-week (N = 97) extension trial in patients with schizophrenia have demonstrated comparable results to short-term trials of 6 weeks. Patients who are able to persist on treatment maintained efficacy and tolerability at cariprazine doses of 1.5 mg to 9 mg daily during maintenance therapy (*Durgam et al 2016, Durgam et al 2017*).
- For the treatment of Tourette's disorder, aripiprazole has demonstrated safe and effective use compared to placebo in trials of 8 to 10 weeks in pediatric patients aged ≥ 6 years. Adverse events most frequently observed included sedation-like effects, nausea, headache, nasopharyngitis, and increased appetite (*Abilify prescribing information 2018*, *Gulisano et al 2011, Yoo et al 2013*).
- For the treatment of irritability associated with autism, one small, low quality study (N = 59) compared the effects of aripiprazole and risperidone in patients aged 4 to 18 years over a period of 8 weeks, although FDA-approval stipulates therapy should be initiated for ages 5 to 6 years. No differences were detected in terms of safety or efficacy; however, the ABC-I scores numerically favored risperidone (p = 0.06) (*Ghanizadeh et al 2014*). Both agents have demonstrated safe and effective use in PC trials (*Marcus et al 2009, McCracken et al 2002, Owen et al 2009, Shea et al 2004, McDougle et al 2005*). Based on current data, both agents appear to have similar efficacy and safety.
- For the treatment of PD psychosis, pimavanserin has demonstrated safe and effective use compared to placebo. Pimavanserin was associated with a significantly lower incidence of orthostatic hypotension *(Cummings et al 2014, Yasue et al 2016, Bozymski et al 2017).*
- For the treatment of MDD, aripiprazole, brexpiprazole, and quetiapine ER have demonstrated effectiveness when combined with adjunctive treatment, generally in trials with a 6-week duration and combined with an SSRI or SNRI. Olanzapine/fluoxetine (Symbyax) has also demonstrated effectiveness in treatment-resistant depression. Most studies have been PC trials. Brexpiprazole is the newest agent to be FDA approved; results from RCTs and an MA demonstrate efficacy vs placebo, and the safety profile appears to be similar to aripiprazole (*Thase et al 2015[a], Thase et al 2015[b]*, *Yoon et al 2017*). One MA found all agents were more effective than antidepressant monotherapy in improving response and remission rates, although adjunctive atypical antidepressant therapy was associated with a higher discontinuation rate due to adverse effects (*Wen et al 2014*). Another MA concluded aripiprazole and quetiapine may have an advantage in reducing remission (NNT, 9) compared to olanzapine/fluoxetine (NNT, 19) (*Spielmans et al 2013*). More well-designed, head-to-head trials are needed to validate conclusions. Treatment was associated with several medication-specific adverse events, including akathisia (aripiprazole), sedation (quetiapine, olanzapine/fluoxetine, and aripiprazole), abnormal metabolic laboratory results (quetiapine and olanzapine/fluoxetine), and weight gain (all drugs, especially olanzapine/fluoxetine).
- For the treatment of bipolar disorder, a number of atypical antipsychotics have demonstrated effective use for managing symptoms associated with manic or mixed episodes; however, only a few agents have demonstrated efficacy for depressive episodes. In adolescents and children, aripiprazole, olanzapine, olanzapine/fluoxetine, risperidone, quetiapine, and asenapine are FDA-approved for manic or mixed episodes, although only quetiapine and olanzapine/fluoxetine have been studied for depressive episodes. An AHRQ SR found that atypical antipsychotics decrease mania, decrease depression symptoms slightly, and improve symptom severity and global functioning to a small extent vs placebo. In addition, they probably increase response and remission rates vs placebo for manic/mixed phases (*Pillay et al 2017*). For depressive episodes, evidence is less clear, but point to efficacy with the FDA approved

agents (*Findling et al 2014, Detke et al 2015*). Support for use of atypical antipsychotics in adult patients with bipolar disorder has been demonstrated in several MAs (*Abou-Setta et al 2012, Muralidharan et al 2013, Lindström et al 2017*). Risperdal Consta (risperidone microspheres) and Abilify Maintena are the only long-acting injection agents in this class that have demonstrated safe and effective use (*Calabrese et al 2017, Macfadden et al 2009, Quiroz et al 2010, Vieta et al 2012, Yatham et al 2007*). Although only lurasidone, quetiapine (immediate- and extended-release), and olanzapine/fluoxetine have demonstrated efficacy for depressive episodes, MAs have concluded that olanzapine/fluoxetine may be the optimal treatment compared to other treatment options for depressive episodes (*Fornaro et al 2016, Silva et al 2013, Taylor et al 2014, Vieta et al 2010*).

- For the treatment of schizophrenia, MAs evaluating the roles of available atypical antipsychotics in the treatment of schizophrenia suggest that all agents are significantly more effective than placebo. Most analyses and studies have demonstrated that with the exception of clozapine, the atypical antipsychotics do not separate out robustly from the typical antipsychotics with respect to overall efficacy and times to treatment discontinuation. The trends for respective efficacy suggest that clozapine, olanzapine, and risperidone may be more effective agents based on relapse and remission rates compared to typical antipsychotics or placebo; however, many atypical antipsychotics haven't been studied to the same extent as these agents. In general, due to high attrition rates in trials, validity is limited, thereby making it difficult to make strong conclusions (*Abou-Setta et al 2012, Asenjo Lobos et al 2010, Asmal et al 2013, Cipriani et al 2011, Citrome et al 2009, Durgam et al 2014, Durgam et al 2015[b], Glick et al 2011, Jones et al 2010, Kane et al 2015[b], Khanna et al 2014, Klemp et al 2011, Komossa et al 2009[a], Komossa et al 2010[a], Komossa et al 2009[b], Komossa et al 2010[b], Komossa et al 2011, Kumar et al 2013, Leucht et al 2009[a], Leucht et al 2009[b], Leucht et al 2013, Lieberman et al 2005, Pagsberg et al 2017, Perlis et al 2006[b], Pillay et al 2017, Riedel et al 2010, Stroupe et al 2006, Stroupe et al 2009, Tarr et al 2011, Vieta et al 2010, Yildiz et al 2011*).
- The use of these agents for the treatment of schizophrenia is recognized by national and international guidelines as a mainstay in therapy. Guidelines vary by indication and the following outlines use in children, adolescents, and adults:

Adults

- Bipolar disorders – Guidelines recommend the use of drugs such as lithium, anticonvulsants and/or antipsychotics for the treatment of bipolar disorders (*Hirschfeld et al 2002, Hirschfeld et al 2005, VA/DoD 2010*).
  - Drugs likely to be beneficial for bipolar mania include lithium, anticonvulsants (eg, valproate, carbamazepine), and atypical antipsychotics. Lithium or valproate may be combined with an atypical antipsychotic.
  - Treatment options for bipolar depression include lithium, lamotrigine, and certain atypical antipsychotics (eg, quetiapine, olanzapine in combination with fluoxetine, and lurasidone).
- MDD – In general, guidelines state that no particular antidepressant agent is superior to another in efficacy or time to response. Choice can be guided by matching patient's symptoms to side effect profile, presence of medical and psychiatric comorbidity, and prior response (*VA/DoD 2016*, *Gelenberg et al 2010*).
  - For the majority of patients, an SSRI, SNRI, bupropion or mirtazapine is optimal for first-line treatment. Atypical antipsychotics may be useful to augment antidepressant therapy (*Gelenberg et al 2010*).
- Schizophrenia – Guidelines recommend that agents should be chosen based on clinical circumstances and side effects. Clozapine has the greatest efficacy on persistent hostility, aggressive behavior, suicidal behavior, and should be considered in patients with suicidal ideation; recent evidence has also demonstrated there may be lower rates of overall mortality with clozapine use. Clozapine should be used to treat persistent psychotic symptoms or treatment-resistant patients. A minimum of 6 weeks is needed for an adequate trial to establish efficacy. If a patient is non-adherent to treatment or has chronic relapse, a long-acting injectable antipsychotic agent may be considered (*Dixon et al 2009, Lehman et al 2004, VA Pharmacy Benefits Management Services 2012*).
- Parkinson's disease psychosis – The American Academy of Neurology Practice Parameter on the treatment of depression, psychosis, and dementia in PD states that clozapine should be considered for the treatment for PD and psychosis, quetiapine may be considered, and olanzapine should not be routinely considered (*Miyasaki 2006*).

Children and Adolescents

- Use of atypical antipsychotics - According to guidelines from the American Academy of Child and Adolescent Psychiatry (AACAP), prior to the initiation of antipsychotic therapy, patients should undergo a thorough diagnostic assessment and evaluation for comorbid medical conditions and concomitant medications. Furthermore, a multidisciplinary plan that includes education and psychotherapy should be established. The prescriber should also have a thorough discussion about the risks and benefits of psychotropic treatment (*Findling et al 2011*).
- Autism Spectrum Disorders (ASD) – AACAP guidelines state that pharmacotherapy may be considered in children with ASD when there is a specific target symptom or comorbid condition. Risperidone and aripiprazole are FDA-

approved for irritability associated with autism; other drugs that have been studied include: clonidine, olanzapine, valproic acid, lamotrigine, levetiracetam, clomipramine, amantadine, pentoxifylline (in combination with risperidone), and naltrexone (*Volkmar et al 2014*).
  - Bipolar disorder – According to AACAP guidelines for treatment of children and adolescents with bipolar disorder, pharmacotherapy is the primary treatment for bipolar mania. Standard therapy includes lithium, valproate, and/or atypical antipsychotic agents, with other adjunctive medications used as indicated (*McClellan et al 2007*).
  - Schizophrenia – According AACAP guidelines, antipsychotics are a primary treatment for schizophrenia spectrum disorders in children and adolescents. The choice of agent is typically based on factors such as FDA-approval status, side effect profile, patient and family preference, and cost (*McClellan et al 2013*).
  - Tourette's disorder– According to AACAP guidelines for the treatment of children and adolescents with tic disorders, pharmacotherapy should be considered for moderate to severe tics causing severe impairment in quality of life, or when psychiatric comorbidities are present that can also be targeted. Most clinicians use atypical antipsychotics before first-generation agents and some prefer α-agonists over antipsychotic medications due to the adverse effect profile. Commonly used drugs include risperidone, aripiprazole, and clonidine (*Murphy et al 2013*).
- Pharmacologic therapy treatment is highly individualized and dependent on a number of patient characteristics and response to treatment. In certain patient groups, such as pediatric patients, liquid formulations are useful for better dose-control, so clinicians may titrate and taper doses in those that may have sensitive responses to treatment. Agents with different chemical structures have different clinical responses and adverse events; therefore, access to the atypical antipsychotic medication class is important in order to tailor therapies to individual patients.

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Therapeutic Class Overview
Respiratory Beta-Agonist Combination Agents

INTRODUCTION

- Respiratory beta$_2$-agonist combination agents include a beta$_2$-agonist combined with an inhaled corticosteroid (ICS), inhaled anticholinergic, or both. Beta$_2$-agonists can be short-acting beta$_2$-agonists (SABA) or long-acting beta$_2$-agonists (LABA); most combinations contain a LABA. Similarly, inhaled anticholinergics, also known as muscarinic antagonists, can be short-acting muscarinic antagonists (SAMA) or long-acting muscarinic antagonists (LAMA); most combinations contain a LAMA.
- Individual beta$_2$-agonist combinations are Food and Drug Administration (FDA) approved for the treatment of asthma, chronic obstructive pulmonary disease (COPD), or both.
  - All combinations of a beta2-agonist and an ICS are indicated for the treatment of asthma, and some are additionally indicated for the treatment of COPD.
  - Combinations of a beta$_2$-agonist and an anticholinergic medication are indicated for COPD, as is the one available triple combination agent (consists of LAMA/LABA/ICS).
  - Refer to Tables 2A, 2B, and 2C for specific indications for each product.
- Asthma is a chronic lung disease that inflames and narrows the airways. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing. Asthma affects people of all ages, but most often starts during childhood. In the United States (U.S.), about 25 million people (8.2%) are known to have asthma, including about 9.6% of children (*National Heart, Lung, and Blood Institute [NHLBI] 2019*, *Centers for Disease Control and Prevention [CDC] 2011*).
- COPD is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities. The abnormalities are usually caused by exposure to noxious particles or gases, and cigarette smoking is a key risk factor. Airflow limitation is caused by a combination of small airway disease (eg, obstructive bronchiolitis) and parenchymal destruction (emphysema). The most common symptoms of COPD include dyspnea, cough, and sputum production (*Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2019*). COPD affects 6.4% of the U.S. population and is a major contributor to mortality from chronic lower respiratory diseases, the third leading cause of death in the U.S. (*CDC 2018*).
- Medispan class/subclass: Sympathomimetics/Adrenergic Combinations

Table 1. Medications Included Within Class Review*

Drug	Generic Availability
Beta$_2$-agonist & corticosteroid combinations	
Advair Diskus & Advair HFA (fluticasone propionate/salmeterol)	✔ ‡
AirDuo RespiClick (fluticasone propionate/salmeterol)	✔ †
Breo Ellipta (fluticasone furoate/vilanterol)	-
Dulera (mometasone furoate/formoterol fumarate dihydrate)	-
Symbicort (budesonide/formoterol fumarate dihydrate)	-
Wixela Inhub (fluticasone propionate/salmeterol)	✔ ‡
Beta$_2$-agonist & anticholinergic combinations	
Anoro Ellipta (umeclidinium/vilanterol)	-
Bevespi Aerosphere (glycopyrrolate/formoterol fumarate)	-
Combivent Respimat (ipratropium/albuterol)	-
Duaklir Pressair (aclidinium/formoterol fumarate)	-
ipratropium/albuterol solution	✔
Stiolto Respimat (tiotropium/olodaterol)	-
Utibron Neohaler (glycopyrrolate/indacaterol)	-
Triple combination	

Drug	Generic Availability
Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol)	-

* Branded product DuoNeb is no longer marketed.
† Authorized generic
‡Wixela Inhub is the generic of Advair Diskus

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2A. FDA-Approved Indications for Beta$_2$-agonist/Corticosteroid Combination Agents

Indication	Advair Diskus	Advair HFA	AirDuo Respi-Click	Breo Ellipta	Dulera	Sym-bicort	Wixela Inhub
Treatment of asthma	✔ (age ≥ 4 years)	✔ (age ≥ 12 years)	✔ (age ≥ 12 years)	✔ (age ≥ 18 years)	✔ (age ≥ 12 years)	✔ (age ≥ 6 years)	✔ (age ≥ 4 years)
Maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema	✔ (250/50 strength only)			✔ (100/25 strength only)		✔ (160/4.5 strength only)	✔ (250/50 strength only)
To reduce exacerbations of COPD in patients with a history of exacerbations	✔ (250/50 strength only)			✔ (100/25 strength only)		✔ (160/4.5 strength only)	✔ (250/50 strength only)

(*Prescribing information: Advair HFA 2019, Advair Diskus 2019, AirDuo RespiClick 2018, Breo Ellipta 2019, Dulera 2019, Symbicort 2017, Wixela Inhub 2019*)

Table 2B. FDA-Approved Indications for Beta$_2$-agonist/Anticholinergic Combination Agents

Indication	Anoro Ellipta	Bevespi Aerosphere	Com-bivent Respimat	Duaklir Pressair	ipratropium/ albuterol solution	Stiolto Res-pimat	Utibron Neohaler
Long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema	✔						
Long-term, once-daily, maintenance treatment of patients with COPD						✔	
Long-term, twice-daily, maintenance treatment of airflow obstruction in patients with COPD		✔		✔			✔
For use in patients with COPD on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator			✔				
For the treatment of bronchospasm associated with COPD in patients requiring more than 1 bronchodilator					✔		

(*Prescribing information: Anoro Ellipta 2017, Bevespi Aerosphere 2017, Combivent Respimat 2016, Duaklir Pressair 2019, ipratropium/albuterol solution 2018, Stiolto Respimat 2019, Utibron Neohaler 2017*)

Table 2C. FDA-Approved Indication for Triple Combination Agent

Indication	Trelegy Ellipta
For the long-term, once-daily, maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema. Trelegy Ellipta is also indicated to reduce exacerbations of COPD in patients with a history of exacerbations.	✔

(*Trelegy Ellipta prescribing information 2019*)

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Beta$_2$-agonist/corticosteroid combinations for asthma and COPD

Comparisons to placebo, monotherapy, combined use of individual components, varied treatments, or usual care:

- Numerous trials have compared the combination ICS/LABA products to their respective individual components as monotherapy, and in general, results have demonstrated that administration of the combination product is more effective than monotherapy for improving lung function and/or achieving control of symptoms in asthma and COPD (*Bateman et al 2001, Bateman et al 2004, Bateman et al 2006, Bateman et al 2014, Bateman et al 2018, Berger et al 2010, Bernstein et al 2015, Bleecker et al 2014, Calverley et al 2003, Corren et al 2007, Eid et al 2010, FDA AirDuo RespiClick Medical Review 2017, Gappa et al 2009, Hanania et al 2003, Jenkins et al 2006, Kerwin et al 2009, Kerwin et al 2013, Kuna et al 2006, Lalloo et al 2003, Lundback et al 2006, Martinez et al 2013, Meltzer et al 2012, Morice et al 2007, Murphy et al 2008, Nathan et al 2006, Nelson et al 2003a, Noonan et al 2006, O'Byrne et al 2014, Pearlman et al 2004, Pearlman et al 2017, Pohl et al 2006, Raphael et al 2018, Rennard et al 2009, Rodrigo et al 2016, Rodrigo et al 2017, Sharafkaneh et al 2012, Sher et al 2017, Tal et al 2002, Tang et al 2019, Tashkin et al 2008, Vaessen-Verberne et al 2010, Vestbo et al 2005, Weinstein et al 2010*). Results for reducing COPD exacerbations have been inconsistent (*Dransfield et al 2013, Ohar et al 2014*).
- Although a synergistic effect of combination inhalers has been suggested by some data, overall there are similar efficacy between the administration of the combination ICS/LABA products and their individual components used in combination (*Chapman et al 1999, Jenkins et al 2006, Marceau et al 2006, Nelson et al 2003b, Noonan et al 2006, Perrin et al 2010, Rosenhall et al 2002*). Improved adherence with combination inhalers has also been suggested but not been shown conclusively (*Marceau et al 2006, Perrin et al 2010*).
- A large, double-blind, randomized trial (N = 6112) compared fluticasone propionate/salmeterol 500/50 mcg twice daily to its individual components and to placebo over a 3-year period in patients with COPD (*Calverley et al 2007*). The primary endpoint, time to death from any cause, for the combination vs placebo failed to reach statistical significance (12.6% vs 15.2%; p = 0.052). However, the difference in mortality between the combination therapy and fluticasone monotherapy did reach statistical significance (12.6% vs 16%; p = 0.007). Treatment with the combination regimen resulted in significantly fewer exacerbations, improved health status, and improved lung function compared with placebo.
- A large, double-blind, randomized trial (SUMMIT; N = 16,590) evaluated the use of fluticasone furoate/vilanterol vs fluticasone furoate alone, vilanterol alone, or placebo in a population of patients with moderate COPD and heightened cardiovascular risk (age ≥ 60 years and receiving medication for >2 of the following: hypercholesterolemia, hypertension, diabetes mellitus, or peripheral arterial disease) (*Vestbo et al 2016a*). Compared with placebo, there was no significant benefit or worsening in all-cause mortality with combination therapy (hazard ratio [HR], 0.88 [95% confidence interval (CI), 0.74 to 1.04; p = 0.137]) or with the components (fluticasone furoate HR, 0.91 [95% CI, 0.77 to 1.08; p = 0.284]; vilanterol HR, 0.96 [95% CI, 0.81 to 1.14; p = 0.655]). Composite cardiovascular events were also similar in the 4 groups (3.9% to 4.4%). All treatments reduced the risk of moderate to severe COPD exacerbations compared to placebo, with percent reductions of 29% (95% CI, 22 to 35), 12% (95% CI, 4 to 19), and 10% (95% CI, 2 to 18) in the fluticasone furoate/vilanterol, fluticasone furoate, and vilanterol groups, respectively.
- A 12-month, randomized, open-label trial (Salford Lung Study; N = 2799) compared the use of fluticasone furoate/vilanterol 100/25 mcg daily to continuation of usual care in a real-world patient population in the United Kingdom

(*Vestbo et al 2016b*). Enrolled patients had COPD, had had ≥ 1 exacerbations in the previous 3 years, and were taking regular maintenance inhaler therapy (≥ 1 long-acting bronchodilators; ICS alone or in combination with a long-acting bronchodilator; or a combination of ICS, LABA, and LAMA). The primary endpoint, the rate of moderate or severe exacerbations among patients who had had an exacerbation within 1 year before the trial, was 1.74 per year in the fluticasone furoate/vilanterol group and 1.90 per year in the usual-care group, for a difference of 8.4% (95% CI, 1.1 to 15.2; p = 0.02). Serious adverse events, including pneumonia, were similar between the 2 groups.

- A meta-analysis of 19 trials evaluated the use of ICS/LABA combinations compared to placebo in patients with COPD, and demonstrated a significant reduction in exacerbation rate between fluticasone propionate/salmeterol and placebo and between budesonide/formoterol and placebo (*Nannini et al 2013a*). For the number of patients who experienced ≥ 1 exacerbations, the differences between fluticasone propionate/salmeterol vs placebo and mometasone furoate/formoterol 200/10 mcg strength vs placebo were not statistically significant; however, the mometasone furoate/formoterol 400/10 mcg strength was associated with a lower proportion of patients experiencing ≥ 1 exacerbation. This meta-analysis also demonstrated that when results for all combined inhalers vs placebo were pooled, there was an overall reduction in mortality (odds ratio [OR], 0.82; 95% CI, 0.68 to 0.99).
- A meta-analysis of 14 trials evaluated the use of ICS/LABA combinations compared to use of the same LABA as monotherapy in patients with COPD (*Nannini et al 2012*). This analysis demonstrated that exacerbation rates were reduced with ICS/LABA combination therapy compared to LABA monotherapy (rate ratio, 0.76; 95% CI, 0.68 to 0.84). However, there was a significant increase in the incidence of pneumonia with combination therapy compared to LABA monotherapy (OR, 1.55; 95% CI, 1.2 to 2.01).
- A meta-analysis of 15 trials evaluated the use of ICS/LABA combinations compared to use of ICS monotherapy in patients with COPD (*Nannini et al 2013b*). This analysis demonstrated that exacerbation rates were significantly reduced with ICS/LABA combination therapy vs ICS monotherapy (rate ratio, 0.87; 95% CI, 0.80 to 0.94). Adverse events were similar between treatments; pneumonia rates as diagnosed by chest x-ray were lower than those reported in earlier trials.
- A meta-analysis of 14 trials (total N = 6641) compared fluticasone furoate/vilanterol to placebo, fluticasone furoate monotherapy, fluticasone propionate monotherapy, vilanterol monotherapy, or fluticasone propionate/salmeterol in patients with asthma (*Dwan et al 2016*). Primary endpoints included health-related quality of life (HRQoL) and severe asthma exacerbations (defined by hospital admission or treatment with oral corticosteroids). Fewer than half of the studies reported on these primary endpoints, and there were few opportunities to combine results from the included studies. One of the 14 studies evaluated HRQoL (as measured by the Asthma Quality of Life Questionnaire [AQLQ]) for fluticasone furoate/vilanterol 100/25 mcg vs placebo; it identified a significant advantage of fluticasone furoate/vilanterol (mean difference, 0.30; 95% CI, 0.14 to 0.46). Two studies compared fluticasone furoate/vilanterol 100/25 mcg vs placebo with respect to exacerbations; both studies reported no exacerbations in either treatment arm. No comparisons relevant to the primary outcomes were found for fluticasone furoate/vilanterol at a higher dose (200/25 mcg) vs placebo. There was insufficient evidence to assess whether once-daily fluticasone furoate/vilanterol had better or worse safety or efficacy compared to twice-daily fluticasone propionate/salmeterol. The authors stated that firm conclusions could not be drawn due to the limited number of studies, variety of endpoints, and short duration of most trials.
- Several large studies focused primarily on safety endpoints, with efficacy endpoints as secondary (*Peters et al 2016, Stempel et al 2016a, Stempel et al 2016b*). The studies compared the use of ICS/LABA combinations to ICS monotherapy in patients with asthma. These studies each demonstrated non-inferiority of the ICS/LABA combination to ICS monotherapy for the risk of serious asthma-related events, offering reassurance for the safety of these agents.
  - A randomized, double-blind study (AUSTRI; N = 11,679) enrolled adults and adolescents (age ≥ 12 years) with persistent asthma and a history of exacerbation within the previous year (*Stempel et al 2016a*). Patients were randomized to receive fluticasone propionate/salmeterol or fluticasone propionate monotherapy for 26 weeks. Patients were stratified by their baseline asthma control questionnaire (ACQ)-6 score and current asthma medication to determine the fluticasone propionate dose (100, 250, or 500 mcg twice daily) and were randomized to receive this dose with or without concomitant salmeterol.
    - The primary safety endpoint was the first serious asthma-related event, a composite endpoint that included death, endotracheal intubation, and hospitalization. There were 36 events in 34 patients in the fluticasone propionate/salmeterol group and 38 events in 33 patients in the fluticasone propionate group (HR, 1.03; 95% CI, 0.64 to 1.66). Fluticasone propionate/salmeterol was shown to be non-inferior to fluticasone propionate for this endpoint. There were no asthma-related deaths.

- The main efficacy endpoint was the first severe asthma exacerbation, defined as asthma deterioration leading to the use of systemic glucocorticoids for ≥ 3 days or an asthma-related hospitalization or emergency department visit leading to the use of systemic glucocorticoids. At least 1 severe asthma exacerbation was reported in 480 patients (8%) in the fluticasone propionate/salmeterol group and in 597 patients (10%) in the fluticasone propionate group (HR, 0.79; 95% CI, 0.70 to 0.89; p < 0.001).

- A similarly designed trial (VESTRI; N = 6208) enrolled pediatric patients 4 to 11 years of age (*Stempel et al 2016b*). Enrolled patients had a history of exacerbation within the previous year and consistent use of asthma medication during the 4 weeks before enrollment. Patients were randomized, on the basis of pretrial medication, Childhood Asthma Control Test (C-ACT) score, and exacerbation history, to receive fluticasone propionate/salmeterol 100/50 mcg or 250/50 mcg or fluticasone propionate alone 100 mcg or 250 mcg twice daily for 26 weeks.
  - The primary safety endpoint, the first serious asthma-related event (death, intubation, or hospitalization), occurred in 27 patients in the fluticasone propionate/salmeterol group and 21 patients in the fluticasone propionate group (HR, 1.28; 95% CI, 0.73 to 2.27); this demonstrated non-inferiority for fluticasone propionate/salmeterol compared to fluticasone propionate (p = 0.006). All of the events were asthma-related hospitalizations; there were no deaths or asthma-related intubations in either group.
  - The primary efficacy endpoint was the first severe asthma exacerbation, defined as asthma deterioration leading to the use of systemic glucocorticoids for ≥ 3 days or a depot injection of glucocorticoids. One or more severe asthma exacerbations occurred in 8.5% of patients in the fluticasone propionate/salmeterol group and 10.0% of patients in the fluticasone propionate group (HR, 0.86; 95% CI, 0.73 to 1.01).
- An additional randomized, double-blind trial (N = 11,693) compared the safety of formoterol/budesonide to budesonide alone in patients ≥ 12 years of age (*Peters et al 2016*). Enrolled patients were receiving daily asthma medication and had had ≥ 1 exacerbation in the previous year. Patients were stratified to a dose level of budesonide on the basis of asthma control and prior treatment. Patients were then randomized to receive budesonide/formoterol (2 actuations of 80/4.5 mcg or 160/4.5 mcg) or budesonide alone (2 actuations of 80 mcg or 160 mcg) twice daily for 26 weeks.
  - The primary safety endpoint, the first serious adverse event (death, intubation, or hospitalization), occurred in 43 of 5,846 patients receiving budesonide/formoterol and 40 of 5,847 patients receiving formoterol alone (HR, 1.07; 95% CI, 0.70 to 1.65); this demonstrated non-inferiority for budesonide/formoterol vs budesonide alone. Two of the events (both in the budesonide/formoterol group) were asthma-related deaths; the remaining events were asthma-related hospitalizations.
  - The primary efficacy endpoint, the first asthma exacerbation (defined as a deterioration of asthma requiring systemic glucocorticoids for ≥ 3 days, inpatient hospitalization for asthma, or an emergency department visit for asthma that resulted in receipt of systemic glucocorticoids) occurred in 9.2% of patients in the budesonide/formoterol group and 10.8% of patients in the budesonide group (HR, 0.84; 95% CI, 0.74 to 0.94).
- A trial of 4215 patients ≥ 12 years of age with mild asthma found that budesonide/formoterol as needed was noninferior to budesonide twice daily for the reduction of severe asthma exacerbation. The annualized rate of severe exacerbations was 0.11 (95% CI, 0.10 to 0.13) and 0.12 (95% CI, 0.10 to 0.14), respectively (rate ratio, 0.97; upper one-sided 95% confidence limit, 1.16) However, budesonide/formoterol was inferior to budesonide for symptom control as the change in ACQ-5 score showed a difference of 0.11 units (95% CI, 0.07 to 0.15) in favor of budesonide maintenance therapy (*Bateman et al 2018*).

Comparisons between different ICS/LABA combinations

- There are some data available comparing different combination ICS/LABA products for the treatment of COPD.
  - One crossover study comparing budesonide/formoterol to fluticasone propionate/salmeterol demonstrated no significant difference between products for the primary endpoint, the increase from baseline in peak expiratory flow 5 minutes after the morning dose (*Partridge et al 2009*). However, the mean morning forced expiratory volume in 1 second (FEV_1) improved more with budesonide/formoterol at 5 minutes and 15 minutes post-dose compared to fluticasone propionate/salmeterol.
  - Several published trials compared fluticasone furoate/vilanterol to fluticasone propionate/salmeterol in patients with COPD. Three of the trials were published together; pooled results demonstrated a greater improvement with fluticasone furoate/vilanterol 100/25 mcg once daily compared to fluticasone propionate/salmeterol 250/50 mcg twice daily on the primary endpoint, the weighted mean (wm) FEV_1 (0 to 24 hr) (*Dransfield et al 2014*). However, 2 of these 3 trials did not demonstrate a significant difference on this endpoint. An additional trial compared fluticasone furoate/vilanterol 100/25 mcg daily to fluticasone propionate/salmeterol 500/50 mcg twice daily, and found no significant difference between groups on the wm FEV_1 (0 to 24 hr) (*Agusti et al 2014*).

- There have been several trials comparing combination ICS/LABA products to one another for the treatment of asthma.
  - Several head-to-head trials have compared budesonide/formoterol to fluticasone propionate/salmeterol. The trials varied in their design and the doses of medications. In general, these head-to-head trials have failed to demonstrate that one product is consistently superior to the other. Some trials showed benefits for fluticasone propionate/salmeterol on some endpoints (*Dahl et al 2006, Fitzgerald et al 2005, Price et al 2007*); some showed benefits for budesonide/formoterol (*Aalbers et al 2004, Palmqvist et al 2001*), and another showed no significant differences between the 2 products (*Busse et al 2008*).
  - A meta-analysis of 5 trials comparing fluticasone propionate/salmeterol 250/50 mcg twice daily vs varied doses of budesonide/formoterol twice daily failed to demonstrate significant differences in exacerbations, asthma-related serious adverse events, FEV_1, rescue medication use, symptom scores, or peak expiratory flow (*Lasserson et al 2011*).
  - A head-to-head trial comparing mometasone/formoterol to fluticasone propionate/salmeterol demonstrated non-inferiority for mometasone/formoterol for the primary endpoint of FEV_1 area under the curve (AUC) (0 to 12 hr) (*Bernstein et al 2011*). Treatment with mometasone/formoterol demonstrated a rapid onset of action, with significantly greater effects on FEV_1 at all time points up to 30 minutes post-dose compared to fluticasone propionate/salmeterol. Other secondary endpoints were not significantly different between groups.
  - A head-to-head trial comparing fluticasone furoate/vilanterol 100/25 mcg daily to fluticasone propionate/salmeterol 250/50 mcg twice daily demonstrated no significant differences between treatments on the primary endpoint, the wm FEV_1 (0 to 24 hr) (*Woodcock et al 2013*). There were also no significant differences in key secondary endpoints, including the time to onset of bronchodilator effect, percentage of patients obtaining ≥ 12% and ≥ 200 mL increase from baseline in FEV_1 at 12 hours and 24 hours, and change from baseline in trough FEV_1. Another trial comparing fluticasone furoate/vilanterol with fluticasone propionate/salmeterol demonstrated noninferiority of fluticasone furoate/vilanterol to fluticasone propionate/salmeterol in evening trough FEV_1 at week 24 (*Bernstein et al 2018*).

<u>ICS/LABA compared to tiotropium or in combination with tiotropium for COPD</u>

- A double-blind, double-dummy, 2-year trial (N = 1323) compared the use of fluticasone propionate/salmeterol 250/50 mcg twice daily to tiotropium 18 mcg daily in patients with COPD (*Wedzicha et al 2008*). This trial demonstrated no significant difference between groups in the rate of exacerbations or post-dose FEV_1. The study demonstrated higher mortality in the tiotropium group (6%) compared to the fluticasone propionate/salmeterol group (3%). This study was limited by the high number of withdrawals, which were unevenly distributed between the study arms.
- A double-blind, double-dummy, 12-week trial (N = 494) compared the use of umeclidinium/vilanterol 62.5/25 mcg daily to tiotropium 18 mcg daily in patients with COPD who had been treated with tiotropium monotherapy at the time of enrollment (*Kerwin et al 2017a*). The primary endpoint, trough FEV_1, showed improved efficacy in the group that stepped up to combination therapy, with a between-group difference of 88 mL (95% CI, 45 to 131; $p < 0.001$). Improvements with umeclidinium/vilanterol were also observed in some secondary endpoints, including the use of rescue medication use and transition dyspnea index (TDI) score.
- A double-blind, double-dummy, 12-week trial (N = 623) evaluated the use of fluticasone furoate/vilanterol 100/25 mcg daily and tiotropium 18 mcg daily in patients with moderate-to-severe COPD and an increased cardiovascular risk (*Covelli et al 2016*). There was no significant difference in the primary endpoint, the change from baseline in wm FEV_1 (0 to 24 hr). Minor differences were noted in some secondary efficacy endpoints and in the safety profiles. Pneumonia occurred more frequently in the fluticasone furoate/vilanterol group, and 2 patients in the tiotropium group died following cardiovascular events. The duration of this trial was not long enough to allow any firm conclusions about the relative efficacy and safety of fluticasone furoate/vilanterol vs tiotropium.
- In a Cochrane review that included the *Covelli et al 2016* trial and 1 additional 12 week trial comparing tiotropium to fluticasone furoate/vilanterol (N = 880 across both trials), there were no differences between treatments when considering the following outcomes: mortality, COPD exacerbation, pneumonia, St. George's respiratory questionnaire (SGRQ) score, hospital admissions, or use of rescue medication (*Sliwka et al 2018*).
- Several trials have evaluated the potential benefits of adding a combination ICS/LABA to tiotropium vs the use of tiotropium alone in patients with COPD. These trials generally demonstrated an improvement in FEV_1 and some other lung function, symptom score, and quality-of-life endpoints (*Hanania et al 2012, Lee et al 2016, Rojas-Reyes et al 2016, Welte et al 2009*). Some trials (*Lee et al 2016, Welte et al 2009*) also demonstrated a reduction in the risk of COPD exacerbations or severe exacerbations; however, other trials and a meta-analysis have not confirmed a significant benefit for exacerbations (*Aaron et al 2007, Hanania et al 2012, Karner et al 2011, Rojas-Reyes et al 2016*).

Beta$_2$-agonist/anticholinergic combinations for COPD

Comparisons of combination beta$_2$-agonist/anticholinergic products to bronchodilator monotherapy:

- Numerous trials have compared the combination beta$_2$-agonist/anticholinergic products to their respective individual components as monotherapy, and in general, results have demonstrated that administration of the combination product is more effective than monotherapy for improving lung function and/or achieving control of symptoms in COPD (*Bateman et al 2015*, *Beeh et al 2015, Bone et al 1994, Buhl et al 2015, Decramer et al 2014, Donohue et al 2013, Dorinsky et al 1999, D'Urzo et al 2014, Friedman et al 1999, Hanania et al 2017, Mahler et al 2015, Martinez et al 2017, Sethi et al 2019, Singh et al 2014*).
- A randomized Phase 3 study of patients with COPD (N = 1594) found that twice-daily aclidinium/formoterol improved lung function compared to once-daily tiotropium by week 24 (*Sethi et al 2019*).
- A Cochrane review (N = 7 trials; 5921 participants) found an improvement in dyspnea, lung function, and number of responders with fixed-dose aclidinium/formoterol compared to monotherapy with individual agents or placebo in patients with stable COPD. However, no significant differences in exacerbations, hospital admissions, mortality, and adverse events were found with fixed-dose aclidinium/formoterol compared to aclidinium, formoterol, or placebo monotherapy (*Ni et al 2018*).
- A large, randomized-controlled trial (N = 7880) of patients with COPD and a history of exacerbations did not find a difference in the rate of exacerbations between LAMA/LABA therapy with tiotropium/olodaterol vs LAMA therapy with tiotropium (relative risk [RR], 0.93; 99% CI, 0.85 to 1.02; p = 0.0498) (*Calverley et al 2018*).
- A systematic review of 23 studies of beta$_2$-agonist/anticholinergic combinations compared to their monocomponents and to other single-agent treatments in patients with COPD was conducted (*Price et al 2016*). The analysis demonstrated that beta$_2$-agonist/anticholinergic combinations significantly improved lung function compared to their individual components. These combinations generally improved other outcomes compared to monotherapies as well, including symptoms and health status, but there were some discrepancies between lung function results and these patient-reported outcomes.
- A systematic review and network meta-analysis (N = 74 trials; 74,832 participants) evaluated the efficacy of SAMAs, LABAs, LAMA/LABAs and LABA/ICSs for maintenance treatment of COPD. At 12 and 24 weeks, LAMA, LAMA/LABAs, and LABA/ICSs led to a significantly greater improvement in trough FEV_1 compared with placebo and SAMA monotherapy. With the exception of aclidinium/formoterol, all other LAMA/LABA therapies were superior to LAMA monotherapy and LABA/ICS therapy in improving trough FEV_1. Furthermore, LAMA/LABA therapy had the highest probability of being the best treatment for in FEV_1 improvement; similar trends were observed for the transition dyspnea index and SGRQ scores. Authors concluded that there were no significant differences among the LAMAs and LAMA/LABAs within their respective classes (*Aziz et al 2018*).
- A systematic review and meta-analysis (N = 8 trials) compared tiotropium 5 or 18 mcg with LAMA/LABA therapy in patients with moderate-to-severe COPD; ICS therapy was also allowed and use ranged from 33.7% to 54.4% among included trials. Therapy with LABA/LAMA was superior to tiotropium monotherapy for all of the following outcomes at 12 and 24 weeks: FEV_1 peak and trough, SGRQ responder rate, mean SGRQ score, and use of rescue medication. At 12 weeks, LABA/LAMA improved FEV_1 trough by 63 ml compared to tiotropium alone (95% CI, 39.2 to 86.8; $p < 0.01$). During the same time period, LABA/LAMA improved mean SGRQ responder rate by 19% (RR, 1.19; 95% CI, 1.09 to 1.28; $p < 0.01$) and reduced SGRQ total score by 1.87 points (95% CI, -2.72 to -1.02; $p < 0.01$) compared to tiotropium (*Han et al 2018).*

Comparisons of combination beta$_2$-agonist/anticholinergic products to each other or to other bronchodilator combinations

- Two head-to-head trials between different LAMA/LABA combinations have been published.
  - An 8-week, open-label, crossover trial compared umeclidinium/vilanterol and tiotropium/olodaterol in 236 patients with COPD (*Feldman et al 2017*). The primary endpoint, change from baseline in trough FEV_1, was shown to be greater for umeclidinium/vilanterol, with a difference of 52 mL (95% CI, 28 to 77; $p < 0.001$ for superiority in the intention-to-treat population). Effects on secondary endpoints were mixed, with umeclidinium/vilanterol demonstrating a small improvement in rescue medication use but no significant differences in COPD Assessment Test (CAT) scores (a health status questionnaire) or EXACT Respiratory Symptoms (E-RS) scores at most weekly assessments.
  - Two 12-week, double-blind, crossover trials compared glycopyrrolate/indacaterol to umeclidinium/vilanterol in a total of 712 patients with COPD (*Kerwin et al 2017b*). The primary endpoint, FEV_1 AUC (0 to 24 hr), was similar between treatment arms in both studies, with differences for glycopyrrolate/indacaterol vs umeclidinium/vilanterol of -11.5 mL

(95% CI, -26.9 to 3.8) and -18.2 mL (95% CI, -34.2 to -2.3) in Studies 1 and 2, respectively. Although the trials failed to demonstrate noninferiority of glycopyrrolate/indacaterol to umeclidinium/vilanterol due to the noninferiority margin used in the study methodology, the differences between treatments were not considered clinically meaningful.

- A 12-week, non-inferiority, randomized, double-blind, triple-dummy, parallel group study (N = 967) compared umeclidinium/vilanterol (62.5/25 mcg once daily) to tiotropium (18 mcg once daily) plus indacaterol (150 mcg once daily) (*Kalberg et al 2016*). When comparing trough FEV_1 on day 85, umeclidinium/vilanterol demonstrated non-inferiority to combination treatment with tiotropium and indacaterol. Other measures, including rescue medication use, TDI focal scores, and SGRQ scores, were also similar between both treatment groups on day 85 (p values not provided).
- A meta-analysis of 26 randomized controlled trials comparing the efficacy of umeclidinium/vilanterol, indacaterol/glycopyrrolate, formoterol plus tiotropium, salmeterol plus tiotropium, or indacaterol plus tiotropium to tiotropium alone found that umeclidinium/vilanterol was comparable to other LAMA/LABA fixed-dose combination agents with respect to trough FEV_1, SGRQ scores, TDI focal scores, and need for rescue medication use (*Huisman et al 2015*).
- Three systematic reviews/meta-analyses compared various LAMA/LABA combinations (*Calzetta et al 2016, Schlueter et al 2016, Sion et al 2017*). Limitations to these analyses included the fact that trials evaluated some formulations/dose regimens not available in the U.S., and comparisons between different combinations were based on indirect data.
  - Overall, these meta-analyses demonstrated that all LAMA/LABA combinations showed improved lung function vs monocomponents, with few differences among products across lung function and patient-reported endpoints.
  - The analysis by *Sion et al* noted that both glycopyrrolate/indacaterol and umeclidinium/vilanterol appeared to improve lung function to a greater extent than tiotropium/olodaterol at 12 weeks, with differences in trough FEV_1 of 52 mL (95% credible interval [CrI], 18 to 86) and 38 mL (95% CrI, 13 to 63), respectively.
  - The *Schlueter et al* meta-analysis included 27 trials (N = 30,361) including 4 LAMA/LABA fixed-dose combination agents (aclidinium/formoterol 400/12 mcg [not FDA approved for use in the U.S.], glycopyrrolate/indacaterol 110/50 mcg, tiotropium/olodaterol 5/5 mcg, and umeclidinium/vilanterol 62.5/25 mcg), and showed non-significant differences in efficacy, exacerbations, and discontinuation rates (*Schlueter et al 2016*). Safety profiles were also similar among the products.

ICS/LABA compared to LAMA/LABA combinations for COPD

- A randomized, double-blind, 12-week trial (N = 717) compared umeclidinium/vilanterol 62.5/25 mcg once daily to fluticasone propionate/salmeterol 500/50 mcg twice daily in patients with moderate to severe COPD and no exacerbations in the previous year (*Singh et al 2015*). It should be noted that the dose of fluticasone propionate was higher than what is recommended in the U.S. for treatment of COPD. Treatment with umeclidinium/vilanterol resulted in greater improvement in lung function than fluticasone propionate/salmeterol, with a difference of 80 mL (95% CI, 46 to 113) in the wm FEV_1 (0 to 24 hr) and a difference of 90 mL (95% CI, 55 to 125) in trough FEV_1. Effects on rescue bronchodilator use, mean TDI focal score, and SGRQ total scores, and the incidence of adverse events, were similar between groups.
- Two randomized, double-blind, 12-week trials (N = 707 and N = 700; reported together) compared umeclidinium/vilanterol 62.5/25 mcg daily to fluticasone propionate/salmeterol 250/50 mcg twice daily in patients with moderate to severe COPD without exacerbations in the previous year (*Donohue et al 2015*). These trials also demonstrated a greater improvement in lung function endpoints for umeclidinium/vilanterol compared to fluticasone propionate/salmeterol, with differences in wm FEV_1 (0 to 24 hr) and trough FEV_1 ranging from 74 to 101 mL ($p < 0.001$ for all comparisons). Adverse event rates and effects on TDI score and SGRQ were similar between groups.
- A randomized, double-blind, 26-week trial (ILLUMINATE; N = 523) compared indacaterol/glycopyrrolate 110/50 mcg daily to fluticasone propionate/salmeterol 500/50 mcg twice daily in patients with COPD and a history of ≥ 1 exacerbation during the previous year (*Vogelmeier et al 2013*). The dosing regimens for indacaterol/glycopyrrolate and fluticasone propionate/salmeterol evaluated in this study are different from those available and/or recommended for COPD in the U.S. The primary endpoint, FEV_1 AUC (0 to 12 hr), was significantly higher with indacaterol/glycopyrrolate than fluticasone propionate/salmeterol, with a treatment difference of 138 mL (95% CI, 100 to 176; $p < 0.0001$). Benefits were also seen for indacaterol/glycopyrrolate for some secondary endpoints, including additional lung function measures, change from baseline in rescue medication use, and TDI focal score; the difference in SGRQ was not statistically significant.
- A large, randomized, double-blind, 52-week trial (FLAME; N = 3362) compared indacaterol/glycopyrrolate 110/50 mcg daily to fluticasone propionate/salmeterol 500/50 mcg twice daily in patients with COPD and a history of ≥ 1 exacerbation during the previous year (*Wedzicha et al 2016*). Again, these dosing regimens varied from U.S.

recommendations. The primary endpoint, the annual rate of all COPD exacerbations, was 11% lower in the indacaterol/glycopyrrolate group than in the fluticasone propionate/salmeterol group (3.59 vs 4.03; rate ratio, 0.89; 95% CI, 0.83 to 0.96; p = 0.003). Lung function was also improved to a greater extent with indacaterol/glycopyrrolate, with a difference in trough FEV_1 of 62 mL between groups (p < 0.001).

- A randomized, double-blind, crossover trial (N = 229) evaluated the use of tiotropium/olodaterol 2.5/5 mcg and 5/5 mcg once daily and fluticasone propionate/salmeterol 250/50 mcg and 500/50 mcg twice daily in patients with moderate to severe COPD; each patient received each of the 4 treatments for 6 weeks separated by 3-week washout periods (*Beeh et al 2016*). The lower dose of each combination is the dose available/recommended for COPD in the U.S. The primary endpoint, FEV_1 AUC (0 to 12 hr), was greater for the tiotropium/olodaterol regimens (range, 295 to 317 mL) than for the fluticasone propionate/salmeterol regimens (range, 188 to 192 mL) (p < 0.0001). FEV_1 AUC (12 to 24 hr) and FEV_1 AUC (0 to 24 hr) also favored tiotropium/olodaterol. Rates of adverse events were similar among the treatments.

Triple combination for COPD

- Fluticasone furoate/umeclidinium/vilanterol is the first FDA-approved "closed triple" inhaler – an inhaler containing 3 active ingredients: an ICS, a LAMA, and a LABA. FDA approval was based primarily on the co-administration of umeclidinium plus the fluticasone furoate/vilanterol combination.
- Two 12-week randomized studies (N = 619 and N = 620; published together) evaluated the efficacy and safety of double-blind treatment with umeclidinium 62.5 mcg, umeclidinium 125 mcg, or placebo when added to open-label fluticasone furoate/vilanterol 100/25 mcg (*Siler et al 2015*). In both studies, the primary endpoint, trough FEV_1, was significantly improved with the addition of umeclidinium, with improvements ranging from 111 to 128 mL (p < 0.001 for all comparisons vs placebo). Improvement was also demonstrated on the secondary endpoint of wm FEV_1 (0 to 6 hr), with improvements ranging from 125 to 153 mL (p < 0.001 for all comparisons vs placebo). SGRQ results were inconsistent. No substantial benefit was observed with umeclidinium 125 mcg over 62.5 mcg, which is consistent with findings in the umeclidinium monotherapy studies.
- Once-daily triple therapy with fluticasone furoate/umeclidinium/vilanterol has also been compared to twice-daily budesonide/formoterol 400/12 mcg in a 24-week, double-blind, double-dummy randomized trial (FULFIL; N = 1810) (*Lipson et al 2017*). The formulation/dosing regimen of budesonide/formoterol in this trial is different from the formulation available in the U.S. The trial demonstrated improvements in the change from baseline in trough FEV_1 (difference, 171 mL; 95% CI, 148 to 194; p < 0.001), SGRQ (difference, -2.2; 95% CI, -3.5 to -1.0; p < 0.001), and the rate of moderate/severe exacerbations (rate ratio, 0.65; 95% CI, 0.49 to 0.86; p = 0.002). Although the comparator regimen is not available in the U.S., this trial further supports the efficacy of triple inhaler therapy with fluticasone furoate/umeclidinium/vilanterol.
- Once-daily triple therapy with fluticasone furoate/umeclidinium/vilanterol was compared to fluticasone furoate/vilanterol and umeclidinium/vilanterol in a 52-week, double-blind, randomized trial among patients with COPD (IMPACT; *Lipson et al 2018*). The primary endpoint of moderate or severe exacerbations was significantly lower with triple therapy in comparison both with fluticasone furoate/vilanterol (rate ratio, 0.85; 95% CI, 0.80 to 0.90) and with umeclidinium/vilanterol (rate ratio, 0.75; 95% CI, 0.70 to 0.81). The annual rate of severe exacerbation resulting in hospitalization was also significantly lower with triple therapy vs umeclidinium/vilanterol (rate ratio, 0.66; 95% CI, 0.56 to 0.78), but not vs fluticasone furoate/vilanterol. The mean change from baseline in trough FEV_1 was significantly increased with triple therapy by 97 and 54 mL vs fluticasone furoate/vilanterol and umeclidinium/vilanterol, respectively. The risk of pneumonia was significantly higher with triple therapy vs umeclidinium/vilanterol (HR, 1.53; 95% CI, 1.22 to 1.92), but not vs fluticasone furoate/vilanterol. Significant improvements in SGRQ total scores also occurred with triple therapy vs fluticasone furoate/vilanterol (mean difference, -1.8; 95% CI, -2.4 to -1.1) and vs umeclidinium/vilanterol (mean difference, -1.8; 95% CI, -2.6 to -1.0).

CLINICAL GUIDELINES

Asthma

- The National Asthma Education and Prevention Program (NAEPP) guideline from the NHLBI states that the initial treatment of asthma should correspond to the appropriate asthma severity category, and it provides a stepwise approach to asthma management. Long-term control medications such as ICS, long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline, and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. ICS are the most potent and consistently effective long-term asthma control medication. Quick-relief medications such as SABAs and anticholinergics are used to provide prompt relief of

bronchoconstriction and accompanying acute symptoms such as cough, chest tightness, and wheezing. Systemic corticosteroids are important in the treatment of moderate or severe exacerbations because these medications prevent progression of the exacerbation, speed recovery, and prevent relapses (*NHLBI 2007*).
  - LABAs are used in combination with ICS for long-term control and prevention of symptoms in moderate or severe persistent asthma.
  - Of the adjunctive treatments available, a LABA is the preferred option to combine with an ICS in patients 12 years of age and older. This combination is also an option in selected patients 5 to 12 years of age.
- The 2019 Global Initiative for Asthma (GINA) pocket guide also provides a stepwise approach to asthma management. It recommends an as-needed ICS/formoterol (mainly budesonide/formoterol) at low doses or daily low-dose ICS as a preferred controller medication choice (lower steps), with increasing doses of ICS/LABA for increasing symptom severity (higher steps). At the highest step, it is recommended that the patient be referred for add-on treatment (eg, tiotropium, anti-IgE, anti-IL5/5R, or anti-IL4R agents) (*GINA pocket guide 2019*).
- The available asthma guidelines are generally similar; however, one difference among them is the recommendation of ICS/formoterol as both maintenance and rescue therapy by the GINA guidelines. The NHLBI do not recommend LABA medications for the management of acute asthma symptoms or exacerbations (*GINA 2018, GINA pocket guide 2019, NHLBI 2007*).
  - A meta-analysis of 16 randomized controlled trials evaluating the use of a LABA/ICS as single maintenance and reliever therapy found that it was associated with a significant reduction in the risk of asthma exacerbations compared with controller therapy with the same dose of ICS and LABA (RR, 0.68; 95% CI, 0.58 to 0.80) (*Sobieraj et al 2018*). Of the 16 trials, 15 studied budesonide/formoterol in a dry powder inhaler. Results were similar in comparisons with doses of ICS and LABA controller therapy that were higher than the combined LABA/ICS, and in comparison with ICS controller therapy only.
- For a step-down process when asthma is well-controlled, GINA recommends reducing the ICS dose or switching to as-needed low dose ICS/formoterol (*GINA pocket guide 2019*). *Chipps et al* propose using ICS/LABA combination with lower doses of ICS or switching from ICS to low-dose ICS/LABA combinations as patients move from higher to lower steps within asthma therapy (*Chipps et al 2019*).

COPD

- The 2019 GOLD guidelines state that the management strategy for stable COPD should be predominantly based on an assessment of the patient's symptoms and risk of exacerbations; the risk of exacerbations is based on a patient's exacerbation history. Key recommendations from the GOLD guidelines are as follows (*GOLD 2019*):
  - Inhaled bronchodilators are central to symptom management in COPD and commonly given on a regular basis to prevent or reduce symptoms. Inhaled bronchodilators are recommended over oral bronchodilators.
- LAMAs and LABAs significantly improve lung function, dyspnea, and health status, and reduce exacerbation rates.
  LAMAs and LABAs are preferred over short-acting agents except for patients with only occasional dyspnea.
  LAMAs have a greater effect on exacerbation reduction compared to LABAs and decrease hospitalizations.
- Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on 1 bronchodilator, treatment should be escalated to 2 bronchodilators.
  - Combination treatment with a LABA and LAMA:
    Reduces exacerbations compared to monotherapy or ICS/LABA.
    Increases FEV_1 and reduces symptoms compared to monotherapy.
- Long-term monotherapy with ICS is not recommended. Long-term treatment with ICS may be considered in association with LABAs for patients with a history of exacerbations despite treatment with long-acting bronchodilators.
  - Triple inhaled therapy of LAMA/LABA/ICS improves lung function, symptoms, and health status and reduces exacerbations compared to ICS/LABA or LAMA monotherapy.
  - Treatment recommendations are given for patients with COPD based on their GOLD patient group (see Table 3 below).
    - Group A: Patients should be offered bronchodilator treatment (short- or long-acting), based on its effect on breathlessness. This should be continued if symptomatic benefit is documented.
    - Group B: Initial therapy should consist of a long-acting bronchodilator (LAMA or LABA). For patients with persistent breathlessness on monotherapy, use of 2 bronchodilators is recommended (LAMA + LABA). For patients with severe breathlessness, initial therapy with 2 bronchodilators may be considered. If the addition of a second

bronchodilator does not improve symptoms, it is suggested that treatment could be stepped down to a single bronchodilator; switching to another device or molecules can also be considered.

- Group C: Initial therapy should be a LAMA. Patients with persistent exacerbations may benefit from adding a second long-acting bronchodilator (LAMA + LABA, preferred) or using an ICS + LABA. For patients who have a history and/or findings suggestive of asthma-COPD overlap or blood eosinophil count ≥ 300 cells/µL, ICS + LABA is preferred.
- Group D: In general, it is recommended to start therapy with a LAMA. For patients with more severe symptoms, especially dyspnea and/or exercise limitation, LAMA/LABA may be considered for initial treatment. In some patients, initial therapy with an ICS + LABA may be the first choice; these patients may have a history and/or findings suggestive of asthma-COPD overlap or blood eosinophil count ≥ 300 cells/µL. In patients who develop further exacerbations on LAMA + LABA therapy, alternative pathways include escalation to a LAMA + LABA + ICS (preferred) or a switch to an ICS + LABA. If patients treated with a LAMA + LABA + ICS still have exacerbations, options for selected patients may include addition of roflumilast, addition of a macrolide, or stopping the ICS.

Table 3. Assessment of Symptoms and Risk of Exacerbations to Determine GOLD Patient Group

Moderate/Severe Exacerbation history	Symptoms	
	mMRC 0 to 1 CAT <10	mMRC ≥ 2 CAT ≥10
≥ 2 (or ≥ 1 leading to hospital admission)	C	D
0 or 1 (not leading to hospital admission)	A	B

Abbreviations: CAT = COPD assessment test; mMRC = modified British Medical Research Council questionnaire

- Guidelines from the American College of Chest Physicians and the Canadian Thoracic Society for prevention of acute exacerbations of COPD state that LAMA/LABA combinations are effective in reducing acute COPD exacerbations, but do not state that this combination is superior to LAMA monotherapy (*Criner et al 2015*).

SAFETY SUMMARY

Beta$_2$-agonist/corticosteroid combinations

- Beta$_2$-agonist/ICS combinations are generally contraindicated for the primary treatment of status asthmaticus or other acute episodes of asthma/COPD where intensive measures are required.
- Advair Diskus, AirDuo RespiClick, Breo Ellipta, and Wixela Inhub are contraindicated in patients with a severe hypersensitivity to milk proteins.
- Previously, ICS/LABA combinations had a boxed warning about an increased risk of asthma-related death, which had been observed with the LABA salmeterol. However, the boxed warning was removed from the prescribing information for ICS/LABA combinations in December 2017 based on an FDA review of 4 large clinical safety trials, which demonstrated that these combinations do not result in a significantly increased risk of asthma-related death, hospitalizations, or the need for intubation compared to ICS alone. There is still a warning/precaution in the prescribing information of ICS/LABA combinations related to the increased risk of asthma-related death with LABA monotherapy. A description of the clinical safety trials with ICS/LABA combinations has been added to the prescribing information for these products (*FDA 2017*).
- Other key warnings and precautions include:
  - Significant cardiovascular effects and fatalities with excessive use of beta$_2$-agonists
  - Cardiovascular and/or central nervous system effects from beta-adrenergic stimulation (seizures, angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia)
  - Paradoxical bronchospasm
  - Hypercorticism and adrenal suppression due to systemic absorption of the corticosteroid
  - The need for caution when transferring patients from systemic corticosteroid therapy (deaths due to adrenal insufficiency have occurred)
  - Lower respiratory tract infections/pneumonia
  - Local infections of the mouth and pharynx with *Candida albicans*

- Reduced growth velocity in pediatric patients
- The potential for drug interactions with strong CYP3A4 inhibitors; concomitant use is not recommended due to the potential for increased systemic effects
- The potential for developing glaucoma, increased intraocular pressure, blurred vision, central serous chorioretinopathy, or cataracts
- Immunosuppression
- Hypersensitivity
- Reduction in bone mineral density

- It is also important to note that ICS/LABA combinations should not be initiated in the setting of disease deterioration or potentially life-threatening episodes.
- Commonly reported adverse events (≥ 5% for at least 1 medication in the class) include oral candidiasis, hoarseness/dysphonia, nasopharyngitis/pharyngitis, pharyngolaryngeal/oropharyngeal pain, sinusitis, upper respiratory tract infection, upper respiratory tract inflammation, bronchitis, cough, headache, gastrointestinal discomfort, and nausea/vomiting.

Beta$_2$-agonist/anticholinergic combinations

- Both albuterol/ipratropium combination products are contraindicated in patients with hypersensitivity to atropine or its derivatives. Anoro Ellipta and Duaklir Pressair are contraindicated in patients with hypersensitivity to any component of the product, as well as in patients with severe hypersensitivity to milk proteins. Bevespi Aerosphere, Duaklir Pressair, Stiolto Respimat, and Utibron Neohaler are all contraindicated in patients with asthma without use of a long-term asthma control medication (and are not indicated for the treatment of asthma).
- There are no boxed warnings for the albuterol/ipratropium combination products and Duaklir Pressair. Anoro Ellipta, Bevespi Aerosphere, Stiolto Respimat and Utibron Neohaler have boxed warnings stating that LABA increase the risk of asthma-related death. Data from a large placebo-controlled U.S. trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including formoterol (an active ingredient in Bevespi Aerosphere and Duaklir Pressair), indacaterol (an active ingredient in Utibron Neohaler), vilanterol (an active ingredient in Anoro Ellipta), and olodaterol (an active ingredient in Stiolto Respimat). The safety and efficacy of Anoro Ellipta, Bevespi Aerosphere, Duaklir Pressair, Stiolto Respimat, and Utibron Neohaler in patients with asthma have not been established, and these products are not indicated for the treatment of asthma.
- Warnings and precautions are very similar among products, and include the following:
  - Paradoxical bronchospasm: May produce paradoxical bronchospasm, which can be life-threatening. If it occurs, the product should be discontinued and alternative therapy instituted.
  - Cardiovascular effect: Beta$_2$-agonists can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, and/or symptoms. If these symptoms occur, the product may need to be discontinued. In addition, electrocardiogram (ECG) changes may occur. These products should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
  - Ocular effects: Ipratropium and other anticholinergic agents may increase intraocular pressure, which may precipitate or worsen narrow-angle glaucoma. They should be used with caution in patients with narrow-angle glaucoma. In addition, patients should avoid spraying product into eyes, as this can cause eye pain and visual symptoms.
  - Urinary retention: Ipratropium and other anticholinergic agents may cause urinary retention. Caution is advised when administering to patients with prostatic hyperplasia or bladder-neck obstruction.
  - The recommended dose should not be exceeded: Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma.
  - Hypersensitivity reactions: Urticaria, angioedema, rash, pruritus, bronchospasm, laryngospasm, oropharyngeal edema, and anaphylaxis may occur. If such a reaction occurs, therapy should be discontinued and alternative treatment considered.
  - Coexisting conditions: Due to the beta$_2$-agonist component, caution is advised in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines.
  - Hypokalemia: β-agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.
  - Drug interactions with strong CYP3A4 inhibitors; increased cardiovascular effects may occur (Anoro Ellipta only).
  - Reports of anaphylactic reactions in patients with severe milk protein allergy (Anoro Ellipta only).

- Deterioration of disease and acute episodes; drug has not been studied in this setting and is not to relieve acute symptoms (Anoro Ellipta, Duaklir Pressair, and Stiolto Respimat only).
- Adverse reactions are similar among products and include back pain, bronchitis, upper respiratory infection, lung disease, headache, dyspnea, nasopharyngitis/pharyngitis, and cough.
- In a 12-week trial comparing Combivent Respimat to Combivent inhalation aerosol, rates of adverse reactions were very similar between groups. In a 48-week safety trial, most adverse reactions were similar in type and rate between treatment groups; however, cough occurred more frequently in patients enrolled in the Combivent Respimat group (7%) than the Combivent inhalation aerosol group (2.6%).
- The choice of a specific LAMA/LABA fixed-dose combination product is not based on any difference in the safety profile (*Matera et al 2016*).

Triple combination (beta$_2$-agonist/anticholinergic/corticosteroid)

- Trelegy Ellipta is contraindicated in patients with severe hypersensitivity to milk proteins or any ingredients in the formulation.
- Similar to other combination agents for COPD (and/or asthma), Trelegy Ellipta has a number of additional warnings and precautions; these include:
  - Increased risk of asthma-related death
  - Not indicated for treatment of asthma
  - Not initiating in patients with rapidly deteriorating COPD
  - Avoiding excess use
  - Local effects of ICS
  - Risk of pneumonia
  - Immunosuppression
  - Using caution when transferring patients from systemic corticosteroid therapy
  - Hypercorticism and adrenal suppression
  - Drug interactions with strong CYP3A4 inhibitors
  - Paradoxical bronchospasm
  - Hypersensitivity reactions
  - Cardiovascular effects
  - Reduction in bone mineral density
  - Glaucoma and cataracts
  - Urinary retention
  - Using caution in patients with certain coexisting conditions such as convulsive disorders or thyrotoxicosis
  - Hypokalemia and hyperglycemia
- The most common adverse reactions with Trelegy Ellipta include headache, back pain, dysgeusia, diarrhea, cough, oropharyngeal pain, and gastroenteritis.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency
Beta$_2$-agonist & corticosteroid combinations			
Advair Diskus (fluticasone propionate/salmeterol)	Inhalation powder	Inhalation	2 times daily
Advair HFA (fluticasone propionate/salmeterol)	Aerosol inhaler	Inhalation	2 times daily
AirDuo RespiClick (fluticasone propionate/salmeterol)	Inhalation powder	Inhalation	2 times daily
Breo Ellipta (fluticasone furoate/vilanterol)	Inhalation powder	Inhalation	Once daily
Dulera (mometasone furoate/formoterol fumarate dihydrate)	Aerosol inhaler	Inhalation	2 times daily
Symbicort (budesonide/formoterol fumarate dihydrate)	Aerosol inhaler	Inhalation	2 times daily
Wixela Inhub (fluticasone propionate/salmeterol)	Inhalation powder	Inhalation	2 times daily
Beta$_2$-agonist & anticholinergic combinations			
Anoro Ellipta (umeclidinium/vilanterol)	Inhalation powder	Inhalation	Once daily

Drug	Available Formulations	Route	Usual Recommended Frequency
Bevespi Aerosphere (glycopyrrolate/formoterol fumarate)	Inhalation spray	Inhalation	2 times daily
Combivent Respimat (ipratropium bromide/albuterol)	Inhalation spray	Inhalation	4 times daily
Duaklir Pressair (aclidinium/formoterol fumarate)	Inhalation powder	Inhalation	2 times daily
ipratropium bromide/albuterol	Nebulizer solution	Inhalation (nebulizer)	4 times daily
Stiolto Respimat (tiotropium bromide/olodaterol)	Inhalation spray	Inhalation	Once daily
Utibron Neohaler (indacaterol/glycopyrrolate)	Inhalation powder	Inhalation	2 times daily
Triple combination			
Trelegy Ellipta (fluticasone furoate/ umeclidinium/vilanterol)	Inhalation powder	Inhalation	Once daily

See the current prescribing information for full details.

CONCLUSION

- Respiratory medications, including bronchodilators and corticosteroids, are a mainstay of treatment for asthma and COPD, and a large amount of clinical evidence supports the safety and efficacy of combination beta$_2$-agonist agents for these indications.
  - Clinical trials have demonstrated that the combination products have superior efficacy compared with the individual separate components when given as monotherapy for the treatment of both asthma and COPD. The combination products are generally well tolerated.
- Several single-ingredient inhalers containing beta$_2$-agonists, ICS, or anticholinergics are also available. Beta$_2$-agonist combinations offer improved convenience over the use of multiple separate inhalers.
  - Trelegy Ellipta is the first fixed-dose combination inhaler combining a LAMA, a LABA, and an ICS, and provides an alternative to the use of multiple inhalers for patients with COPD in whom triple therapy is indicated.
- GINA guideline supports the use of combination ICS/LABA products for long-term control and prevention of symptoms and exacerbations in patients with asthma.
  - Single-agent LABA therapy should not be used for asthma management due to the increased risk of asthma-related death, as well as asthma-related hospitalization in pediatric and adolescent patients. However, recent drug safety information from the FDA states that no significantly increased risk of serious asthma outcomes has been seen with the use of ICS/LABA combinations, and boxed warnings about this potential risk have been removed from the prescribing information for the ICS/LABA combinations.
  - An advantage of the ICS/LABA combinations is that their use ensures that patients are not using a LABA without a concomitant ICS.
- GOLD guidelines recommend the use of combination ICS/LABA products as an option for some patients at higher risk of exacerbations, a history and/or findings suggestive of asthma-COPD overlap, or blood eosinophil count ≥ 300 cells/μL; however, the use of 1 or more bronchodilator without an ICS is recommended as first-line treatment for most COPD patients.
  - A LAMA is recommended as first-line treatment in most patients with COPD, with the exception of low-risk patients with milder symptoms, or patients with more severe symptoms.
- The current asthma or COPD treatment guidelines do not recommend the use of one specific combination product over another. GINA guideline discusses the use of budesonide/formoterol as the preferred as-needed low dose ICS/formoterol combination in lower steps of therapy.
  - Administration instructions and inhalation devices vary among products and should be considered in product selection.

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Therapeutic Class Overview
Opioid Use Disorder Agents

INTRODUCTION

Products for Treatment of Opioid Dependence

- The American Psychiatric Association (APA) defines opioid use disorder as a syndrome characterized by a problematic pattern of opioid use, leading to clinically significant impairment or distress (*APA 2013*).
  - In 2015, approximately 2 million Americans had a substance use disorder involving prescription pain relievers and 591,000 had a substance use disorder involving heroin (*American Society of Addiction Medicine [ASAM] 2016*).
- Methadone, buprenorphine (with or without naloxone), and naltrexone are Food and Drug Administration (FDA)-approved for the detoxification and maintenance treatment of opioid dependence (*Micromedex 2.0 2019*).
  - Methadone products, when used for the treatment of opioid addiction in detoxification or maintenance programs, may be dispensed only by opioid treatment programs (and agencies, practitioners or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration and approved by the designated state authority. Certified treatment programs may dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (Code of Federal Regulations, Title 42, Sec 8).
  - The Drug Addiction Treatment Act of 2000 expanded the clinical context of medication-assisted opioid addiction treatment by allowing qualified physicians to dispense or prescribe specifically approved medications, like buprenorphine, for the treatment of opioid addiction in treatment settings other than the traditional Opioid Treatment Program. In addition, DATA reduced the regulatory burden on physicians who choose to practice opioid addiction therapy by permitting qualified physicians to apply for and receive waivers of the special registration requirements defined in the Controlled Substances Act (*Center for Substance Abuse Treatment 2004*).
  - Naltrexone, an opioid antagonist, is only indicated for the prevention of relapse after opioid detoxification; patients must be opioid-free for at least 7 to 10 days prior to initiation of naltrexone therapy in order to avoid precipitation of withdrawal.
- All buprenorphine products are Schedule III controlled substances (*Drugs@FDA 2019*).
- In 2012, Reckitt Benckiser Pharmaceuticals notified the FDA that they were voluntarily discontinuing production of Suboxone (buprenorphine/naloxone) sublingual tablets as a result of increasing concerns over accidental pediatric exposure with the tablets. The unique child-resistant, unit-dose packaging of the film formulation is believed to be a contributing factor to reduce exposure rates in children. Generic formulations of the sublingual tablets remain available.
- In November 2017, the FDA approved Sublocade (buprenorphine ER) subcutaneous injection for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days.
  - Sublocade is injected as a liquid and the subsequent precipitation of the polymer creates a solid depot which contains buprenorphine. Buprenorphine is released via diffusion from, and the biodegradation of, the depot.
- On September 7, 2018, a new dosage strength of buprenorphine/naloxone sublingual films was approved by the FDA under the brand name Cassipa. However, the launch of this product has been delayed pending patent litigation against Dr. Reddy's generic Suboxone film product (see footnotes in Table 1). The current estimated launch date of Cassipa is unknown.
- Lofexidine, an oral central alpha-2 agonist, was approved in May 2018 for the mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults. This product is indicated for short-term use, up to 14 days, during the period of peak opioid withdrawal symptoms.
- Included in this review are the products that are FDA-approved to be used in the treatment of opioid dependence; however, methadone products are not included since they must be dispensed in an opioid treatment program when used for the treatment of opioid addiction in detoxification.
- Medispan Class: Opioid Use Disorder Agents

Table 1. Medications for Treatment of Opioid Dependence Included Within Class Review

Drug	Generic Availability
Single Entity Agents	
Lucemyra (lofexidine) tablet	-
naltrexone hydrochloride* tablet	✔
Sublocade (buprenorphine) subcutaneous injection	-
Subutex (buprenorphine)* sublingual tablet	✔
Vivitrol (naltrexone) intramuscular injection	-
Combination Products	
Bunavail (buprenorphine/naloxone) buccal film	-
buprenorphine/naloxone* sublingual tablets	✔
Suboxone (buprenorphine/naloxone) sublingual film	✔ †
Zubsolv (buprenorphine/naloxone) sublingual tablets	- §

*Brand name product was discontinued; however, generic formulations are available.
†Dr. Reddy, Mylan, and Alvogen received FDA approval for AB-rated generic versions of the Suboxone sublingual film; the launch of these generics was delayed/blocked pending patent litigation against Dr. Reddy. The manufacturer of the branded product, Indivior, launched an authorized generic version (distributed by Sandoz) on February 20, 2019, after the Federal Circuit Court of Appeals issued a decision vacating the primary injunction against Dr. Reddy. Indivior will file an application to the Supreme Court of the United States requesting a stay of the mandate pending resolution of its forthcoming petition for certiorari seeking to overturn the Federal Circuit Courts of Appeals' primary injunction vacatur.
§Generic version not anticipated until 2032.

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

Products for Emergency Treatment of Opioid Overdose

- Opiate overdose continues to be a major public health problem in the United States (U.S.). It has contributed significantly to accidental deaths among those who use or abuse illicit and prescription opioids. The number of opioid overdoses has risen in recent years, partly due to a nearly 4-fold increase in the use of prescribed opioids for the treatment of pain. Overdose deaths involving opioids increased to more than 42,000 deaths in 2016 (*Substance Abuse and Mental Health Services Administration [SAMHSA] 2018*).
- Death following opioid overdose can be averted by emergency basic life support and/or the timely administration of an opioid antagonist such as naloxone. As a narcotic antagonist, naloxone displaces opiates from receptor sites in the brain and reverses respiratory depression, which is usually the cause of overdose deaths *(SAMHSA 2018, World Health Organization [WHO] 2014)*.
- Naloxone is provided to patients through the regular course of medical care, by pharmacist-initiated collaborative practice agreements, or through community-based opioid overdose prevention programs (*Doe-Simkins 2014*).
- Recognizing the potential value of providing naloxone to laypersons, some states have passed laws and changed regulations authorizing prescribers to provide naloxone through standing orders and/or to potential overdose witnesses as well as protecting those who administer naloxone from penalties for practicing medicine without a license (*Morbidity and Mortality Weekly Report [MMWR] 2012, Coffin 2018*).
- In December 2018, the U.S. Department of Health & Human Services (HHS) recommended prescribing or co-prescribing naloxone to all patients who are at risk for opioid overdose, including: patients receiving opioids at a dosage of 50 milligram morphine equivalents (MME) per day or greater; patients with respiratory conditions who are prescribed opioids; patients who have been prescribed benzodiazepines along with opioids; and patients prescribed opioids who have a non-opioid substance use disorder, report excessive alcohol use, or have a mental health disorder (*HHS 2018*).
- In patients with opioid overdose, naloxone begins to reverse sedation, respiratory depression, and hypotension within 1 to 2 minutes after intravenous (IV) administration, 2 to 5 minutes after intramuscular (IM) or subcutaneous (SC) administration, and 8 to 13 minutes after intranasal (IN) administration. Since the half-life of naloxone is much shorter than that of most opioids, repeated administration may be necessary (*Lexicomp 2019*).
- Naloxone was first approved by the FDA in 1971. In April 2014, an auto-injector formulation of naloxone was approved (Evzio) which incorporates both audio and visual instructions to guide the person administering the drug during a medical emergency. In November 2015, the FDA approved the first IN formulation of naloxone (Narcan nasal spray). Prior to the approval of these products, naloxone was only available in glass vials and ampules, which were distributed with syringes and needles for manual injection or with syringes and atomizers for off-label IN administration (*Evzio FDA Summary Review 2014*).

- Included in this review are the naloxone products that are FDA-approved for opioid overdose.
- Medispan Class: Opioid Antagonists

Table 2. Medications for Emergency Treatment of Opioid Overdose Included Within Class Review

Drug	Generic Availability
Evzio (naloxone hydrochloride [HCl]) auto-injector	-
naloxone HCl* injection	✔
Narcan (naloxone HCl) nasal spray	-

*Brand name product was discontinued; however, generic formulations are available

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 3. Food and Drug Administration Approved Indications for Buprenorphine and Buprenorphine/Naloxone Products

Indication	Single Entity Agent		Combination Products			
	Sublocade (buprenorphine) subcutaneous injection	Subutex (buprenorphine) sublingual tablets	Bunavail (buprenorphine/ naloxone) film	buprenorphine /naloxone sublingual tablets	Suboxone (buprenorphine/ naloxone) film	Zubsolv (buprenorphine /naloxone) sublingual tablets
Treatment of opioid dependence			✔		✔	✔
Treatment of opioid dependence and is preferred for induction		✔				
Maintenance treatment of opioid dependence				✔		
Treatment of moderate to severe opioid use disorder*	✔					

*For use in patients who initiated treatment with transmucosal buprenorphine-containing product, followed by dose adjustment for at least 7 days.

(*Prescribing information: buprenorphine sublingual tablets 2018, buprenorphine/naloxone sublingual tablets 2018, Bunavail 2018, Sublocade 2018, Suboxone film 2018, Zubsolv 2018*)

Table 4. Food and Drug Administration Approved Indications for Naltrexone Agents Used in Opioid Dependence

Indication	naltrexone hydrochloride tablets	Vivitrol (naltrexone HCl) injection
Blockade of the effects of exogenously administered opioids	✔	
Treatment of alcohol dependence	✔	✔
Prevention of relapse to opioid dependence following opioid detoxification		✔

(*Prescribing information: naltrexone tablets 2017, Vivitrol 2018*)

Table 5. Food and Drug Administration Approved Indications for Other Agents Used in Opioid Dependence

Indication	Lucemyra (lofexidine) tablets
Mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation	✔

(*Prescribing information: Lucemyra 2018*)

Table 6. Food and Drug Administration Approved Indications for Naloxone Products

Indication	Evzio (naloxone HCl) auto-injector	naloxone HCl injection	Narcan (naloxone HCl) nasal spray
Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system (CNS) depression	✔		✔
Complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids, including propoxyphene, methadone, and certain mixed agonist-antagonist analgesics: nalbuphine, pentazocine, butorphanol, and cyclazocine		✔	
Diagnosis of suspected or known acute opioid overdosage		✔	
Adjunctive agent to increase blood pressure in the management of septic shock		✔	

(*Prescribing information: Evzio 2016, naloxone injection 2015, Narcan nasal spray 2017*)

Limitations of use

- Prescription of Narcan nasal spray 2 mg should be restricted to opioid-dependent patients expected to be at risk for severe opioid withdrawal in situations where there is a low risk for accidental or intentional opioid exposure by household contacts.

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

Products for Treatment of Opioid Dependence

- Clinical trials have demonstrated that buprenorphine/naloxone is practical and safe for use in diverse community treatment settings including primary care offices (*Amass et al 2004, Fiellin et al 2008*).
- Studies have shown that in adult patients with opioid dependence, the percentage of opioid negative urine tests was significantly higher for both buprenorphine and buprenorphine/naloxone compared to placebo, while no significant difference was seen between the 2 active treatment groups (*Daulouede et al 2010, Fudala et al 2003*). In addition, a small randomized controlled trial (N=32) also showed no significant difference in withdrawal symptoms between buprenorphine and buprenorphine/naloxone (*Strain et al 2011*).
- Several studies have compared the effectiveness of short-term detoxification to medium- or long-term maintenance treatment with buprenorphine monotherapy or buprenorphine/naloxone. Three studies have shown higher treatment retention rate or self-reported drug use with longer treatment duration compared to detoxification; however, 1 of the studies showed no significant difference in the percentage of positive urine tests between the 2 treatment groups at 12 weeks (*Kakko et al 2003, Woody et al 2008, Weiss 2011*).

- In a meta-analysis of 21 randomized controlled trials, patients receiving buprenorphine at doses ≥16 mg/day were more likely to continue treatment compared to patients receiving doses <16 mg/day; however, no significant difference was seen in the percentage of opioid positive urine tests between the high- and low-dose groups (*Fareed et al 2012*).
- Studies that compared different dosing regimens of buprenorphine showed no difference in rate of treatment retention, percentage of urine tests positive for opioids, or withdrawal symptoms (*Bickel et al 1999, Gibson et al 2008, Petry et al 1999, Schottenfeld et al 2000*).
- One study found that buprenorphine/naloxone sublingual film was comparable to the sublingual tablet form in dose equivalence and clinical outcomes (*Lintzeris et al 2013*).
- A randomized, parallel-group, noninferiority trial (N=758) found that for the treatment of patients with opioid dependence, Zubsolv (buprenorphine/naloxone) sublingual tablets was noninferior to generic buprenorphine sublingual tablets during induction and was noninferior to buprenorphine/naloxone sublingual film during early stabilization (*Gunderson et al 2015*).
- Buprenorphine has been compared to methadone in several clinical studies and reviewed in multiple meta-analyses. Overall, studies have demonstrated that buprenorphine-based therapy was as effective as methadone in the management of opioid dependence (*Farre et al 2002, Gibson et al 2008, Gowing et al 2017, Johnson et al 1992, Kamien et al 2008, Law et al 2017, Meader et al 2010, Perry et al 2013, Petitjean et al 2001, Soyka et al 2008, Strain et al 2011).* However, when low doses of buprenorphine were studied (≤8 mg/day), high doses of methadone (≥50 mg/day) proved to be more efficacious *(Farre et al 2002, Ling et al 1996, Mattick et al 2014, Schottenfeld et al 1997*).
- In a 24-week, Phase 3, double blind, placebo-controlled, randomized controlled trial (N=504), the efficacy and safety of multiple subcutaneous injections of buprenorphine (100 mg and 300 mg) over 24 weeks were assessed in treatment-seeking patients with opioid use disorder. Buprenorphine injection was shown to be superior vs placebo in achieving more illicit opioid-free weeks ($p < 0.0001$). The proportion of patients achieving treatment success (defined as any patient with at least 80% of urine samples negative for opioids combined with self-reports negative for illicit opioid use from week 5 through week 24) was statistically significantly higher in both groups receiving buprenorphine compared to the placebo group (28.4% [300 mg/100 mg], 29.1% [300 mg/300mg], and 2% [placebo]) ($p < 0.0001$) *(FDA Advisory Committee Briefing Document, Sublocade Prescribing Information)*.
- Extended-release intramuscular naltrexone was compared to buprenorphine/naloxone sublingual film in a 24-week, open-label, randomized controlled trial (N=570). More induction failures were seen with extended-release intramuscular naltrexone; as a result, in the intention-to-treat analysis, relapse-free survival was lower with extended-release intramuscular naltrexone compared to sublingual buprenorphine/naloxone. However, among patients who were able to successfully initiate treatment, extended-release intramuscular naltrexone had similar efficacy to buprenorphine/naloxone in terms of relapse prevention (*Lee et al 2018*). A 12-week, randomized, open-label, noninferiority trial (N=159) similarly found that extended-release intramuscular naltrexone was noninferior to oral buprenorphine/naloxone in terms of negative urine drug tests and days of opioid use (*Tanum et al 2017).*
- In a meta-analysis examining the efficacy of oral naltrexone for maintenance treatment of opioid dependence, oral naltrexone was no better than placebo or no pharmacologic treatment in terms of treatment retention or use of the primary substance of abuse. Based on the results of 1 study, it was also not significantly different from buprenorphine for retention, abstinence, and side effects (*Minozzi et al 2011*).
- The safety and efficacy of lofexidine for inpatient treatment of opioid withdrawal symptoms was examined in an 8-day, randomized, double-blind, placebo-controlled trial (N=264). In this study, patients treated with lofexidine had lower scores on the Short Opioid Withdrawal Scale (SOWS) Gossop scale on day 3 compared to placebo. More patients in the placebo group terminated study participation early (*Gorodetzky et al 2017).* Similar resulted were found in another, unpublished trial *(Lucemyra prescribing information 2018)*. Meta-analyses have found that although lofexidine reduces withdrawal symptoms compared to placebo, it is less effective than buprenorphine for managing opioid withdrawal in terms of withdrawal severity, withdrawal duration, and likelihood of treatment completion *(Gowing et al 2016, Gowing et al 2017)*. It is likely to be less effective than buprenorphine or methadone for opioid detoxification (*Meader 2010*).

Products for Emergency Treatment of Opioid Overdose

- The approval of Evzio auto-injector and Narcan nasal spray were based on pharmacokinetic bioequivalence studies comparing these products to a generic naloxone product, delivered SC or IM. No clinical studies were required by the FDA (*Prescribing information: Evzio 2016, Narcan 2017*).

- The manufacturers also conducted a human factors validation study in which participants were asked to deliver a simulated dose of the drug to a mannequin without training and most demonstrated appropriate use of the device (*FDA Summary Review: Evzio 2014, Narcan nasal spray 2015*).

- Studies have suggested that IN naloxone is an effective option in the treatment of opioid overdose (*Kelly et al 2005, Kerr et al 2009, Merlin et al 2010, Robertson et al 2009, Sabzghabaee et al 2014*).
- A meta-analysis of naloxone studies found that lay administration of naloxone was associated with significantly increased odds of recovery compared with no naloxone administration (odds ratio: 8.58, 95% confidence interval [CI], 3.90 to 13.25) (*Giglio et al 2015*).
- A 2-year, non-randomized intervention study found that prescription of naloxone to patients who were prescribed long-term opioids for chronic pain was associated with a 47% decrease in opioid-related emergency visits per month after 6 months and a 63% decrease after 1 year compared to those who did not receive naloxone (*Coffin et al 2016*).

CLINICAL GUIDELINES

- The American Academy of Pediatrics (AAP), APA, American Society of Addiction Medicine (ASAM), Center for Substance Abuse Treatment (CSAT)/United States Substance Abuse and Mental Health Services Administration (SAMHSA), and the Veterans Health Administration (VHA) have published guidelines for the treatment of opioid dependence. In general, these guidelines support access to pharmacological therapy for the management of opioid dependence. Buprenorphine/naloxone combination products may be used for induction and maintenance. In pregnant women for whom buprenorphine therapy is selected, buprenorphine alone (ie, without naloxone) is recommended. Naltrexone may be considered for the prevention of relapse, although outcomes with this medication are often adversely affected by poor adherence. Extended-release injectable naltrexone may reduce, but not eliminate, some of the problems with oral naltrexone adherence. The VHA guideline recommends extended-release injectable naltrexone if opioid agonist treatment is not feasible; it does not recommend for or against oral naltrexone (*CSAT 2004, CSUP 2016, Kampman 2015, Kleber et al 2006, Kraus et al 2011, SAMHSA 2018, VHA 2015*).
- Clinical practice guidelines from ASAM and VHA recommend against withdrawal management alone due to the high risk of relapse compared with treatment with maintenance therapy. However, opioid withdrawal can be managed with either gradually tapering doses of opioid agonists or use of alpha-2 adrenergic agonists (eg, clonidine) along with other non-narcotic medications *(Kampman 2015, VHA 2015).*
  - Using tapering doses of opioid agonists has been shown to be superior to alpha-2 adrenergic agonists in terms of retention and opioid abstinence. However, the use of non-opioid medications may be the only option available to clinicians in some healthcare settings and may also facilitate the transition of patients to opioid antagonist medications (eg, naltrexone) and help prevent subsequent relapse.
- Various organizations including the World Health Organization (WHO) and the ASAM have endorsed the availability of naloxone for patients, bystanders, and first responders for the emergency management of suspected opioid overdose. It is recommended that people who are likely to witness an overdose should have access to and be trained in the use of naloxone (*WHO 2014, Kampman 2015*).
  - According to the WHO guidelines for community management of opioid overdose, naloxone is effective when delivered by IV, IM, SC, and IN routes of administration. Persons using naloxone should select a route of administration based on the formulation available, their skills in administration, the setting, and local context.

SAFETY SUMMARY

Products for Treatment of Opioid Dependence

- Buprenorphine and buprenorphine/naloxone products are contraindicated in patients with known hypersensitivity to the active ingredients.
- Buprenorphine products have several warnings and precautions, including: abuse potential; respiratory depression; CNS depression; unintentional pediatric exposure; neonatal opioid withdrawal; adrenal insufficiency; risk of opioid withdrawal with abrupt discontinuation of treatment; hepatitis and hepatic events; hypersensitivity reactions; precipitation of opioid withdrawal signs and symptoms; use in patients with impaired hepatic function; impairment of ability to drive or operate machinery; orthostatic hypotension; elevation of cerebrospinal fluid pressure; elevation of intracholedochal pressure; and effects in acute abdominal conditions
- Concomitant use of buprenorphine and benzodiazepines or other CNS depressants increases the risk for adverse events, including overdose, respiratory depression, and death. Cessation of benzodiazepines or other CNS depressants

is preferred in most cases of concomitant use. This additional warning was added to opioid products in February 2018 after data demonstrated an increased risk of mortality in patients receiving benzodiazepines while on opioid maintenance treatment (*Abrahamsson et al 2017, FDA Drug Safety Communication 2017*).

- The buprenorphine subcutaneous injection also has several unique warnings and precautions, including: serious harm or death could result if administered IV (boxed warning); risks associated with treatment of emergent acute pain; use in patients at risk for arrhythmia.
- In the treatment of addiction involving opioid use in pregnant women, the buprenorphine/naloxone combination product is not recommended for use (insufficient evidence); however, the buprenorphine monoproduct is a reasonable and recommended option for use.
- Similar to other opiate products, these products may increase intracholedochal pressure, increase cerebrospinal fluid pressure, and obscure diagnosis or exacerbate acute abdominal symptoms.
- These products should not be used as analgesics.
- The most common adverse reactions observed with buprenorphine and buprenorphine/naloxone products include headache, insomnia, nausea, pain, sweating, and withdrawal syndrome.
- All of the buprenorphine-containing products have an associated risk evaluation and mitigation strategy (REMS) program (*REMS@FDA 2019*).
- Lofexidine has several warnings and precautions, including: risk of hypotension, bradycardia, and syncope; risk of QT prolongation; increased risk of CNS depression with concomitant use of CNS depressant drugs; and increased risk of opioid overdose in patients who complete opioid discontinuation and resume opioid use.
- Sudden discontinuation of lofexidine can cause a marked rise in blood pressure and symptoms that include diarrhea, insomnia, anxiety, chills, hyperhidrosis, and extremity pain. Lofexidine should be discontinued by gradually reducing the dose.
- The most common adverse reactions observed with lofexidine include orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth.
- The safety of lofexidine in pregnancy has not been established.
- Naltrexone products are contraindicated in: patients receiving opioid analgesics; patients currently dependent on opioids (including those currently maintained on opioid agonists); patients in acute opioid withdrawal; individuals who have failed a naloxone challenge test or have a positive urine screen for opioids; individuals with a history of sensitivity to naltrexone or other components of the product; and individuals with acute hepatitis or liver failure (oral naltrexone only). Extended-release injectable naltrexone is contraindicated in patients with hypersensitivity to polylactide-co-glycolide (PLG), carboxymethylcellulose, or any other component of the diluent.
- Naltrexone can precipitate withdrawal if given to an opioid-dependent patient. Prior to initiating naltrexone, an opioid-free interval of 7 to 10 days is recommended for patients previously dependent on short-acting opioids; patients transitioning from buprenorphine or methadone may be vulnerable to precipitation of withdrawal symptoms for up to 2 weeks. A naloxone challenge test may be helpful to determine whether or not the patient has had a sufficient opioid-free period prior to initiating naltrexone.
- Patients may be more vulnerable to opioid overdose after discontinuation of naltrexone due to decreased opioid tolerance.
- Monitor patients on naltrexone for the development of depression or suicidality.
- Warnings unique to extended-release intramuscular naltrexone include: injection site reactions, which may be severe; eosinophilic pneumonia; hypersensitivity reactions, including anaphylaxis; use in patients with thrombocytopenia or any coagulation disorder; and interference with certain immunoassay methods of urine opioid detection.
- The most common adverse reactions observed with oral naltrexone include difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea/vomiting, low energy, joint and muscle pain, and headache. The most common adverse reactions observed with extended-release intramuscular naltrexone include hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache.
- There are no adequate and well-controlled studies of naltrexone in pregnant women; it should be used only if the potential benefit justifies the potential risk to the fetus.
- Extended-release intramuscular naltrexone has a REMS program due to the risk of severe injection site reactions (*REMS@FDA 2019*).

Products for Emergency Treatment of Opioid Overdose

- These products are contraindicated in patients with hypersensitivity to naloxone or to any of the other ingredients.

- These products carry warnings and precautions for risks of recurrent respiratory and CNS depression, limited efficacy with partial agonists or mixed agonists/antagonists (eg, buprenorphine, pentazocine), and precipitation of severe opioid withdrawal.
- Naloxone may precipitate acute withdrawal symptoms in opioid-dependent patients including anxiety, tachycardia, sweating, piloerection, yawning, sneezing, rhinorrhea, nausea, vomiting, diarrhea, increased blood pressure, and abdominal or muscle cramps. Opioid withdrawal signs and symptoms in neonates also include convulsions, excessive crying, and hyperactive reflexes.

DOSING AND ADMINISTRATION

Table 7a. Dosing and Administration for Products for Treatment of Opioid Dependence

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single Entity Agents				
Lucemyra (lofexidine)	Tablet	Oral	Four times daily at 5- to 6-hour intervals	• May be continued for up to 14 days with dosing guided by symptoms • Adjust dose for patients with hepatic or renal impairment
Naltrexone hydrochloride	Tablet	Oral	Single daily dose May also be dosed every other day or every 3 days	• Contraindicated in patients with acute hepatitis or liver failure • Use caution in patients with hepatic or renal impairment
Sublocade (buprenorphine)	Subcutaneous injection	SC	Monthly (minimum 26 days between doses)	• Can only be administered by a healthcare provider • Patients with moderate or severe hepatic impairment are not candidates for this product
Subutex (buprenorphine)	Sublingual tablets	Oral	Single daily dose	• Severe hepatic impairment: Consider reducing the starting and titration incremental dose by half and monitor for signs and symptoms of toxicity or overdose.
Vivitrol (naltrexone extended-release)	Intramuscular injection	IM	Monthly or every 4 weeks	• Can only be administered by a healthcare provider • Use caution in patients with moderate to severe renal impairment
Combination Products				
Bunavail, Suboxone, Zubsolv (buprenorphine/ naloxone)	Buccal film (Bunavail) Sublingual film (Suboxone) Sublingual tablet (Zubsolv; generics equivalent to Suboxone tablet)	Oral	Bunavail: Single daily dose (except day 1 of induction for patients dependent on heroin or other short-acting opioid products: start with an initial dose of 2.1 mg/0.3 mg and repeat at approximately 2 hours, under supervision, to a total dose of 4.2 mg/0.7 mg based on the control of acute withdrawal symptoms) Suboxone: Single daily dose (except day 1 of induction: titrate in	• These products should generally be avoided in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			buprenorphine 2 mg to 4 mg increments at approximately 2 hour intervals based on the control of acute symptoms) Sublingual tablet generics (Suboxone): Single daily dose Zubsolv: Single daily dose (except day 1 of induction: divided into doses of 1 to 2 tablets of 1.4 mg/0.36 mg at 1.5 to 2 hour intervals)	

See the current prescribing information for full details

Table 7b. Equivalent Doses of Buprenorphine/Naloxone Combination Products*

Bunavail buccal film	buprenorphine/naloxone sublingual tablets and/or Suboxone sublingual film	Zubsolv sublingual tablets
-	2 mg/0.5 mg	1.4 mg/0.36 mg
2.1 mg/ 0.3 mg	4 mg/1 mg	2.9 mg/0.71 mg
4.2 mg/ 0.7 mg	8 mg/2 mg	5.7 mg/1.4 mg
6.3 mg/1 mg	12 mg/3 mg	8.6 mg/2.1 mg
	16 mg/4 mg	11.4 mg/2.9 mg

*Systemic exposures of buprenorphine and naloxone may differ when patients are switched from tablets to films or vice versa.

Table 8. Dosing and Administration for Products for Emergency Treatment of Opioid Overdose

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Evzio (naloxone HCl)	Auto-injector	IM/SC	• After initial dose, additional doses should be administered, using a new device, if the patient does not respond or responds and then relapses into respiratory depression. • Additional doses may be given every 2 to 3 minutes until emergency medical assistance arrives.	• The requirement for repeat doses depends upon the amount, type, and route of administration of the opioid being antagonized.
Naloxone HCl	Vials, prefilled syringe, solution cartridge	IV	*Adults:* • An initial dose may be administered IV. It may be repeated at 2 to 3 minute intervals if the desired degree of counteraction and improvement in respiratory functions are not obtained. *Children:* • The usual initial dose in	• IM or SC administration may be necessary if the IV route is not available. • The American Academy of Pediatrics, however, does not endorse SC or IM administration in opiate intoxication since absorption may be erratic or delayed.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			children is given IV; a subsequent dose may be administered if the desired degree of clinical improvement is not obtained.	
Narcan (naloxone HCl)	Nasal spray	Intranasal	• A single spray should be administered into 1 nostril. • Additional doses should be administered, using a new nasal spray device in alternating nostrils, if the patient does not respond or responds and then relapses into respiratory depression. Additional doses may be given every 2 to 3 minutes until emergency medical assistance arrives.	

See the current prescribing information for full details

CONCLUSION

Products for Treatment of Opioid Dependence

- Buprenorphine sublingual tablets, buprenorphine/naloxone sublingual tablets, Bunavail (buprenorphine/naloxone) buccal film, Sublocade (buprenorphine) subcutaneous injection, Suboxone (buprenorphine/naloxone) sublingual film, and Zubsolv (buprenorphine/naloxone) sublingual tablets are used for the treatment of opioid dependence. Some products are indicated for maintenance treatment only, while others are indicated for both induction and maintenance.
- Buprenorphine is suggested as a first-line maintenance treatment for opioid use disorder; it may be preferred over methadone because it is safer and does not require clinic-based treatment. Buprenorphine is typically administered in a combination product with naloxone, an opioid antagonist, to discourage abuse. These agents are Schedule III controlled substances (*Strain 2018*).
- Clinical trials have demonstrated that buprenorphine/naloxone is practical and safe for use in diverse community treatment settings including primary care offices (*Amass et al 2004, Fiellin et al 2008*).
- Physicians prescribing buprenorphine for opioid dependency must undergo specialized training due to the potential for abuse and diversion. Because of these risks, buprenorphine monotherapy should be reserved for patients who are pregnant or have a documented allergy to naloxone (*DATA 2000, CSAT 2004*).
- Overall, studies have demonstrated that buprenorphine-based therapy was as effective as methadone in the management of opioid dependence (*Farre et al 2002, Gibson et al 2008, Gowing et al 2017, Johnson et al 1992, Kamien et al 2008, Meader et al 2010, Petitjean et al 2001, Soyka et al 2008, Mattick et al 2014, Strain et al 2011*).
- The most common adverse reactions observed with buprenorphine and buprenorphine/naloxone products include headache, insomnia, nausea, pain, sweating, and withdrawal syndrome. These products also have REMS criteria.
- Lofexidine is an oral central alpha-2 agonist indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation.
- Meta-analyses have found that although lofexidine reduces withdrawal symptoms compared to placebo, it is less effective than buprenorphine for managing opioid withdrawal in terms of withdrawal severity, withdrawal duration, and likelihood of treatment completion *(Gowing et al 2016, Gowing et al 2017)*. It is likely to be less effective than buprenorphine or methadone for opioid detoxification (*Meader 2010*).
- The most common adverse reactions observed with lofexidine include orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth.

- Naltrexone is an opioid antagonist. Oral naltrexone is indicated for the treatment of alcohol dependence and blockade of the effects of exogenously administered opioids. Extended-release intramuscular naltrexone is indicated for the treatment of alcohol dependence and the prevention of relapse to opioid dependence following opioid detoxification. In order to initiate naltrexone treatment, patients must be opioid-free for at least 7 to 10 days to avoid precipitation of withdrawal.
- In a meta-analysis examining the efficacy of oral naltrexone for maintenance treatment of opioid dependence, oral naltrexone was no better than placebo or no pharmacologic treatment in terms of treatment retention or use of the primary substance of abuse. Based on the results of 1 study, it was also not significantly different from buprenorphine for retention, abstinence, and side effects (*Minozzi et al 2011*). Extended-release intramuscular naltrexone has been shown to have similar efficacy to oral buprenorphine/naloxone among patients who are able to successfully initiate treatment (*Lee et al 2018, Tanum et al 2017*).
- The most common adverse reactions observed with oral naltrexone include difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea/vomiting, low energy, joint and muscle pain, and headache. The most common adverse reactions observed with extended-release intramuscular naltrexone include hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache. Extended-release intramuscular naltrexone also has a REMS program.
- The AAP, APA, ASAM, CSAT/SAMHSA, and VHA publish guidelines for the treatment of opioid dependence. These guidelines support access to pharmacological therapy for the management of opioid dependence. Buprenorphine/naloxone combination products may be used for induction and maintenance. In pregnant women for whom buprenorphine therapy is selected, buprenorphine alone (ie, without naloxone) is recommended. Naltrexone may be considered for the prevention of relapse, although outcomes with this medication are often adversely affected by poor adherence. Extended-release injectable naltrexone may reduce, but not eliminate, some of the problems with oral naltrexone adherence. The VHA guideline recommends extended-release injectable naltrexone if opioid agonist treatment is not feasible; it does not recommend for or against oral naltrexone (*CSAT 2004, CSUP 2016, Kampman et al 2015, Kleber et al 2006, Kraus et al 2011, VHA 2015).*
- Clinical practice guidelines from ASAM and VHA recommend against withdrawal management alone due to the high risk of relapse compared with treatment with maintenance therapy. However, opioid withdrawal can be managed with either gradually tapering doses of opioid agonists or use of alpha-2 adrenergic agonists (eg, clonidine) along with other non-narcotic medications. Lofexidine has not been added to practice guidelines but it likely has a similar place in therapy as clonidine *(Kampman 2015, VHA 2015).*

Products for Emergency Treatment of Opioid Overdose

- Naloxone is the standard of care to treat opioid overdose. It has been used by medical personnel for over 40 years and its use outside of the medical setting has gained traction through improvements in legislation and community-based opioid overdose prevention programs.
- Evzio (naloxone HCl) auto-injector, naloxone HCl injection, and Narcan (naloxone HCl) nasal spray are approved for treatment of known or suspected opioid overdose. Prior to the approval of Evzio and Narcan nasal spray, naloxone was only available in glass vials and ampules, which were distributed with syringes and needles for manual injection or with syringes and atomizers for off-label IN administration (*Evzio FDA Summary Review 2014*).
- Naloxone can be administered IV, IM, or SC using naloxone vials/syringes as well as IM or SC using an auto-injector device (Evzio). Although Narcan nasal spray is the first IN formulation to be FDA-approved, naloxone has historically been given IN off-label via kits containing a syringe and an atomization device. Potential advantages of IN administration of naloxone include easier disposal, no needle stick risk, and avoidance of needle anxiety. Both Evzio and Narcan nasal spray are designed for use by laypersons.
- The approval of Evzio and Narcan nasal spray were based on pharmacokinetic bioequivalence studies. No new clinical studies were required by the FDA.
- Various organizations including WHO and ASAM have endorsed the availability of naloxone for patients, bystanders, and first responders for the emergency management of suspected opioid overdose. It is recommended that people who are likely to witness an overdose should have access to and be trained in the use of naloxone (*WHO 2014, Kampman 2015*).
  - According to the WHO guidelines for community management of opioid overdose, naloxone is effective when delivered by IV, IM, SC, and IN routes of administration. Persons using naloxone should select a route of administration based on the formulation available, their skills in administration, the setting, and local context.

- The U.S. HHS has recommended prescribing or co-prescribing naloxone to all patients who are at risk for opioid overdose, including: patients receiving opioids at a dosage of 50 MME per day or greater; patients with respiratory conditions who are prescribed opioids; patients who have been prescribed benzodiazepines along with opioids; and patients prescribed opioids who have a non-opioid substance use disorder, report excessive alcohol use, or have a mental health disorder (*HHS 2018*).

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OPTUMRx®

RxOutlook®

3rd Quarter 2019

Welcome to RxOutlook®, the OptumRx quarterly report summarizing the latest pipeline drug information, trend news, upcoming generic launches, and emerging therapies in today's pharmaceutical market.

This edition focuses on twelve near-term pipeline drugs that are expected to receive an FDA approval decision by the end of 2019, with an emphasis on the 4th quarter. These drugs are notable because of their potential for clinical impact, economic impact, or public health interest. This edition is a slight departure from previous issues because many of the highlighted drugs are intended for mainstream conditions affecting large populations, whereas previous issues focused on rare conditions and orphan drugs, many of which were specialty drugs.

Eight drugs in this issue will be available as oral formulations while four could be covered under the medical benefit due to their route of administration (eg, intraocular injection, implant). The central nervous system therapeutic category is featured very prominently with five drugs including two new treatments for acute migraine headache, a condition that has not seen a new mechanism of action in two decades. Migraine headache is an area that will continue to see ongoing development activity in 2020. Finally, many of the drugs included in this report are entering therapeutic areas with multiple existing treatment options, including generic alternatives. Understanding the defining characteristics of these pipeline drugs will be vital to identifying their potential place in therapy and recognizing what questions remain to be answered.

Key pipeline drugs with FDA approval decisions expected by the end of the 4th quarter 2019

Drug Name	Manufacturer	Indication/Use	Expected FDA Decision Date
Darolutamide	Bayer	Prostate cancer	7/30/2019 (Approved)
Fedratinib	Celgene	Primary or secondary myelofibrosis*	8/16/2019 (Approved)
Tenapanor	Ardelyx	Irritable bowel syndrome with constipation	9/13/2019
Diroximel fumarate	Alkermes/Biogen	Multiple sclerosis	10/17/2019
Brolucizumab	Novartis	Neovascular age-related macular degeneration	11/2019
Lasmiditan	Eli Lilly	Acute migraine headache	11/14/2019
Ubrogepant	Allergan	Acute migraine headache	12/2019
RVT-802	Enzyvant/Roivant	Congenital athymia*	12/2019
Luspatercept	Celgene/Acceleron	Beta-thalassemia*; myelodysplastic syndromes (MDS)*	12/4/2019 (beta-thalassemia)
Lemborexant	Eisai/Imbrium Therapeutics	Insomnia	12/27/2019
Lumateperone	Intra-Cellular Therapies	Schizophrenia	12/27/2019
Cabotegravir/ rilpivirine	ViiV Healthcare	HIV-1 infection	12/29/2019

* Orphan Drug Designation

OptumRx closely monitors and evaluates the drug development pipeline to identify noteworthy upcoming drug approvals and reports the essential findings here in RxOutlook. The report is organized in in the following manner:

Detailed Drug Insights

This section reviews the important characteristics (eg, therapeutic use, clinical profile, competitive environment and regulatory timeline) for key pipeline drugs with potential FDA approvals by the end of the 4th quarter.

Read more

Extended Generic Pipeline Forecast

This section provides a summary of upcoming first-time generic drugs and biosimilars that may be approved in the upcoming two years.

Read more

Extended Brand Pipeline Forecast

This table provides a summary of developmental drugs, including both traditional and specialty medications that may be approved in the upcoming two years.

Read more

Key Pending Indication Forecast

This table provides a summary of key new indications that are currently under review by the FDA and may be approved in the upcoming 12 months.

Read more

Past and future reviews

Please note that RxOutlook highlights select near-term approvals. Some drugs may not appear in this issue because they have been reviewed in previous editions of RxOutlook. Drugs of interest that are earlier in development or with expected approvals beyond 4th quarter 2019 may appear in future reports; however, for those who need an initial look at the full pipeline, please refer to the Brand Pipeline Forecast Table found later in this report.

Drugs reviewed in detail in the 1Q:2019 and 2Q:2019 report:

- Afamelanotide
- Celiprolol (Edsivo™)
- Dolutegravir/lamivudine (Dovato®)
- Entrectinib
- Esketamine (Spravato™)
- Golodirsen
- Mannitol (inhaled formulation)
- Metoclopramide (Gimoti™)
- NKTR-181
- Onasemnogene abeparvovec (Zolgensma®)
- Pexidartinib
- Pitolisant
- Polatuzumab vedotin
- Quizartinib
- Risankizumab (Skyrizi™)
- Selinexor (Xpovio™)
- Semaglutide (oral formulation)
- Tafamidis (Vyndaqel®) and tafamidis meglumine (Vyndamax®)
- Upadacitinib

Past issues of RxOutlook can be found at https://professionals.optumrx.com/publications.html.

Getting acquainted with pipeline forecast terms

Clinical trial phases

Phase I trials	Researchers test an experimental drug or treatment in a small group of people for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.
Phase II trials	The experimental study drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety.
Phase III trials	The experimental study drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the experimental drug or treatment to be used safely.
Phase IV trials	Post marketing studies delineate additional information including the drug's risks, benefits, and optimal use.

Pipeline acronyms

ANDA	Abbreviated New Drug Application
BLA	Biologic License Application
CRL	Complete Response Letter
FDA	Food and Drug Administration
MOA	Mechanism of Action
NME	New Molecular Entity
NDA	New Drug Application
sBLA	Supplemental Biologic License Application
sNDA	Supplemental New Drug Application
OTC Drugs	Over-the-Counter Drugs
PDUFA	Prescription Drug User Fee Act
REMS	Risk Evaluation and Mitigation Strategy

Detailed insights on key drugs

Darolutamide (Brand Name: Nubeqa®)

Manufacturer: Bayer/Orion
Regulatory designations: Fast Track
FDA approval date: 7/30/2019 *(approved ahead of originally anticipated approval date)*

Therapeutic use

Darolutamide was approved for the treatment of patients with non-metastatic castration-resistant prostate cancer (nmCRPC).

Prostate cancer is the third most commonly diagnosed malignancy in the U.S. In 2019, it is estimated that there will be 174,650 new cases of prostate cancer and an estimated 31,620 people will die of the disease.

CRPC is an advanced form of the disease where the cancer keeps progressing even when the amount of testosterone is reduced to very low levels in the body. Most men with advanced prostate cancer eventually stop responding to androgen deprivation therapy (ie, castration) and require additional therapy when prostate specific antigen (PSA) levels begin to rapidly rise.

- Treatment of patients with nmCRPC

Clinical profile

Darolutamide is an androgen receptor inhibitor with a distinct chemical structure that competitively inhibits androgen binding, androgen receptor nuclear translocation, and androgen receptor-mediated transcription. Darolutamide decreased prostate cancer cell proliferation in vitro and tumor volume in mouse xenograft models of prostate cancer.

Pivotal trial data:
Darolutamide was evaluated in a double-blind, placebo-controlled, randomized study (ARAMIS) in 1,509 patients with nmCRPC. All patients received a gonadotropin-releasing hormone analog (GnRH) concurrently or had a bilateral orchiectomy. The major efficacy endpoint was metastasis free survival (MFS). The median MFS was 40.4 months for darolutamide-treated patients vs. 18.4 months for the placebo group (hazard ratio 0.41; 95% CI: 0.34, 0.50; $p < 0.0001$). Overall survival data were not mature at the time of final MFS analysis.

Safety:
The most common adverse events with darolutamide use were fatigue, pain in extremity, and rash.

Dosing:
The recommended dose of darolutamide is 600 mg (two 300 mg tablets) orally, twice daily. Patients receiving darolutamide should also receive a GnRH analog concurrently or should have had a bilateral orchiectomy.

- Androgen receptor inhibitor
- Oral formulation
- Median MFS: 40.4 months vs. 18.4 months for placebo ($p < 0.0001$)
- Common AEs: fatigue, pain in extremity, rash
- Dosing: twice a day

Darolutamide (Brand Name: Nubeqa) (continued...)

Competitive environment

Darolutamide provides an additional oral treatment option for patients with nmCRPC. Erleada™ (apalutamide) and Xtandi® (enzalutamide) are androgen receptor inhibitors also approved for nmCRPC; however, darolutamide's distinct chemical structure appears to provide a superior safety profile vs. both of those products (eg, Erleada and Xtandi both carry a warning for increased risk of falls/fractures and seizures).

However, the efficacy (eg, improvement in median MFS) of darolutamide appears to be similar to Erleada and Xtandi and darolutamide was not compared against either product in clinical trials. In addition, darolutamide must be dosed orally twice a day whereas Erleada and Xtandi are both once a day.

The WAC for darolutamide is $11,550 per 30 days.

- Advantages: additional treatment option for nmCRPC, safety advantages vs. competitors (Erleada, Xtandi), oral
- Disadvantages: similar efficacy to existing treatment options, lack of head-to-head trial data vs. Erleada and Xtandi, twice a day dosing
- WAC = $11,550 per 30 days

Fedratinib (Brand Name: Inrebic®)

Manufacturer: Celgene
Regulatory designations: Orphan Drug
FDA approval date: 8/16/2019

Therapeutic use

Fedratinib was approved for the treatment of adult patients with intermediate-2 or high-risk primary or secondary (post-polycythemia vera or post-essential thrombocythemia) myelofibrosis (MF)

Myelofibrosis is a rare bone marrow disorder that disrupts the body's normal production of blood cells. Bone marrow is gradually replaced with fibrous scar tissue, which limits the ability of the bone marrow to make red blood cells. A key hallmark of the disease is an enlarged spleen. In the U.S. myelofibrosis occurs in 1.5 of every 100,000 people each year.

The only curative treatment is hematopoietic stem cell transplantation (HSCT) which is reserved for patients with severe myelofibrosis.

- Treatment of patients with primary or secondary myelofibrosis

Fedratinib (continued...)

Clinical profile

Fedratinib is a highly selective Janus Associated Kinase 2 (JAK2) inhibitor. Abnormal activation of JAK2 is associated with myeloproliferative neoplasms, including myelofibrosis and polycythemia vera.

Pivotal trial data:
Fedratinib was evaluated in a double-blind, placebo-controlled, randomized study (JAKARTA) in 289 patients with primary or secondary myelofibrosis, as well as a single-arm, open-label study (JAKARTA2) in 97 patients with primary or secondary myelofibrosis previously exposed to Jakafi® (ruxolitinib). Jakafi is a JAK1/JAK2 inhibitor also approved for myelofibrosis. The primary endpoint in both studies was spleen response rate at week 24 (or 6 cycles), defined as the proportion of patients who had a reduction in spleen volume (as determined by a blinded CT and MRI) of at least 35%.

In the JAKARTA study, a significant reduction in spleen volume was achieved in 37% of patients receiving fedratinib vs. 1% with placebo ($p < 0.0001$). In JAKARTA2 (previous treatment with ruxolitinib), 31% (95% CI: 22, 41) of patients treated with fedratinib achieved the primary endpoint of spleen volume reduction.

Safety:
The most common adverse events with fedratinib use were anemia, diarrhea, nausea, and vomiting.

Dosing:
In the pivotal trials, fedratinib was administered orally once a day.

- JAK2 inhibitor
- Oral formulation
- Spleen response rate: 37% vs. 1% with placebo ($p < 0.0001$)
- Spleen response rate (in prior Jakafi-treated patients): 31% (95% CI: 22, 41)
- anemia, diarrhea, nausea, vomiting
- Dosing: once daily

Competitive environment

Fedratinib offers an additional treatment option for myelofibrosis. There is a high unmet need for treatment of this condition, particularly in patients who are non-responders or cannot tolerate Jakafi. In addition, fedratinib is dosed orally once a day while Jakafi is dosed twice a day.

However, a safety signal for Wernicke's encephalopathy, a rare neurological disorder associated with vitamin B1 deficiency, was identified after the JAKARTA trial which originally halted development for fedratinib. A boxed warning for encephalopathy is included in the fedratinib drug label.

In addition, there are no head-to-head data comparing fedratinib vs. Jakafi and no overall survival (OS) data is currently available for fedratinib.

For reference, the WAC price for Jakafi is $13,000 per 30 days.

- Advantages: additional treatment option for myelofibrosis, high unmet need, oral, once a day
- Disadvantages: boxed warning for encephalopathy, lack of head-to-head data vs. Jakafi, lack of OS data
- Reference WAC (Jakafi) = $13,000 per 30 days

Tenapanor (Brand Name: Ibsrela)

Manufacturer: Ardelyx
Expected FDA decision: 9/13/2019

Therapeutic use

Tenapanor is in development for the treatment of patients with irritable bowel syndrome with constipation (IBS-C).

IBS is a chronic gastrointestinal (GI) disorder characterized by abdominal pain and altered bowel habits. In patients with IBS-C, chronic abdominal pain is associated with constipation. It is estimated that about 11 million people in the U.S. are affected by IBS-C.

- Treatment of patients with IBS-C

Clinical profile

Tenapanor is a novel sodium transporter sodium-hydrogen exchanger 3 (NHE3) inhibitor. It is believed to work in IBS-C by reducing sodium absorption in the GI tract which increases intestinal fluid. Data from preclinical studies also suggest that tenapanor reduces abdominal pain caused by IBS-C through the inhibition of transient receptor potential vanilloid 1 (TRPV-1) dependent signaling. TRPV-1 is a pain target known for transmitting painful stimuli.

- Sodium transporter NHE3 inhibitor
- Oral formulation
- Responder rate: 27.0% to 36.5% vs. 18.7 to 23.7% with placebo
- Common AEs: diarrhea, nausea, abdominal distension
- Dosing: twice a day

Pivotal trial data:
Tenapanor was evaluated in two, double-blind, placebo-controlled, randomized trials (T3MPO-1 and T3MPO-2) in 1,203 patients with IBS-C. The primary endpoint was the combined responder rate (6/12 weeks), which was defined as at least a 30% reduction in abdominal pain and an increase of one or more complete spontaneous bowel movements in the same week for at least 6 of the 12 weeks of the treatment period.

In the T3MPO-1 trial, a greater proportion of tenapanor-treated patients vs. placebo-treated patients achieved the primary endpoint (27.0% vs. 18.7%, respectively; $p = 0.02$). Similar results were observed in T3MPO-2, with 36.5% and 23.7% of patients meeting the primary endpoint with tenapanor and placebo, respectively ($p < 0.001$).

Safety:
The most common adverse events with tenapanor use were diarrhea, nausea, and abdominal distension.

Dosing:
In the pivotal trials, tenapanor was administered orally twice a day.

Tenapanor (continued...)

Competitive environment

Tenapanor offers a novel mechanism of action (MOA) for the treatment of IBS-C. There is an unmet need for novel therapies for IBC, particularly due to the heterogeneity of the condition. In addition, tenapanor is also in development for the treatment of hyperphosphatemia, which could potentially add to its future market potential.

While tenapanor does offer a novel MOA for the treatment of IBS-C, it is a relatively late market entry and there are several alternatives available, including Linzess® (linaclotide), Trulance® (plecanatide), and Amitiza® (lubiprostone). Tenapanor also demonstrated modest efficacy in the trials and compared indirectly, does not appear to be more efficacious vs. existing treatment options. Tenapanor also must be dosed twice a day whereas several treatment options currently available may be dosed once a day (eg, Trulance, Linzess).

For reference, the WAC price for Linzess and Trulance is approximately $5,000 per year.

- Advantages: novel MOA, unmet need, oral, also in development for the treatment of hyperphosphatemia
- Disadvantages: alternatives available, modest efficacy, twice a day dosing
- Reference WAC (Linzess, Trulance) = ~$5,000 per year

Diroximel fumarate (Brand Name: Vumerity)

Manufacturer: Alkermes/Biogen
Expected FDA decision: 10/17/2019

Therapeutic use

- Treatment of relapsing forms of MS

Diroximel fumarate is in development for the treatment of relapsing forms of multiple sclerosis (MS).

MS is a chronic, inflammatory, autoimmune disease of the central nervous system. MS affects nearly 1 million people in the U.S. and it is among the most common causes of neurological disability in young adults.

Clinical profile

- Nrf2 pathway activator
- Oral formulation
- ARR: 79% reduction over one year when compared to baseline
- Common AEs: flushing, pruritus, GI side effects
- Dosing: twice a day

Diroximel fumarate is designed to be rapidly metabolized to monomethyl fumarate, which is the active metabolite of Tecfidera® (dimethyl fumarate). Tecfidera is also approved for the treatment of relapsing MS.

The mechanism by which fumarate products exert their therapeutic effect in MS is unknown. Monomethyl fumarate has been shown to activate the Nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway. The Nrf2 pathway is involved in the cellular response to oxidative stress.

Pivotal trial data:
Alkermes/Biogen are seeking approval of diroximel fumarate under the 505(b)(2) regulatory pathway, referencing Tecfidera efficacy data. In addition, the FDA filing was also supported by an open-label, two-year safety study in patients with relapsing forms of MS. In 696 MS patients, diroximel fumarate showed a significant reduction in the annualized relapse rate (ARR) by 79% over one year when compared to baseline.

Safety:
The most common adverse events with diroximel fumarate use were flushing, pruritus, and GI side effects.

The GI tolerability of diroximel fumarate was compared vs. Tecfidera in a double-blind, active-controlled, five-week trial. The primary endpoint was the number of days patients reported GI symptoms with a symptom intensity score ≥ 2 on the Individual Gastrointestinal Symptom and Impact Scale (IGISIS) (0 = not at all; 10 = extreme). Diroximel fumarate was statistically superior to Tecfidera, with patients treated with diroximel fumarate self-reporting significantly fewer days of key GI symptoms with intensity scores ≥ 2 on the IGISIS ($p = 0.0003$). The most common adverse events reported in the study for both treatment groups were flushing, diarrhea and nausea (32.8%, 15.4% and 14.6% for diroximel fumarate; 40.6%, 22.3% and 20.7% for Tecfidera). The proportion of patients with an adverse event leading to study discontinuation was 1.6% for diroximel fumarate and 6.0% for Tecfidera. Of those, the proportion of patients who discontinued due to GI adverse events was 0.8% for diroximel fumarate and 4.8% for Tecfidera.

Dosing:
In the pivotal trials, diroximel fumarate was administered orally twice a day.

Diroximel fumarate (continued...)

Competitive environment

If approved, diroximel fumarate would provide an additional oral treatment option for MS with potentially superior GI tolerability vs. Tecfidera.

However, diroximel fumarate would be entering a crowded marketplace with several oral and injectable alternatives available for treating relapsing forms of MS. Diroximel fumarate has a similar clinical profile as Tecfidera with no data suggesting improved efficacy. Like Tecfidera, it must also be dosed twice a day.

For reference, the WAC price for Tecfidera is approximately $95,000 per year.

- Advantages: potentially superior GI tolerability vs. Tecfidera, oral
- Disadvantages: alternatives available, similar clinical profile as Tecfidera, twice a day
- Reference WAC (Tecfidera) = ~$95,000 per year

Brolucizumab (Brand Name: Beovu)

Manufacturer: Novartis
Expected FDA decision: 11/2019

Therapeutic use

Brolucizumab is in development for the treatment of neovascular (wet) age-related macular degeneration (AMD).

The American Academy of Ophthalmology estimates that 15 million North Americans currently have AMD with about 10% to 15% suffering from neovascular (wet) AMD. Wet AMD is a degenerative disease of the central portion of the retina characterized by growth of abnormal vessels in the subretinal space; this results in loss of central vision and, if untreated, can lead to blindness.

- Treatment of neovascular (wet) AMD

Brolucizumab (continued...)

Clinical profile

Brolucizumab is a vascular endothelial growth factor (VEGF) inhibitor. Increased signaling through the VEGF pathway is associated with pathologic ocular angiogenesis and retinal edema. Inhibition of the VEGF pathway has been shown to reduce the growth of neovascular lesions, resolve retinal edema and improve vision in patients with retinal vascular diseases.

Brolucizumab differs from currently available VEGF inhibitors because it is a humanized single-chain antibody fragment (others are full length monoclonal antibodies). Due to their small size, single-chain antibody fragments can provide enhanced tissue penetration and rapid clearance from systemic circulation.

Pivotal trial data:
The efficacy of brolucizumab was evaluated in two double-masked, active-controlled, randomized studies (HAWK and HARRIER) in 1,817 untreated wet AMD patients. Patients were randomized to brolucizumab or Eylea® (aflibercept). Brolucizumab was administered as a maintenance dose every 8 or 12 weeks (depending on disease activity) vs. every 8 weeks for Eylea. At week 48 in both trials, brolucizumab demonstrated noninferiority to Eylea for the primary endpoint of mean best-corrected visual acuity (BCVA) change from baseline ($p < 0.001$).

At week 16, fewer brolucizumab patients had disease activity vs. Eylea in HAWK (24.0% vs. 34.5%; $p = 0.001$) and HARRIER (22.7% vs. 32.2%; $p = 0.002$). Other anatomic retinal fluid outcomes also favored brolucizumab.

Safety:
The most common adverse events with brolucizumab use were conjunctival hemorrhage, reduced visual acuity, and eye pain.

Dosing:
In the pivotal trials, brolucizumab was administered as an intravitreal injection. Patients received a loading dose of three monthly injections, followed by injections every 12 weeks. The interval could be adjusted to every 8 weeks if disease activity was present.

- VEGF inhibitor
- Intravitreal formulation
- Non-inferior to Eylea for mean BCVA change from baseline
- Demonstrated superiority to Eylea for improvements in disease activity and other anatomical retinal fluid outcomes
- Common AEs: conjunctival hemorrhage, reduced visual acuity, eye pain
- Maintenance dosing: every 8 to 12 weeks

Competitive environment

If approved, brolucizumab would provide an additional VEGF inhibitor treatment option for wet AMD. Other approved VEGF inhibitors for wet AMD include Eylea and Lucentis® (ranibizumab). While brolucizumab did not demonstrate superiority for the primary endpoint, key secondary outcomes did favor brolucizumab vs. Eylea. Brolucizumab may also be administered every 12 weeks. The recommended dosing frequency for Eylea is every 8 weeks. The dosing frequency for Eylea can be extended to every 12 weeks after one year of effective therapy but it is not as effective as the recommended every 8 week dosing regimen. The recommended dosing frequency for Lucentis is once every month (approximatly 28 days)

However, in the clinical trials about 50% of brolucizumab-treated patients required dosing every 8 weeks. In addition, brolucizumab is a relatively late market entry for the treatment of wet AMD and the other VEGF inhibitors are also approved for other ophthalmic indications (eg, macular edema following retinal vein occlusion, diabetic macular edema, diabetic retinopathy). Brolucizumab may also face future competition as Allergan's abicipar pegol could be available in late 2020.

For reference, the WAC price for Eylea is approximately $30,000 per year.

- Advantages: potential improved efficacy vs. Eylea, potential for fewer intravitreal injections (every 12 weeks)
- Disadvantages: ~50% of patients still required injections every 8 weeks, late market entry, currently available VEGF inhibitors are also approved for other ophthalmic indications, potential future competition (eg, abicipar pegol)
- Reference WAC (Eylea) = ~$30,000 per year

Lasmiditan (Brand Name: To be determined)

Manufacturer: Eli Lilly
Expected FDA decision: 11/14/2019

Therapeutic use

Lasmiditan is in development for the acute treatment of migraine headaches in adults.

Patients suffering from migraines have recurrent episodes of severe headache accompanied by other symptoms including nausea, vomiting, sensitivity to light and sound, and changes in vision. An estimated 30 million adults in the U.S. experience migraine headaches.

- Acute treatment of migraine headaches in adults

Clinical profile

Lasmiditan is a first-in-class drug which selectively targets serotonin 5-HT1F receptors, including those expressed in the trigeminal pathway.

Triptans such as sumatriptan and rizatriptan are the current standard of care for the acute treatment of migraine headaches. Triptans are serotonin 5-HT1B/1D receptor agonists. They can cause vasoconstriction due to activation of the 5-HT1B receptors which is thought to drive a small increased risk of serious cardiovascular adverse events.

Pivotal trial data:
The efficacy of lasmiditan was evaluated in two double-blind, placebo-controlled, randomized trials (SAMURAI and SPARTAN). The co-primary endpoints were the proportion of patients headache pain-free and most bothersome symptom (MBS)-free (eg, sensitivity to light or sound, or nausea) at 2 hours post-dose.

In SAMURAI, more patients dosed with lasmiditan 100 mg and 200 mg were free of headache pain at 2 hours after dosing vs. placebo (28.2% and 32.2% vs. 15.3%, respectively; $p < 0.001$ for both doses). More patients dosed with lasmiditan 100 mg and 200 mg were also free of their MBS compared with placebo (40.9% and 40.7% vs. 29.5%; $p < 0.001$ for both doses).

Similar results were observed in the SPARTAN trial. Lasmiditan was associated with significantly more patients free of headache at 2 hours post-dose (lasmiditan 200 mg: 38.8%, $p < 0.001$; 100 mg: 31.4%, $p < 0.001$; 50 mg: 28.6%, $p = 0.003$ vs. placebo 21.3%) and freedom from MBS (lasmiditan 200 mg: 48.7%, $p < 0.001$; 100 mg: 44.2%, $p< 0.001$; 50 mg: 40.8%, $p = 0.009$ vs. placebo 33.5%).

Safety:
The most common adverse events with lasmiditan use were dizziness, somnolence, and paresthesia.

Dosing:
In the pivotal trials, lasmiditan was administered orally as needed after onset of migraine headache.

- Serotonin 5-HT1F receptor agonist
- Oral formulation
- Headache pain-free at 2 hrs post-dose: 32.2% to 38.8% with lasmiditan 200 mg vs. 15.3% to 21.3% with placebo
- MBS-free at 2 hrs post-dose: 40.7% to 48.7% with lasmiditan 200 mg vs. 29.5% to 33.5% with placebo
- Safety: dizziness, somnolence, paresthesia
- Dosing: as needed after onset of migraine headache

Lasmiditan (continued...)

Competitive environment

If approved, lasmiditan would add to the treatment armamentarium for acute migraine treatment and it has a novel MOA as a selective serotonin 5-HT1F agonist. Lasmiditan's selectivity for 5-HT1F could make it a potentially attractive alternative treatment option in patients who have contraindications or are non-responders to triptan therapies.

The triptans and lasmiditan both target serotonin activity, but with different sub-receptor selectivity. There are lingering questions whether this difference in MOA will result in true efficacy or safety differences between the two classes. Lasmiditan would likely be reserved as a second-line agent due to the availability of several generic triptan alternatives and a lack of head-to-head data for lasmiditan vs. triptans. In addition, lasmiditan will potentially have competition for this niche of patients (triptan non-responders and patients unable to use triptans) as oral anti-calcitonin related-gene peptide (CGRP) antagonists are also in development for acute treatment of migraine.

The projected average WAC price for lasmiditan is approximately $1,750 per year; however this will vary patient to patient since lasmiditan is administered as needed.

- Advantages: novel MOA, unmet need in patients who do not respond or cannot use triptans, oral
- Disadvantages: generic alternatives available, lack of head-to-head data vs. triptans, potential future competition with oral CGRP antagonists
- Projected WAC = ~$1,750 per year

Ubrogepant (Brand Name: To be determined)

Manufacturer: Allergan
Expected FDA decision: 12/2019

Therapeutic use

Similar to lasmiditan, ubrogepant is also in development for the acute treatment of migraine headaches in adults.

- Acute treatment of migraine headaches in adults

Clinical profile

Ubrogepant is a highly potent CGRP receptor antagonist. CGRP and its receptors are expressed in regions of the nervous system associated with migraine pathophysiology.

- CGRP antagonist
- Oral formulation

Pivotal trial data:
The efficacy of ubrogepant was evaluated in two double-blind, placebo-controlled, randomized studies (ACHIEVE I and ACHIEVE II). The co-primary endpoints were the proportion of patients that were headache pain-free and MBS-free at 2 hours post-dose.

In the ACHIEVE I trial, more patients dosed with ubrogepant 50 mg and 100 mg were free of headache pain at 2 hours after dosing vs. placebo (19.2% and 21.2% vs. 11.8%, respectively; 50 mg vs. placebo p = 0.0023, 100 mg vs. placebo, p = 0.0003). More patients treated with ubrogepant were also free of their MBS compared with placebo, (38.6% and 37.7% vs. 27.8%, respectively, p = 0.0023 for both doses).

- Headache pain-free at 2 hrs post-dose: 19.2% to 21.8% vs. 11.8% to 14.3% with placebo
- MBS-free at 2 hrs post-dose: 37.7% to 38.9% vs. 27.4% to 27.8% with placebo

Similar results were observed in the ACHIEVE II trial, which evaluated ubrogepant 25 mg and 50 mg. More patients dosed with ubrogepant were free of headache pain at 2 hours after dosing vs. placebo (20.7% and 21.8% vs. 14.3%, respectively; 25 mg vs. placebo, p = 0.0285, 50 mg vs. placebo, p = 0.0129). Compared with placebo, more patients dosed with ubrogepant 50 mg were also free of their MBS (38.9% vs. 34.1%, p = 0.0129). However, ubrogepant 25 mg failed to demonstrate statistical significance vs. placebo for this endpoint (p = 0.0711).

Safety:
The most common adverse events with ubrogepant use were nausea, somnolence, dry mouth, and liver enzyme elevations.

- Common AEs: nausea, somnolence, dry mouth, liver enzyme elevations

Dosing:
In the pivotal trials, ubrogepant was administered orally as needed after onset of migraine headache.

- Dosing: as needed after onset of migraine headache

Ubrogepant (continued...)

Competitive environment

If approved, ubrogepant would represent the first approved oral CGRP antagonist. Subcutaneously administered CGRP antagonists are only approved for migraine prophylaxis. Similar to lasmiditan, ubrogepant would be a potential treatment option in acute migraine patients who have contraindications to triptans or who are non-responders to triptan therapy.

Ubrogepant would likely be reserved as a second-line agent due to the availability of generic triptan alternatives and a lack of head-to-head data vs. triptans, the well-established standard of care. It would also be competing with lasmiditan and other oral CGRP antagonists in development for acute migraine treatment (eg, rimegepant), which are expected to enter the market in 2020.

Compared indirectly vs. lasmiditan, ubrogepant appears to be better tolerated but also appears to be less efficacious for acute migraine treatment; however, it is difficult to compare results across different clinical trials.

The projected average WAC price for ubrogepant is approximately $1,750 per year; however this will vary from patient to patient since it is administered as needed.

- Advantages: potentially first approved oral CGRP antagonist, unmet need in patients who do not respond to or cannot use triptans, oral
- Disadvantages: generic alternatives available, lack of head-to-head data vs. triptans, potential future competition with lasmiditan and other oral CGRP antagonists (eg, rimegepant)
- Projected WAC = ~$1,750 per year

RVT-802 (Brand Name: To be determined)

Manufacturer: Enzyvant/Roivant
Regulatory designations: Orphan Drug, Breakthrough Therapy, Regenerative Medicine Advanced Therapy
Expected FDA decision: 12/2019

Therapeutic use

RVT-802 is in development for the treatment of primary immune deficiency resulting from congenital athymia.

Congenital athymia is a rare condition where patients are born without a thymus, resulting in a severe immunodeficiency due to the inability to produce normally functioning T cells. In a healthy, functioning immune system, T cells that start as stem cells in bone marrow become fully developed in the thymus. Approximately 20 infants are born each year in the U.S. with congenital athymia, which is fatal if untreated. Death typically occurs in the first 24 months of life due to infection.

Currently, there are no FDA-approved therapies for this condition and the standard of care has been investigational thymic tissue transplantation or HSCT.

- Treatment of primary immune deficiency resulting from congenital athymia

RVT-802 (continued...)

Clinical profile

RVT-802 is an allogeneic cultured postnatal thymus tissue-derived product manufactured from tissue obtained from unrelated donors under the age of 9 months. RVT-802 is designed to replicate this process in the absence of a thymus.

Pivotal trial data:
At the time of the FDA filing, a total of 93 patients received RVT-802 across multiple clinical studies, including 85 patients who met the criteria for inclusion in the efficacy analysis. The Kaplan-Meier estimates of survival at year 1 and year 2 post-treatment were 76% (95% CI: 66, 84) and 75% (95% CI: 66, 83), respectively. For patients surviving 12 months post-treatment, there was a 93% probability of surviving 10 years post-treatment.

Safety:
The most commonly reported adverse events with RVT-802 use include thrombocytopenia, neutropenia, pyrexia, and proteinuria.

Dosing:
RVT-802 is administered as a one-time therapy. It is inserted into a patient's quadriceps muscles by means of an open surgical procedure.

- Tissue-based therapy (allogeneic thymic tissue)
- Implantation via quadriceps
- Survival at year 2 post-treatment: 75% (95% CI: 66, 83)
- Common AEs: thrombocytopenia, neutropenia, pyrexia, proteinuria
- Dosing: one-time therapy

Competitive environment

While RVT-802 has been available as an investigational therapy, it could potentially be the first FDA-approved therapy for congenital athymia. There is a significant unmet need for the treatment of congenital athymia as death typically occurs in children within 24 months if untreated.

While the number of patients treated with RVT-802 over several clinical studies is small, the survival estimates do appear to be strong (75% at two years post-treatment). RVT-802 does require implantation into the quadriceps muscles and administration may be limited to specific centers that are able to perform the procedure.

- Advantages: potentially first FDA-approved therapy for congenital athymia, significant unmet need
- Disadvantages: implantation via an open surgical procedure, administration likely to be limited to specific centers of care

Luspatercept (Brand Name: To be determined)

Manufacturer: Celgene/Acceleron
Regulatory designations: Orphan Drug, Fast Track
Expected FDA decision: 12/4/2019 (beta-thalassemia); 4/4/2020 (myelodysplastic syndromes [MDS])

Therapeutic use

Luspatercept is in development for the treatment of adult patients who require red blood cell (RBC) transfusions with: beta-thalassemia-associated anemia or very low to intermediate-risk MDS-associated anemia.

Beta-thalassemia is a rare hereditary blood disorder characterized by reduced levels of functional hemoglobin. Symptomatic cases occur in approximately 1 in 100,000 individuals. HSCT can be curative; however it is limited by availability of donors and risks associated with the procedure. The current standard of care for management of severe beta-thalassemia is life-long RBC transfusions and iron chelation.

MDS are a rare group of blood disorders that occur as a result of disordered development of blood cells within the bone marrow. RBCs, white blood cells and platelets are affected. In some affected individuals, MDS may progress to life-threatening failure of the bone marrow or develop into an acute leukemia. Approximately 20,000 new cases of MDS are diagnosed each year in the U.S. Similar to beta-thalassemia, HSCT is the only curative treatment. Supportive care for patients with anemia can include erythropoietin stimulating agents (ESAs) or RBC transfusions.

- Treatment of adult patients with beta-thalassemia-associated anemia or very low to intermediate-risk MDS-associated anemia

Luspatercept (continued...)

Clinical profile

Luspatercept is a novel, first-in-class erythroid maturation agent. Luspatercept inhibits members of the TGF-beta superfamily which are involved in late stages of erythropoiesis and which inhibit RBC maturation. Luspatercept attempts to restore RBC production.

Pivotal trial data:
The efficacy of luspatercept was evaluated in a double-blind, placebo-controlled, randomized study (BELIEVE) in 336 adult patients with beta-thalassemia-associated anemia who require RBC transfusions. Patients received luspatercept or placebo and all patients received background best supportive care. The primary endpoint was the proportion of patients experiencing a reduction in transfusion burden (≥ 33%) during weeks 13 to 24. Overall, 21.4% of patients receiving luspatercept experienced a reduction in transfusion burden vs. 4.5% with placebo (p <0.0001).

Luspatercept was also evaluated in a double-blind, placebo-controlled, randomized trial (MEDALIST) in 229 adults with RBC transfusion-dependent MDS who were either refractory, intolerant, or not candidates for ESA therapy. Transfusion independence for ≥ 8 weeks during first 24 weeks of the trial was achieved in 37.9% of patients treated with luspatercept vs. 13.2% with placebo (p < 0.0001).

Safety:
The most common adverse events with luspatercept use were thromboembolic events (deep venous thrombosis, pulmonary embolism, portal vein thrombosis, ischemic stroke, thrombophlebitis, and superficial phlebitis), bone pain, hypertension, diarrhea, and nausea.

Dosing:
In the pivotal trials, luspatercept was administered subcutaneously (SC) every 21 days.

- Erythroid maturation agent
- SC formulation
- Beta-thalassemia – reduction in transfusion burden at wks 13 to 24: 21.4% vs. 4.5% with placebo (p < 0.0001)
- MDS – transfusion independence (for ≥ 8 wks of 24 wks): 37.9% vs. 13.2% with placebo (p < 0.0001)
- Common AEs: thromboembolic events, bone pain, hypertension, diarrhea/nausea
- Dosing: every 21 days

Competitive environment

Luspatercept offers a novel MOA for the treatment of both beta-thalassemia and MDS. There is a high unmet need for treatments for both conditions and it would potentially be the first FDA-approved therapy for beta-thalassemia. Aside from curative HSCT, these conditions have primarily been managed with blood transfusions which can be costly and associated with complications (eg, iron overload).

Luspatercept does require SC administration by a healthcare provider and while it may reduce or eliminate the need for blood transfusions in some patients, luspatercept is a chronic therapy and it may soon have competition from a potentially curative therapy. LentiGlobin/Zynteglo is a one-time gene therapy treatment for beta-thalassemia that is preparing to file with the FDA and could become available in mid-to-late 2020.

Additionally, luspatercept was associated with a higher overall rate of thromboembolic events (3.6% vs. 0.9% with placebo) in the beta-thalassemia trial; although, all luspatercept-affected patients reportedly had multiple risk factors for thrombotic events.

- Advantages: novel MOA, potentially first approved therapy for beta-thalassemia, high unmet need (can reduce or eliminate the need for blood transfusions)
- Disadvantages: requires SC administration by a healthcare provider, not curative, potential future gene therapy competition for beta-thalassemia, potential safety signal for thromboembolic events

Lemborexant (Brand Name: To be determined)

Manufacturer: Eisai/Imbrium Therapeutics
Expected FDA decision: 12/27/2019

Therapeutic use

- Treatment of insomnia in adult patients

Lemborexant is in development for the treatment of insomnia in adult patients.

Insomnia affects approximately 30% of the adult population worldwide and is characterized by difficulty falling asleep, staying asleep, or both.

Clinical profile

- Orexin receptor 1 and 2 antagonist
- Oral formulation
- Superiority vs. placebo for all primary and key secondary sleep endpoints
- Common AEs: somnolence, headache, nasopharyngitis
- Dosing: once a day at bedtime

Lemborexant inhibits orexin signaling by binding competitively to both orexin receptor subtypes (orexin receptor 1 and 2). In individuals with sleep-wake disorders, orexin signaling is believed to regulate wakefulness and inhibiting inappropriate orexin signaling may enable initiation and maintenance of sleep.

Pivotal trial data:
The efficacy of lemborexant was evaluated in a double-blind, placebo-controlled, active comparator, randomized trial (SUNRISE-1) in 1,006 patients 55 years and older with insomnia disorder. In this study, patients were randomized to receive placebo or one of three treatment regimens (lemborexant 5 mg, lemborexant 10 mg, zolpidem ER 6.25 mg). In addition, lemborexant was evaluated in a double-blind, placebo-controlled, randomized study (SUNRISE-2) in 949 patients between the ages of 18 to 88 years. SUNRISE-2 did not include zolpidem ER as an active control. The primary endpoint was sleep onset, as measured by latency to persistent sleep.

In the pooled analysis of both trials, median reductions from baseline in subjective sleep onset latency were larger for lemborexant 5 mg and 10 mg vs. placebo during the first seven days of treatment (-12.9 minutes for lemborexant 5 mg, -13.6 minutes for lemborexant 10 mg, -2.9 minutes for placebo) and at the end of month one of treatment (-16.1 minutes for lemborexant 5 mg, -17.9 minutes for lemborexant 10 mg, -5.2 minutes for placebo). Lemborexant also demonstrated superiority vs. placebo for key secondary sleep endpoints (eg, sleep efficiency, wake after sleep onset [WASO]) and demonstrated statistical superiority vs. zolpidem ER for WASO in the second half of the night.

Safety:
The most common adverse events with lemborexant use were somnolence, headache, and nasopharyngitis.

Dosing:
In the pivotal trials, lemborexant was administered orally once a day at bedtime.

Lemborexant (continued...)

Competitive environment

Insomnia represents a large market with approximately 30% of the population affected by the disorder. The FDA also recently added a boxed warning for several insomnia drugs (ie, eszopiclone, zaleplon, and zolpidem), for rare but serious injuries due to sleep behaviors, including sleepwalking, sleep driving, and engaging in other activities while not fully awake. The label for Belsomra® (suvorexant), another orexin receptor antagonist, was not updated with this boxed warning; therefore it is unlikely that lemborexant would be impacted by this limitation as well.

However, many of the drugs used for insomnia are available generically and lemborexant is a late market entry. Aside from drugs with different MOAs, Belsomra has also been available since 2014. Similar to other insomnia drugs, including Belsomra, lemborexant would likely require DEA scheduling.

For reference, the WAC price for Belsomra is approximately $350 per 30 days.

- Advantages: potential superiority vs. zolpidem ER, large market, oral, once a day
- Disadvantages: generic alternatives available, late market entry, likely DEA scheduling
- Reference WAC (Belsomra) = ~$350 per 30 days

Lumateperone (Brand Name: To be determined)

Manufacturer: Intra-Cellular Therapies
Regulatory designations: Fast Track
Expected FDA decision: 12/27/2019

Therapeutic use

Lumateperone is in development for the treatment of adult patients with schizophrenia.

Schizophrenia is a common severe mental illness that affects approximately 2.4 million people in the U.S. It is characterized by positive symptoms (eg, hallucinations, delusions, disorganized thoughts), negative symptoms (eg, diminished expression, apathy), and impairments in cognition. Mood and anxiety symptoms are also common in schizophrenia.

Lumateperone (continued...)

- Treatment of adult patients with schizophrenia

Clinical profile

Lumateperone is a first-in-class serotonin, dopamine, and glutamate modulator. Lumateperone is a potent serotonin 5-HT2A receptor antagonist, a dopamine receptor phosphoprotein modulator acting as a presynaptic partial agonist and postsynaptic antagonist at dopamine D2 receptors, and a dopamine D1 receptor-dependent indirect modulator of glutamate. In addition, lumateperone also has serotonin reuptake inhibitor properties.

Pivotal trial data:
The efficacy of lumateperone was evaluated in three double-blind, placebo-controlled, randomized pivotal trials. In two of the trials, risperidone, a second generation atypical antipsychotic, was also included as an active control. The primary endpoint in all three studies was the change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score. In a pooled analysis of the three trials, lumateperone 60 mg demonstrated a statistically significant improvement in the PANSS total score vs. placebo ($p = 0.003$). The exact numerical differences between lumateperone and placebo from the pooled analysis have not been reported. However, in 1 of the 3 individual trials, lumateperone failed to demonstrate superiority vs. placebo.

Safety:
The most common adverse events with lumateperone use were somnolence and sedation.

Dosing:
In the pivotal trials, lumateperone was administered orally once a day.

- Serotonin, dopamine, and glutamate modulator
- Oral formulation
- Statistically significant improvement in the PANSS total score vs. placebo in a pooled analysis of three pivotal studies; failed to achieve primary endpoint in 1 of the 3 pivotal trials
- Common AEs: somnolence, sedation
- Dosing: once daily

Competitive environment

Lumateperone offers a novel MOA for the treatment of schizophrenia. Second-generation antipsychotics are the standard of care for schizophrenia treatment and they work as modulators of serotonin and dopamine. However, these drugs are primarily only effective in treating the positive symptoms of schizophrenia and can be associated with significant AEs. Of note, lumateperone demonstrated fewer metabolic disturbances and less weight gain vs. risperidone in the clinical trials.

However, there are many alternative oral treatment options for schizophrenia, some of which are available generically. Long-acting injectable antipsychotics are also available for patients who do not want the daily reminder of oral medications. In addition, while lumateperone may confer safety benefits vs. the current standard of care, lumateperone failed to achieve its primary endpoint vs. placebo in one of the pivotal trials and there is no data suggesting that lumateperone is superior to existing treatment options.

For reference, the WAC price for Vraylar® (cariprazine), a recently approved oral antipsychotic, is approximately $14,500 per year.

- Advantages: novel MOA, potentially fewer AEs vs. second-generation atypical antipsychotics, oral, once a day
- Disadvantages: generic oral and long-acting injectable alternatives available, failed to achieve primary endpoint vs. placebo in one clinical trial, lack of data demonstrating superiority vs. standard of care
- Reference WAC (Vraylar) = ~$14,500 per year

Cabotegravir/rilpivirine (Brand Name: To be determined)

Manufacturer: ViiV Healthcare
Expected FDA decision: 12/29/2019

Therapeutic use

Cabotegravir/rilpivirine is in development for the treatment of human immunodeficiency virus (HIV)-1 infection in adults whose viral load is suppressed and who are not resistant to cabotegravir or rilpivirine.

Clinical profile

Cabotegravir is a novel HIV integrase inhibitor and rilpivirine is a non-nucleoside reverse transcriptase inhibitor (NNRTI).

Pivotal trial data:
The efficacy of cabotegravir/rilpivirine was evaluated in two open-label, active-controlled, randomized non-inferiority pivotal trials (ATLAS and FLAIR) in over 1,100 patients with HIV-1 infection. In the ATLAS trial, cabotegravir/rilpivirine was assessed vs. continuation of a patient's current three-drug oral antiretroviral therapy. In the FLAIR trial, all patients received 20 weeks of induction therapy with Triumeq® tablets (abacavir, dolutegravir, and lamivudine) and then were randomized to cabotegravir/rilpivirine or continuation of Triumeq therapy.

In the ATLAS trial, cabotegravir/rilpivirine demonstrated non-inferiority as measured by the proportion of participants with detectable HIV, defined as plasma HIV-1 RNA ≥ 50 copies/mL (cabotegravir/ rilpivirine: 1.6% vs. current antiretroviral therapy: 1.0%; $p < 0.05$). Similar viral results and non-inferiority were observed in the FLAIR trial.

Safety:
The most common adverse events with cabotegravir/rilpivirine use were injection site reactions, nasopharyngitis, headache, and diarrhea.

Dosing:
In the pivotal trials, cabotegravir/rilpivirine was administered as an intramuscular (IM) injection every 4 weeks.

As part of the regulatory submission package to the FDA, ViiV Healthcare also submitted a second New Drug Application for a single-agent, oral tablet formulation of cabotegravir. The oral formulation would be taken as a lead-in with an already-approved, once-daily, oral tablet formulation of rilpivirine.

Cabotegravir/rilpivirine (continued...)

- Treatment of HIV-1 infection in adults whose viral load is suppressed
- Cabotegravir: HIV integrase inhibitor; rilpivirine: NNRTI
- IM formulation
- Non-inferior for viral suppression vs. continuation of current antiretroviral therapy or Triumeq
- Common AEs: injection site reactions, nasopharyngitis, headache, diarrhea
- Dosing: once every 4 weeks

Competitive environment

If approved, cabotegravir/rilpivirine would be the first long-acting regimen for treatment of HIV-1 infection. The current standard of care includes multi-drug, oral regimens that require daily administration. A once monthly dosing schedule could be attractive in a niche of HIV-infected patients who struggle with adherence to oral medications or would otherwise benefit from less-frequent once monthly dosing. In the pivotal trials, the two-drug regimen was shown to be non-inferior to commonly used first-line, three-drug HIV regimens. In addition, an every 2 month dosing schedule is being investigated with topline results expected in the third quarter of 2019.

While cabotegravir/rilpivirine does offer an alternative long-acting treatment option, it is entering a crowded marketplace with many once daily oral options already available. Cabotegravir/rilpivirine also requires administration in a healthcare setting via IM injection into the gluteal muscles. Resistance is also a lingering concern with new two-drug HIV regimens vs. traditional three-drug regimens. This concern is heightened with cabotegravir/rilpivirine because a missed clinic visit or appointment could result in a prolonged duration of time that a patient is without antiretroviral therapy.

For reference, the WAC price for Dovato® (dolutegravir/lamivudine), a recently approved oral two-drug HIV regimen, is approximately $28,000 per year.

- Advantages: potentially first long-acting regimen for HIV, non-inferiority demonstrated vs. commonly used oral three-drug regimens
- Disadvantages: alternatives available, requires IM injection by a healthcare provider, concerns about long-term emergence of resistance
- Reference WAC (Dovato) = ~$28,000 per year

Extended generic pipeline forecast

OptumRx generic pipeline forecast

Brand name	Generic name	Brand manufacturer	Dosage form	Strengths available as generic	Possible launch date
2019 Possible launch date					
CUVPOSA	glycopyrrolate	Merz	Oral solution	All	2019
PREPOPIK	citric acid/magnesium oxide/sodium picosulfate	Ferring Pharmaceuticals	Oral packet	All	2019
TRAVATAN Z	travoprost	Alcon	Ophthalmic	All	2019
BYETTA	exenatide	AstraZeneca	Subcutaneous	All	2019
DESONATE	desonide	LEO Pharma	Gel	All	2019
SUPRENZA	phentermine	Citius/Akrimax	Tablet, orally disintegrating	All	2019
VIVLODEX	meloxicam	Iroko/iCeutica	Capsule	All	2019
PRESTALIA	perindopril/amlodipine	Symplmed	Tablet	All	2019
APTENSIO XR	methylphenidate	Rhodes	Capsule, extended-release	All	2H-2019
NUVARING	etonogestrel/ethinyl estradiol	Merck	Vaginal ring	All	2H-2019
RITUXAN	rituxumab	Genentech/Roche/Biogen Idec	Intravenous	All	2H-2019
SAMSCA	tolvaptan	Otsuka	Tablet	All	2H-2019
PYLERA	bismuth subcitrate potassium/metronidazole/ tetracycline	Allergan/Aptalis	Capsule	All	2H-2019
EVZIO	naloxone	Kaléo Pharma	Injection	All	2H-2019
ENBREL	etanercept	Amgen	Subcutaneous	All	2H-2019
RESTASIS	cyclosporine	Allergan	Ophthalmic	All	2H-2019
FORTEO	teriparatide	Eli Lilly	Injection	All	2H-2019
APRISO	mesalamine	Bausch Health	Capsule, extended-release	All	08-2019
EDLUAR	zolpidem	Meda/Orexo	Tablet, sublingual	All	09-2019
MYOBLOC	botulinum toxin type B	US WorldMeds	Intramuscular	All	09-2019
EMEND	fosaprepitant dimeglumine	Merck	Intravenous	150 mg	09-2019
FERRIPROX	deferiprone	ApoPharma/Apotex	Tablet	All	4Q-2019

Brand name	Generic name	Brand manufacturer	Dosage form	Strengths available as generic	Possible launch date
ZOHYDRO ER	hydrocodone	Persion/Currax	Capsule, extended-release	All	4Q-2019
JADENU	deferasirox	Novartis	Tablet; oral granules	All	10-2019
VERMOX	mebendazole	Janssen	Tablet, chewable	All	10-2019
OSMOPREP	sodium biphosphate/sodium phosphate	Bausch Health	Tablet	All	11-2019
AMELUZ	aminolevulinic acid	Biofrontera	Gel	All	11-2019
DUREZOL	difluprednate	Alcon	Ophthalmic	All	11-2019
OMNARIS	ciclesonide	Covis	Intranasal	All	12-2019
THALOMID	thalidomide	Celgene	Capsule	All	12-2019
2020 Possible launch date					
MYCAMINE	micafungin	Astellas	Intravenous	All	2020
CIPRODEX	ciprofloxacin/ dexamethasone	Alcon	Otic	All	2020
DORYX MPC	doxycycline hyclate	Mayne	Oral solution	All	2020
SYNDROS	dronabinol	Insys Therapeutics	Tablet, delayed-release	All	2020
SAPHRIS	asenapine	Allergan	Tablet, sublingual	All	1H-2020
NOXAFIL	posaconazole	Merck	Tablet; oral suspension	All	01-2020
DALIRESP	roflumilast	AstraZeneca	Tablet	All	01-2020
SILENOR	doxepin	Pernix	Tablet	All	01-2020
ELIGARD	leuprolide	QLT/Tolmar	Subcutaneous	All	03-2020
SOMATULINE DEPOT	lanreotide	Ipsen	Subcutaneous	All	03-2020
TAYTULLA	ethinyl estradiol/ norethindrone/ ferrous fumarate	Allergan	Tablet	All	03-2020
MOXEZA	moxifloxacin	Alcon	Ophthalmic	All	03-2020
ZORTRESS	everolimus	Novartis	Tablet	All	03-2020
RENOVA	tretinoin	Bausch Health	Cream	All	03-2020
TOTECT	dexrazoxane	Cumberland	Injection	All	03-2020
APTIVUS	tipranavir	Boehringer Ingelheim	Capsule; oral solution	All	04-2020
DEPO-SUBQ PROVERA	medroxyprogesterone	Pfizer	Subcutaneous	All	05-2020
NYMALIZE	nimodipine	Arbor	Oral solution	All	05-2020

Brand name	Generic name	Brand manufacturer	Dosage form	Strengths available as generic	Possible launch date
MYDAYIS	amphetamine/ dextroamphetamine mixture	Shire	Capsule, extended-release	All	06-2020
DEXILANT	dexlansoprazole	Takeda	Capsule, delayed-release	All	06-2020
DENAVIR	penciclovir	Mylan	Cream	All	06-2020
LUCENTIS	ranibizumab	Roche	Intravitreal	All	06-2020
ENTEREG	alvimopan	Merck	Capsule	All	2H-2020
VELPHORO	sucroferric oxyhydroxide	Fresenius	Tablet, chewable	All	3Q-2020
KINERET	anakinra	Swedish Orphan Biovitrum/Savient/Amgen	Subcutaneous	All	07-2020
SYNERA	lidocaine/tetracaine	Galen	Transdermal patch	All	07-2020
PEGASYS	peginterferon alfa-2A	Roche	Subcutaneous	All	08-2020
PEG-INTRON	peginterferon alfa-2B	Merck	Subcutaneous	All	08-2020
MARQIBO KIT	vincristine	Talon Therapeutics/Spectrum	Intravenous	All	09-2020
TYKERB	lapatinib	Novartis	Tablet	All	09-2020
BIDIL	isosorbide dinitrate/hydrazaline	Arbor	Tablet	All	09-2020
TRUVADA	emtricitabine/tenofovir	Gilead	Tablet	200 mg/300 mg	09-2020
ATRIPLA	efavirenz/emtricitabine/ tenofovir	Gilead/Bristol-Myers Squibb	Tablet	All	09-2020
KUVAN	sapropterin	BioMarin	Tablet; oral solution	All	10-2020
RISPERDAL CONSTA	risperidone	Janssen	Injection, extended-release	All	11-2020
XOLEGEL	ketoconazole	Almirall	Gel	All	11-2020
DULERA	formoterol fumarate/ mometasone furoate	Merck	Inhalation	All	11-2020
EPIDUO FORTE	adapalene/ benzoyl peroxide	Galderma	Gel	All	12-2020
OFIRMEV	acetaminophen	Mallinckrodt	Intravenous	All	12-2020
ABSORICA	isotretinoin	Sun	Capsule	All	12-2020
TOVIAZ	fesoterodine	Pfizer	Tablet, extended-release	All	12-2020
2021 Possible launch date					
BEPREVE	bepotastine	Bausch Health	Ophthalmic	All	2021
ACTEMRA	tocilizumab	Roche/Chugai	Intravenous; subcutaneous	All	2021

Brand name	Generic name	Brand manufacturer	Dosage form	Strengths available as generic	Possible launch date
KERYDIN	tavaborole	Pfizer	Topical solution	All	2021
VIIBRYD	vilazodone	Forest/Allergan	Tablet	All	2021
EMTRIVA	emtricitabine	Gilead	Oral; capsule	All	1H-2021
AMITIZA	lubiprostone	Sucampo/Takeda	Capsule	All	01-2021
VELCADE	bortezomib	Takeda	Intravenous	All	01-2021
CRIXIVAN	indinavir	Merck	Capsule	All	02-2021
NORTHERA	droxidopa	H. Lundbeck	Capsule	All	02-2021
MYALEPT	metreleptin	Aegerion	Subcutaneous	All	02-2021
FORTICAL	calcitonin salmon recombinant	Upsher-Smith	Intranasal	All	02-2021
YONSA	abiraterone	Sun	Tablet	All	03-2021
IMPAVIDO	miltefosine	Knight Therapeutics	Capsule	All	03-2021
ACTOPLUS MET XR	pioglitazone/metformin	Takeda	Tablet, extended-release	All	03-2021
OVIDREL	choriogonadotropin	EMD Serono/Merck	Intramuscular; subcutaneous	All	03-2021
NEUPRO	rotigotine	UCB	Transdermal patch	All	03-2021
LYRICA CR	pregabalin	Pfizer	Tablet, extended-release	All	04-2021
ERAXIS	anidulafungin	Pfizer	Intravenous	All	04-2021
TECFIDERA	dimethyl fumarate	Biogen	Capsule, delayed-release	All	05-2021
ZOMIG	zolmitriptan	Impax/Grunenthal	Intranasal	All	05-2021
QUTENZA	capsaicin	Grunenthal	Transdermal patch	All	06-2021
PERFOROMIST	formoterol fumarate	Mylan	Inhalation	All	06-2021
APTIOM	eslicarbazepine	Sunovion/Bial	Tablet	All	06-2021
SEEBRI NEOHALER	glycopyrrolate	Novartis	Inhalation	All	06-2021
INTELENCE	etravirine	Janssen	Tablet	All	06-2021
FLOVENT HFA	fluticasone propionate	GlaxoSmithKline	Inhalation; aerosol	All	2H-2021
ORENCIA	abatacept	Bristol-Myers Squibb	Intravenous; subcutaneous	All	07-2021

Brand name	Generic name	Brand manufacturer	Dosage form	Strengths available as generic	Possible launch date
FERAHEME	ferumoxytol	AMAG Pharmaceuticals	Intravenous	All	07-2021
RESCULA	unoprostone isopropyl	R-Tech Ueno	Ophthalmic	All	07-2021
ALTRENO	tretinoin	Bausch Health	Lotion	All	08-2021
BALCOLTRA	levonorgestrel/ethinyl estradiol/ferrous bisglycinate	Avion	Tablet	All	08-2021
SUTENT	sunitinib	Pfizer	Capsule	All	08-2021
SELZENTRY	maraviroc	ViiV Healthcare	Tablet	All	08-2021
POMALYST	pomalidomide	Celgene	Capsule	All	08-2021
VERAMYST	fluticasone fumarate	GlaxoSmithKline	Intranasal	All	08-2021
JEVTANA KIT	cabazitaxel	Sanofi	Intravenous	All	09-2021
BYSTOLIC	nebivolol	Allergan	Tablet	All	09-2021
PRADAXA	dabigatran etexilate mesylate	Boehringer Ingelheim	Capsule	All	4Q-2021
INNOPRAN XL	propranolol	Ani Pharmaceuticals	Capsule, extended-release	All	10-2021
BIJUVA	estradiol/progesterone	TherapeuticsMD	Capsule	All	10-2021
MIRCERA	methoxy polyethylene glycol-epoetin beta	Roche/Royalty Pharma	Subcutaneous	All	11-2021
ENTYVIO	vedolizumab	Takeda	Intravenous	All	11-2021
BRYHALI	halobetasol	Bausch Health	Lotion	All	11-2021
BROVANA	arformoterol	Sunovion	Inhalation	All	11-2021
ONEXTON	clindamycin/benzoyl peroxide	Bausch Health	Gel	All	12-2021
EPANED KIT	enalapril	Silvergate	Oral solution	All	12-2021
CHANTIX	varenicline	Pfizer	Tablet	All	12-2021
CAYSTON	aztreonam lysine	Gilead	Inhalation	All	12-2021
BETHKIS	tobramycin	Chiesi	Inhalation	All	12-2021
MYTESI	crofelemer	Napo	Table, delayed-release	All	12-2021
EXPAREL	bupivacaine	Pacira	Injection	All	12-2021
SUPREP BOWEL PREP KIT	magnesium sulfate anhydrous/potassium sulfate / sodium sulfate	Braintree	Oral solution	All	12-2021

+ = may launch during the stated date or later

Extended brand pipeline forecast

OptumRx brand pipeline forecast

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
2019 Possible launch date									
S-649266	cefiderocol	Shionogi/ GlaxoSmithKiline	cephalosporin antibiotic	Bacterial infections	IV	Filed NDA	8/14/2019	Yes	No
Nouriast	istradefylline	Kyowa Hakko Kogyo	A2A adenosine receptor antagonist	Parkinson's disease	PO	Filed NDA	8/27/2019	No	No
Rexista XR	oxycodone ER	IntelliPharmaCeutic	opioid agonist	Pain	PO	Filed NDA	8/28/2019	No	No
NKTR-181	NKTR-181	Nektar	opioid agonist	Pain	PO	Filed NDA	8/29/2019	No	No
tadalafil VersaFilm	tadalafil VersaFilm	IntelGenx	phosphodiesterase-5 (PDE-5) inhibitor	Erectile dysfunction	PO	Filed NDA	Mid-2019	Yes	No
fosphenytoin sodium/ sulfobutylether beta-cyclodextrin sodium	fosphenytoin sodium/ sulfobutylether beta-cyclodextrin sodium	Sedor	anticonvulsant	Seizures	IM/IV	Filed NDA	Mid-2019	Yes	No
XeriSol Glucagon	glucagon	Xeris	glucagon analog	Diabetes mellitus	SC	Filed NDA	9/10/2019	No	No
RDX-5791 (AZD-1722)	tenapanor	Ardelyx	sodium-hydrogen exchanger-3 (NHE-3) inhibitor	Irritable bowel syndrome-constipation	PO	Filed NDA	9/13/2019	No	No
Imvamune; MVA-BN	Imvamune; MVA-BN	Bavarian Nordic	vaccine	Smallpox	SC	Filed BLA	9/15/2019	Yes	No

659

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
NN-9924 (OG-217SC)	semaglutide (oral)	Novo Nordisk/ Emisphere Technologies	glucagon-like peptide-1 (GLP-1) receptor agonist	Diabetes mellitus	PO	Filed NDA	9/20/2019	Yes	No
Valtoco	diazepam	Neurelis	benzodiazepine	Seizures	Intranasal	Filed NDA	2H2019	No	Yes
Fasenra (self-administered)	benralizumab	AstraZeneca	interleukin-5 receptor (IL-5R) alpha inhibitor	Asthma	SC	Filed sNDA	2H2019	Yes	No
Scenesse	afamelanotide	Clinuvel	melanocortin receptor 1 (MC-1) agonist	Erythropoietic protoporphyria (EPP)/ Polymorphous light eruption (PLE/PMLE)/ Vitiligo	SC	Filed NDA	10/6/2019	Yes	Yes
PF-708	teriparatide	Pfenex/ Alvogen	parathyroid hormone	Osteoporosis	SC	Filed NDA	10/7/2019	Yes	No
Vumerity	monomethyl fumarate (diroximel fumarate)	Biogen/ Alkermes	Nrf2 pathway activator	Multiple sclerosis (MS)	PO	Filed NDA	10/17/2019	Yes	No
HP-3070	asenapine maleate	Noven Hisamitsu Pharmaceutical	5-HT2a and dopamine D1/D2 antagonist	Schizophrenia	TOP	Filed NDA	10/17/2019	No	No
Xipere	triamcinolone acetonide	Clearside	corticosteroid	Macular edema	intraocular/ subretinal	Filed NDA	10/19/2019	Yes	No
synthetic ACTH depot	cosyntropin	Assertio	adrenocorticotropic hormone (ACTH)	adrenocortical insufficiency	INJ	Filed NDA	10/19/2019	Yes	No
FMX-101 (ARK-E021)	minocycline	Foamix	tetracyclines	Acne vulgaris	TOP	Filed NDA	10/20/2019	No	No
ET-202	phenylephrine	Eton	alpha-1 adrenergic receptor agonist	Hypotension	IV	Filed NDA	10/21/2019	Yes	No

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
JDP-205	cetirizine	JDP Therapeutics	second generation antihistamine	Urticaria	IV	Filed NDA	10/30/2019	No	No
Zimhi	naloxone	Adamis	opioid antagonist	Opioid dependence	IM	Filed NDA	10/31/2019	No	No
RediTrex	methotrexate	Cumberland	dihydrofolate reductase (DHFR) inhibitor	Psoriasis; arthritis	SC	Filed NDA	11/1/2019	Yes	No
Talicia	rifabutin/ amoxicillin/ pantoprazole	RedHill Biopharma	RNA polymerase inhibitor/ penicillin/ proton pump inhibitor (PPI)	Bacterial infections	PO	Filed NDA	11/2/2019	No	No
Tlando	testosterone	Lipocine	androgen	Hypogonadism	PO	Filed NDA	11/9/2019	No	No
LY-573144 (COL-144)	lasmiditan	Eli Lilly	serotonin 5-HT1F receptor agonist	Acute migraines	PO	Filed NDA	11/14/2019	No	No
RTH-258 (ESBA-1008, DLX-1008)	brolucizumab	Novartis	anti-VEGF antibody	wet age-related (neovascular) macular degeneration (AMD)	Intravitreal	Filed BLA	11/15/2019	Yes	No
Twirla	ethinyl estradiol/ levonorgestrel	Agile Therapeutics	hormonal combination contraceptive	Pregnancy prevention	TOP	Filed NDA	11/17/2019	No	No
YKP-3089	cenobamate	SK Biopharmaceuticals	undisclosed	Seizure	PO	Filed NDA	11/21/2019	Yes	No
AQST-117	riluzole	Aquestive Therapeutics	glutamate release inhibitor	Amyotrophic lateral sclerosis (ALS)	SL/ Transmucosal	Filed NDA	11/30/2019	No	Yes
ACE-536 (RAP-536)	luspatercept	Celgene/ Acceleron	Modified type II activin receptor recombinant fusion protein	Anemia	SC	Filed BLA	12/4/2019	Yes	Yes
RVT-802	RVT-802	Enzyvant/Roivant	Tissue-based therapy	Congenital athymia	Implant	Filed NDA	12/2019	Yes	Yes

661

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
MK-1602 (AGN-241689)	ubrogepant	Allergan/ Merck	calcitonin gene-related peptide (CGRP) receptor antagonist	Acute migraines	PO	Filed NDA	12/15/2019	No	No
IDP-123	IDP-123	Bausch Health	retinoid	Acne	TOP	Filed NDA	12/22/2019	No	No
Brinavess (Kynapid)	vernakalant	Correvio	potassium channel blocker	Arrhythmia	IV	Filed NDA	12/24/2019	Yes	No
E-2006	lemborexant	Eisai/ Purdue	orexin receptor antagonist	Insomnia	PO	Filed NDA	12/27/2019	No	No
ITI-007 (ITI-722)	lumateperone	Intra-Cellular Therapies	antipsychotic	Schizophrenia	PO	Filed NDA	12/27/2019	No	No
Posidur	SABER-bupivacaine CR	Novartis/ Durect	local anesthetic	Pain	SC	Filed NDA	12/27/2019	No	No
S-265744 (S/GSK-1265744)	cabotegravir	ViiV Healthcare	HIV integrase inhibitor	Human immunodeficiency virus (HIV)	PO	Filed NDA	12/29/2019	Yes	No
TMC-278-LA	cabotegravir (long-acting)/ rilpivirine (long-acting)	ViiV Healthcare	HIV integrase inhibitor/ non-nucleoside reverse transcriptase inhibitor (NNRTI)	HIV-1	IM	Filed NDA	12/29/2019	Yes	No
MitoGel	mitomycin C	UroGen	alkylating agent	Bladder cancer	Intravesical	InTrial	4Q2019	No	Yes
Xyrosa	doxycycline	Sun Pharma	tetracyclines	Rosacea	PO	Tentative Approval	4Q2019	No	No
2020 Possible launch date									
OMS-721	narsoplimab	Omeros	anti-MASP-2	Hemolytic uremic	IV/SC	InTrial	2020	Yes	Yes

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
			monoclonal antibody	syndrome (HUS)/ Renal diseases					
CCP-08	CCP-08	Tris Pharma	undisclosed	Viral rhinitis	PO	CRL	2020	Yes	No
tamsulosin DRS	tamsulosin delayed-release	Veru	alpha-adrenergic antagonist	Benign prostatic hyperplasia (BPH)	PO	InTrial	2020	No	No
Zalviso	sufentanil, ARX-01	AcelRx	opioid analgesic	Pain	SL	CRL	2020	Yes	No
ELI-200	oxycodone/ naltrexone	Elite	opioid agonist	Pain	PO	CRL	2020	No	No
APL-130277	apomorphine	Sumitomo Dainippon/ MonoSol Rx/ Sunovion	non-ergoline dopamine agonist	Parkinson's disease	SL	CRL	2020	No	No
Entyvio (SC formulation)	vedolizumab	Takeda	integrin receptor antagonist	Ulcerative colitis (UC)/ Crohn's disease (CD)	SC	Filed sBLA	1/1/2020	Yes	No
AR-101	AR-101	Aimmune/ Regeneron/ Sanofi	peanut protein capsule	Peanut allergy	PO	Filed BLA	1/2020	No	No
SEG-101	crizanlizumab	Novartis	P-selectin antagonist	Sickle cell disease	IV	Filed BLA	1/15/2020	Yes	Yes
E-7438 (EPZ-6438)	tazemetostat	Epizyme/ Eisai	methyltransferase EZH2 inhibitor	Sarcoma	PO	Filed NDA	1/23/2020	Yes	Yes
Rykindo	risperidone ER	Luye	atypical antipsychotic	Schizophrenia/ Schizoaffective disorder	IM	Filed NDA	1/28/2020	Yes	No

663

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
FP-001 (LMIS)	leuprolide mesylate	Foresee	gonadotropin-releasing hormone (GnRH) analog	Prostate cancer	SC	Filed NDA	1/29/2020	Yes	No
ALN-AS1	givosiran	Alnylam	RNAi therapeutic agent	Porphyria	SC	Filed NDA	2/4/2020	Yes	Yes
BLU-285	avapritinib	Blueprint Medicines	selective KIT and PDGFRa inhibitor	Gastrointestinal stromal tumors (GIST)	PO	Filed NDA	2/14/2020	Yes	Yes
BMS-927711 (BHV-3000)	rimegepant sulfate	Portage Biotech/ Biohaven/ Bristol-Myers Squibb	calcitonin gene-related peptide (CGRP) receptor antagonist	Acute migraines	PO	Filed NDA	2/20/2020	Yes	No
ETC-1002	bempedoic acid	Esperion Therapeutics	ATP citrate (pro-S)-lyase and stimulating AMP-activated protein kinase (AMPK)	Hypercholesterolemia	PO	Filed NDA	2/21/2020	No	No
ALD-403	eptinezumab	Alder	calcitonin gene-related peptide (CGRP) receptor antagonist	Migraine prevention	IV/SC	Filed BLA	2/22/2020	No	No
ETC-1002/ ezetimibe	bempedoic acid/ ezetimibe	Esperion Therapeutics	ATP citrate (pro-S)-lyase and stimulating AMP-activated protein kinase (AMPK)/ cholesterol absorption inhibitor	Hypercholesterolemia	PO	Filed NDA	2/26/2020	No	No
CD-5789	trifarotene	Galderma	retinoid receptor agonist	Acne	TOP	Filed NDA	2/28/2020	No	No
RV-001 (Roche-1, R-1507)	teprotumumab	Horizon/ Chugai/ Roche/ Genmab	insulin-like growth factor 1 (IGF-1) receptor antagonist	Thyroid eye disease	IV	Filed BLA	3/6/2020	Yes	Yes
naloxone nasal spray	naloxone	Insys Therapeutics	opioid antagonist	Opioid dependence	Intranasal	Filed NDA	3/15/2020	No	No

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
ASG-22M6E (ASG-22CE, ASG-22ME)	enfortumab vedotin	Astellas/ Seattle Genetics	nectin-4 antagonist	Bladder cancer	IV	Filed BLA	3/16/2020	Yes	No
ET-105	lamotrigine	Eton	anticonvulsant	Epilepsy	PO	Filed NDA	3/17/2020	No	No
VX-445	elexacaftor	Vertex	cystic fibrosis transmembrane conductance regulator (CFTR) corrector	Cystic fibrosis (CF)	PO	Filed NDA	3/20/2020	Yes	No
ozanimod	ozanimod	Celgene	sphingosine 1-phosphate 1 (S1PR1) and 5 (S1PR5) receptor modulator	Multiple sclerosis/ Ulcerative colitis (UC)	PO	Filed NDA	3/25/2020	Yes	No
Corplex	donepezil transdermal system	Corium International	anticholinergic	Alzheimer's disease	TOP	InTrial	1Q2020	No	No
ITCA-650 (sustained release exenatide)	exenatide sustained-release	Intarcia/ Quintiles/ Servier	glucagon-like peptide-1 (GLP-1) receptor agonist	Diabetes mellitus	SC implant	CRL	1Q2020	Yes	No
PPP-002	PPP-002	Tetra Bio-Pharma	botanical drug	Pain	Undisclosed	InTrial	1Q2020	No	No
Barhemsys	amisulpride	Acacia	dopamine receptor antagonist	Nausea/ Vomiting	IV	CRL	1Q2020	No	No
Bronchitol	mannitol	Pharmaxis	osmotic gradient enhancer; mucus clearance enhancer	Asthma/ Cystic fibrosis	INH	CRL	1Q2020	No	Yes

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
Prochymal	remestemcel-L	Mesoblast/ JCR/ Mallinckrodt/ Osiris Therapeutics	mesenchymal stem cells	Graft vs. Host disease (GvHD)/ Crohn's disease/ Gastrointestinal injury post radiation exposure/ Heart failure (HF)	IV	InTrial	1Q2020	Yes	Yes
LCI-699	osilodrostat	Novartis	aldosterone synthase inhibitor	Cushing's syndrome	PO	Filed NDA	1Q2020	No	Yes
TG-1303	ublituximab/ TGR-1202	TG Therapeutics	CD-20 monoclonal antibody/ phosphoinositide-3 kinase (PI3K) delta inhibitor	Chronic lymphocytic leukemia (CLL)/ Diffuse large B-cell lymphoma (DLBCL)/ Non-Hodgkin lymphoma (NHL)	IV/PO	InTrial	1Q2020	Yes	Yes
empagliflozin, linagliptin, metformin XR	empagliflozin, linagliptin, metformin XR	Eli Lilly/ Boehringer Ingelheim	sodium glucose co-transporter-2 (SGLT-2) inhibitor, dipeptidyl peptidase 4 (DPP4) inhibitor, biguanide	Diabetes mellitus	PO	Filed NDA	1Q2020	No	No
Taclantis	paclitaxel injection concentrate for suspension	Sun Pharma Advanced Research Company (SPARC)	taxane	Breast Cancer; Lung Cancer; Pancreatic Cancer	IV	Filed NDA	1Q2020	No	No
bimatoprost sustained release	bimatoprost sustained release	Allergan	prostaglandin agonist	Glaucoma	Implant	Filed NDA	4/1/2020	N/A	No
UX-007	triheptanoin	Ultragenyx/ Baylor Research Institute/ Uniquest	medium chain fatty acid	Glucose transport type 1 deficiency syndrome (G1DS)	PO	Filed NDA	4/1/2020	Yes	Yes
CNS-7056 (ONO-[illegible]	remimazolam	Cosmo/ Hana/	benzodiazepine	Procedural sedation	IV	Filed NDA	4/3/2020	Yes	No

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
2745)		Paion/ Pharmascience/ R-Pharm/ Yichang Humanwell							
Viaskin Peanut	Viaskin Peanut	DBV Technologies	Immunotherapy	Peanut allergy	TOP	Filed BLA	4/7/2020	No	No
Men Quad TT	meningococcal polysaccharide (serogroups A, C, Y, and W135) tetanus toxoid conjugate vaccine	Sanofi	antibacterial	meninococcus/ tetanus	IM	Filed BLA	4/25/2020	No	No
Ongentys	opicapone	Neurocrine Biosciences/ Bial/ Ono	catechol-O-methyltransferase (COMT) inhibitor	Parkinson disease	PO	Filed NDA	4/26/2020	No	No
Trevyent	treprostinil	SteadyMed	prostacyclin analog	Pulmonary arterial hypertension (PAH)	SC	Filed NDA	4/27/2020	Yes	Yes
isatuximab	isatuximab	Sanofi/ ImmunoGen	CD38 antagonist	Multiple myeloma/ Acute lymphoblastic leukemia (ALL) or lymphoblastic lymphoma (LBL)	IV	Filed BLA	4/30/2020	Yes	Yes
SEP-225289 (DSP-225289, SEP-289)	dasotraline	Sumitomo Dainippon/ Sunovion	triple reuptake inhibitor	Attention deficit hyperactivity disorder (ADHD)/ Eating disorders	PO	Filed NDA	5/14/2020	No	No
FMX-103	minocycline	Foamix	tetracyclines	Rosacea	TOP	InTrial	6/5/2020	No	No

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
Bafiertam	monomethyl fumarate	Banner Life Sciences	prodrug	Multiple sclerosis	PO	Tentative Approval	6/20/2020	Yes	No
V-114	pneumococcal conjugate vaccine	Merck	vaccine	Bacterial infection	IM	InTrial	2Q2020	Yes	No
KP-415	D-threo-methylphenidate controlled-release	KemPharm	CNS stimulant	Attention deficit hyperactivity disorder (ADHD)	PO	InTrial	2Q2020	No	No
Gimoti	metoclopramide	Evoke Pharma	antidopiminergics	Diabetic gastroparesis	Intranasal	CRL	2Q2020	No	No
PEGPH-20	pegvorhyaluronidase alfa	Halozyme/ Nektar	hyaluronic acid	Pancreatic cancer/ Non-small cell lung cancer (NSCLC)	IV	InTrial	1H2020	Yes	Yes
ZEBOV	VS-EBOV (rVSV-EBOV; rVSV-ZEBOV-GP)	Merck/ NewLink Genetics	vaccine	Ebola	IM	Filed BLA	1H2020	Yes	No
Lenti-D	elivaldogene tavalentivec	Bluebird Bio	gene therapy	Adrenomyeloneuropathy	Undisclosed	InTrial	1H2020	Yes	Yes
IMMU-132	sacituzumab govitecan	Immunomedics/ Royalty Pharma	RS7-SN-38 antibody-drug conjugate	Breast cancer/ Pancreatic cancer/ Pancreatic cancer/ Small cell lung cancer (SCLC)/ Non-small cell lung cancer (NSCLC)/ Colorectal cancer/ Esophageal cancer/ Urinary bladder cancer	IV	CRL	1H2020	Yes	Yes
FT-218	sodium oxybate	Avadel	dopamine receptor	Narcolepsy	PO	InTrial	1H2020	Yes	No

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
	extended-release		agonist						
Apealea (Paclical)	paclitaxel	Oasmia	taxane	Ovarian cancer	IV	InTrial	1H2020	Yes	Yes
Traumakine	interferon-beta -1a	Faron/ Maruishi	interferon	Acute respiratory distress syndrome (ARDS)	IV	InTrial	1H2020	Yes	No
ropeginterferon alfa-2b	ropeginterferon alfa-2b	PharmaEssentia/ AOP Orphan	interferon	Polycythemia vera (PV)/ Myelofibrosis (MF)/ Essential thrombocythemia (ET)	SC	InTrial	1H2020	Yes	Yes
Rizaport (VersaFilm)	rizatriptan	IntelGenx / Red Hill Biopharma	triptans	Acute migraines	PO	CRL	1H2020	No	No
Zynteglo (LentiGlobin)	lentiviral beta-globin gene transfer	Bluebird Bio	gene therapy	Sickle cell disease/ Beta thalassemia	IV	InTrial	1H2020	Yes	Yes
MC2-01 (MC-201)	calcipotriene/ betamethasone	MC2 Therapeutics	vitamin D analog/ corticosteroid	Psoriasis	TOP	InTrial	1H2020	No	No
R-667 (RG-667)	palovarotene	Clementia/ Roche	selective retinoic acid receptor agonist (RAR-gamma)	Fibrodysplasia ossificans progressiva (FOP)	PO	InTrial	1H2020	Yes	Yes
DS-8201	[fam-] trastuzumab deruxtecan	Daiichi Sankyo	HER2-targeting antibody-drug conjugate	Breast cancer	IV	InTrial	1H2020	Yes	No
SA-237 (RG-6168)	satralizumab	Roche/ Chugai	interleukin-6 (IL-6) monoclonal antibody	Neuromyelitis optica (NMO)	SC	InTrial	1H2020	Yes	Yes

699

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
FG-4592 (ASP-1517)	roxadustat	FibroGen/ Astellas/ AstraZeneca	hypoxia-inducible factor prolyl hydroxylase (HIF-PHI)	Anemia	PO	InTrial	1H2020	Yes	No
RT-002	daxibotulinumtoxinA	Revance Therapeutics	botulinum toxins	Cosmetic/ Cervical dystonia/ Plantar fasciitis	IM	InTrial	1H2020	Yes	Yes
Ryplazim	human plasminogen	ProMetic/ Hematech	plasminogen	Plasminogen deficiency	IV	InTrial	1H2020	Yes	Yes
JCAR-017	lisocabtagene maraleucel	Juno/ Celgene	chimeric antigen receptor (CAR) T cell therapy	Diffuse large B-cell lymphoma (DLBCL)/ Acute lymphocytic leukemia (ALL)/ Follicular lymphoma/ Mantle cell lymphoma	IV	InTrial	Mid-2020	Yes	Yes
Sarasar	lonafarnib	Eiger Biopharmaceuticals	prenylation inhibitor	Hepatitis D (HDV); Hutchinson-Gilford Progeria Syndrome (HGPS or progeria) and progeroid laminopathies	PO	InTrial	Mid-2020	Yes	Yes
GSK-2857916	GSK-2857916	GlaxoSmithKline/ Seattle Genetics	anti-BCMA antibody-drug conjugate	Multiple myeloma	SC	InTrial	Mid-2020	Yes	Yes
Ryaltris	mometasone furoate/ olopatadine HCl	Glenmark	corticosteroid/ antihistamine	Allergic rhinitis	NA	CRL	Mid-2020	No	No
QVM-149	indacaterol/ glycopyrronium bromide/	Novartis/ Sosei	long-acting beta 2 adrenergic receptor agonist (LABA)/ long-	Asthma	INH	InTrial	Mid-2020	No	No

670

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
	mometasone furoate		acting muscarinic receptor antagonist (LAMA)/ corticosteroid						
RG-7916 (RO-7034067)	Risdiplam	Roche/ PTC Therapeutics	SMN2 splicing modifier	Spinal muscular atrophy	PO	InTrial	Mid-2020	Yes	Yes
SRP-4045	casimersen	Sarepta	morpholino antisense oligonucleotide	Duchenne muscular dystrophy (DMD)	IV	InTrial	Mid-2020	Yes	Yes
idebenone	idebenone	Santhera	co-enzyme Q-10 analog	Duchenne muscular dystrophy	PO	CRL	Mid-2020	Yes	Yes
Amphora	Amphora	Neothetics	spermicidal agent	Pregnancy prevention/ Bacterial infections	VG	CRL	Mid-2020	No	No
GBT-440 (GTx-011)	voxelotor	Global Blood Therapeutics	hemoglobin modulator	Sickle cell anemia	PO	InTrial	Mid-2020	Yes	Yes
TGR-1202	umbralisib	TG Therapeutics/ Rhizen	phosphoinositide-3 kinase (PI3K) delta inhibitor	Diffuse large B-cell lymphoma (DLBCL)/ Chronic lymphocytic leukemia (CLL)	PO	InTrial	Mid-2020	Yes	Yes
3-F8 (Hu-3F8)	naxitamab	Y-mAbs Therapeutics	GD2 antagonist	Neuroblastoma	IV	InTrial	Mid-2020	Yes	Yes
Winlevi/ Breezula	cortexolone 17alpha-propionate (CB-03-01)	Intrepid	androgen antagonist	Acne vulgaris/ alopecia	TOP	InTrial	Mid-2020	No	No

671

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
Darzalex	daratumumab (with recombinant human hyaluronidase)	Johnson & Johnson / Genmab	humanized anti-CD38 monoclonal antibody	Multiple myeloma/ Amyloidosis	SC	Filed BLA	7/10/2020	Yes	Yes
BMN-270	valoctocogene roxaparvovec	BioMarin	gene therapy	Hemophilia	IV	InTrial	3Q2020	Yes	Yes
TBR-652 (TAK-652, CVC)	cenicriviroc	Tobira Therapeutics/ Takeda	C-C chemokine receptor 5 (CCR5) and receptor 2 antagonist	HIV/ Non-alcoholic steatohepatitis (NASH)	PO	InTrial	3Q2020	Yes	No
BCX-7353	BCX-7353	BioCryst	kallikrein inhibitor	Hereditary angioedema (HAE)	PO	InTrial	3Q2020	Yes	Yes
PPP-001	delta-9-tetrahydrocannabinol/ cannabidiol	PhytoPain Pharma	cannabinoid product	Pain	INH	InTrial	3Q2020	Yes	Yes
TRC-101	TRC-101	Tricida	carrier protein modulator	Chronic kidney disease (CKD)	PO	InTrial	3Q2020	Yes	No
Brixadi	buprenorphine	Camurus/ Braeburn	opioid receptor agonist (partial)	Opioid dependence/ Pain	SC	Tentative Approval	11/1/2020	Yes	No
IdeS (immunoglobulin G-degrading enzyme of Streptococcus pyogenes)	imlifidase	Hansa Medical	bacterial enzyme	Kidney transplant/ Thrombotic thrombocytopenic purpura (TTP)/Goodpasture's disease	IV	InTrial	2H2020	Yes	Yes

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
INCB-54828	pemigatinib	Incyte	selective FGFR1/2/3 inhibitor	Biliary tract cancer	PO	InTrial	2H2020	Yes	Yes
BMS-663068 (BMS-626529 prodrug)	fostemsavir (temsavir prodrug)	Bristol-Myers Squibb	HIV attachment inhibitor	Human immunodeficiency virus (HIV)	PO	InTrial	2H2020	Yes	No
LIQ-861	treprostinil	Liquidia Technologies	prostacyclin analog	Pulmonary arterial hypertension (PAH)	INH	InTrial	2H2020	Yes	No
Olinvo	oliceridine	Trevena	opioid receptor agonist	Pain	IV	CRL	2H2020	No	No
INP-104	POD-dihydroergotamine mesylate (POD-DHE)	Impel/ 3M	ergot derivative	Acute migraines	NA	InTrial	2H2020	No	No
BGB-3111	zanubrutinib	BeiGene	selective inhibitor of Bruton tyrosine kinase (BTK)	Waldenström's Macroglobulinemia (WM)/ Chronic lymphocytic leukemia (CLL)	PO	InTrial	2H2020	Yes	Yes
EGP-437	dexamethasone phosphate (iontophoretic)	EyeGate	corticosteroid	Uveitis	OP	InTrial	2H2020	Yes	No
Libervant	diazepam	Aquestive Therapeutics	benzodiazepine	Seizures	SL/ Transmucosal	InTrial	2H2020	No	Yes
EM-100	ketotifen	Eton	antihistamine	Allergic conjunctivitis/ Dry eyes	OP	CRL	2H2020	No	No
MAGH-22	margetuximab	MacroGenics/ Green Cross	HER2 oncoprotein antagonist	Breast cancer	IV	InTrial	2H2020	Yes	No

673

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
Sci-B-Vac	hepatitis B vaccine	VBI Vaccines	vaccine	Hepatitis B (HBV)	IM	InTrial	2H2020	No	No
sulopenem	sulopenem	Iterum	carbapenem	Bacterial infection	IV/PO	InTrial	2H2020	No	No
quizartinib	quizartinib	Daiichi Sankyo	FLT-3 receptor tyrosine kinase inhibitor	Acute myeloid leukemia (AML)	PO	CRL	2H2020	Yes	Yes
VP-102	VP-102	Verrica	antiviral	Molluscum/ Verruca vulgaris	TOP	InTrial	2H2020	No	No
GLPG-0634	filgotinib	Galapagos NV/ Gilead	janus associated kinase-1 (JAK) inhibitor	Rheumatoid arthritis/ Crohn's disease/ Ulcerative colitis (UC)/ Sjogren's syndrome/ Ankylosing spondylitis/ Psoriatic arthritis	PO	InTrial	2H2020	Yes	No
NX-1207 (NYM-4805, REC 0482)	fexapotide triflutate	Nymox	pro-apoptotic	Benign prostatic hyperplasia (BPH)/ Prostate cancer	Intratumoral	InTrial	2H2020	Yes	No
AKB-6548	vadadustat	Akebia Therapeutics	hypoxia-inducible factor-prolyl hydroxylase (HIF-PH) inhibitor	Anemia	PO	InTrial	2H2020	Yes	No
NexoBrid	bromelain	MediWound/ BL&H/ CrystalGenomics/ Kaken	peptide hydrolase replacement agent	Burns/ Skin injury	TOP	InTrial	2H2020	No	Yes
LOXO-292	LOXO-292	Loxo Oncology/ Eli Lilly	RET inhibitor	Solid tumors; non-small cell lung cancer (NSCLC); thyroid cancer	PO	InTrial	2H2020	Yes	No

674

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
NPI-2358	plinabulin	BeyondSpring	tumor vascular disrupting agent (tVDA)	Neutropenia/ Non-small cell lung cancer (NSCLC)	IV	InTrial	2H2020	Yes	No
PXT-3003	baclofen/ naltrexone/ sorbitol	Pharnext	gamma-aminobutyric acid (GABA)-ergic agonist/ opioid receptor antagonist/ sorbitol combination	Charcot-Marie Tooth disease	PO	InTrial	2H2020	No	Yes
ZP-4207 (ZP-GA-1)	dasiglucagon	Zealand Pharma	glucagon analog	Diabetes mellitus	SC	InTrial	2H2020	No	Yes
Zeftera	ceftobiprole	Basilea	cephalosporin antibiotic	Bacterial infections	IV	InTrial	2H2020	Yes	No
Vicinium (VB-4-845)	oportuzumab monatox	Eleven Biotherapeutics	anti-ECAM exotoxin A fusion protein	Bladder cancer	Intravesical	InTrial	2H2020	Yes	No
LJPC-0118	LJPC-0118	La Jolla Pharmaceutical	protozoacide	Malaria	Undisclosed	InTrial	2H2020	No	No
selumetinib	selumetinib	AstraZeneca/ Array BioPharma/ Cancer Research UK	selective MEK kinase inhibitor	Uveal melanoma/ Thyroid cancer	PO	InTrial	2H2020	Yes	Yes
Mycapssa (Octreolin)	octreotide	Chiasma	somatostatin analog	Acromegaly	PO	CRL	2H2020	Yes	Yes
Doria	risperidone	Laboratorios Farmacéuticos Rovi	atypical antipsychotic	Schizophrenia	IM	InTrial	2H2020	Yes	No
Iomab-B	iodine I 131 monoclonal antibody BC8	Actinium	anti-CD45 monoclonal antibody	Acute myeloid leukemia (AML)/ Myelodysplastic syndrome (MDS)	IV	InTrial	2H2020	Yes	Yes
SPN-812	SPN-812	Supernus	selective norepinephrine reuptake inhibitor	Attention deficity hyperactivity disorder (ADHD)	PO	InTrial	2H2020	No	No

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
PRX-102	alpha galactosidase (pegunigalsidase alfa)	Protalix	enzyme replacement	Fabry disease	IV	InTrial	2H2020	Yes	No
ASTX-727	decitabine and E-7727	Otsuka/ Astex Pharmaceuticals	nucleoside metabolic inhibitor	Myelodysplastic syndrome (MDS)	PO	InTrial	2H2020	Yes	No
arimoclomol	arimoclomol	Orphazyme	cytoprotectives	Niemann-Pick Disease (NPD)/ Sporadic Inclusion Body Myositis (IBM)/ Amyotrophic lateral sclerosis (ALS)	PO	InTrial	2H2020	Yes	Yes
PRT-201	vonapanitase	Proteon Therapeutics	human elastase (recombinant)	End stage renal diease (ESRD)/Peripheral artery disease (PAD)/ Vascular access in hemodialysis	TOP	InTrial	2H2020	Yes	Yes
bb-2121	idecabtagene vicluecel	Celgene/ Bluebird Bio	chimeric antigen receptor (CAR) T cell therapy	Multiple myeloma/ Brain cancer	IV	InTrial	2H2020	Yes	Yes
KPI-121 0.25%	loteprednol etabonate	Kala	corticosteroid	Dry eyes	OP	CRL	2H2020	No	No
Anti-VEGF DARPin	abicipar pegol	Allergan	VEGF-A inhibitor	Age-related macular degeneration (AMD)	Intravitreal	InTrial	2H2020	Yes	No
AmnioFix	dehydrated human amnion/chorion membrane (dHACM)	MiMedx	amniotic tissue membrane	Plantar fasciitis/ Achilles tendonitis/ Osteoarthritis	INJ	InTrial	4Q2020	Yes	No

676

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
tramadol	tramadol	Avenue Therapeutics	opioid receptor agonist	Pain	IV	InTrial	4Q2020	No	No
Estelle	estetrol/ drospirenone	Mithra/ Fuji/ Zhejian Xianju	estrogen receptor agonist	Pregnancy prevention	PO/SL/ Transmucosal	InTrial	4Q2020	No	No
Infacort	hydrocortisone	Diurnal Group	corticosteroid	Adrenal insufficiency	PO	InTrial	4Q2020	No	Yes
MOR-208 (MOR-00208, XmAB-5574)	tafasitamab	MorphoSys/ Xencor	CD-19 antagonist	Diffuse large B-cell lymphoma (DLBCL)/ Acute lymphocytic leukemia (ALL)/ Chronic lymphocytic leukemia (CLL)	IV	InTrial	4Q2020	Yes	Yes
Melflufen (Ygalo)	melphalan-flufenamide	Oncopeptides AB	alkylating agent/ DNA synthesis inhibitor	Multiple myeloma/ Non-small cell lung cancer (NSCLC)/ Ovarian cancer	IV	InTrial	4Q2020	No	Yes
BLU-667	BLU-667	Blueprint Medicines	RET inhibitor	Non-Small Cell Lung Cancer (NSCLC)	PO	InTrial	4Q2020	Yes	Yes
Qtrypta	zolmitriptan	Zosano	triptans	Acute migraines	TOP	InTrial	4Q2020	No	No
Qarziba (Isqette)	dinutuximab beta	EUSA/ Aperion/ Endo/ Gen Ilac/ Medison	disialoganglioside	Neuroblastoma	SC	InTrial	2020	Yes	Yes
Multikine	Leukocyte Interleukin (CS-001P3)	CEL-SCI	immunomodulator	Head and Neck cancer/ Squamous cell carcinoma	SC	InTrial	2020	Yes	Yes

677

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
HTX-011	bupivacaine/ meloxicam	Heron Therapeutics	anesthetic/ Nonsteroidal Anti-inflammatory Drug (NSAID)	Pain	Instillation	CRL	2020	No	No
ublituximab (LFB-R603, TG20, TGTX-1101, TG-1101, Utuxin)	ublituximab	TG Therapeutics	CD-20 monoclonal antibody	Chronic lymphocytic leukemia (CLL)/ Small cell lymphocytic lymphoma (SLL)/ Mantle cell lymphoma (MCL)/ Multiple sclerosis	IV	InTrial	2020	Yes	Yes
INCB-028060	capmatinib	Novartis/ Incyte	cMET inhibitor	Non-small cell lung cancer (NSCLC)	PO	InTrial	2020	Yes	No
Oralair Mites	dust mite peptide	Stallergenes/ Shionogi	vaccine	Dust mite allergic rhinitis	SL	InTrial	2020	Yes	No
Deltyba	delamanid	Otsuka	mycolic acid biosynthesis inhibitor	Tuberculosis	PO	InTrial	2020	No	No
JNJ-872 (VX-787)	JNJ-872 (VX-787)	Johnson & Johnson/ Vertex	viral protein inhibitor	Influenza	PO	InTrial	2020	No	No
Zynquista	sotagliflozin	Sanofi/ Lexicon	sodium-dependent glucose transporter 1 (SGLT-1) and SGLT-2 inhibitor	Diabetes mellitus	PO	CRL	2020	No	No
NeoCart	autologous chondrocyte tissue implant	Histogenics/ Purpose	autologous chondrocyte tissue implant	Joint repair	Undisclosed	InTrial	2020	Yes	No

678

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
NNC-0195-0092 (NN-8640)	somapacitan	Novo Nordisk	recombinant human growth hormone (rhGH)	Short stature/ Growth hormone deficiency	SC	InTrial	2020	Yes	No
Sativex	nabiximols	GW Pharmaceuticals/ Otsuka	cannabinoid product	Multiple sclerosis (MS)/ Pain	SL/ SPR	InTrial	2020	No	No
Contepo	fosfomycin	Nabriva Therapeutics	cell wall inhibitor	Bacterial infections	IV	CRL	2020	Yes	No
VivaGel	astodrimer sodium (SPL-7013)	Starpharma	viral attachment inhibitor	Bacterial infections	VG	CRL	2020	No	No
CM-AT	CM-AT	Curemark	protein absorption enhancer	Autism	PO	InTrial	2020	Yes	No
MLN-4924 (TAK-92)	pevonedistat	Takeda	Nedd 8 Activating Enzyme (NAE) antagonist	Acute myeloid leukemia (AML)/ Chronic myelogenous leukemia (CML)/ Myelodysplastic syndrome (MDS)	PO	InTrial	2020	Yes	No
N-1539	meloxicam	Recro Pharma/ Alkermes	nonsteroidal anti-inflammatory drug (NSAID)	Pain	IV	CRL	2020	Yes	No
ND-0612H	levodopa/ carbidopa	NeuroDerm	dopamine precursor/ dopa-decarboxylase inhibitor	Parkinson's disease (PD)	SC	InTrial	2020	Yes	No
Pedmark (STS)	sodium thiosulfate	Fennec	reducing agent	Hearing loss	IV	InTrial	2020	Yes	Yes
ursodeoxycholic acid	ursodeoxycholic acid	Retrophin/ Asklepion	bile acid derivative	Primary biliary cirrhosis/cholangitits	PO	InTrial	2020	Yes	No

629

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
Travivo	gepirone ER	GSK/Fabre-Kramer	5-HT-1A receptor agonist	Major depressive disorder (MDD)	PO	CRL	2020	No	No
Dexasite	dexamethasone	InSite Vision	corticosteroid	Blepharitis/ Ocular inflammation	TOP	InTrial	2020	No	No
APC-8000	tadalafil	Adamis	phosphodiesterase-5 (PDE-5) inhibitor	Erectile dysfunction	PO	CRL	2020	Yes	No
ND-0612L	levodopa/ carbidopa	NeuroDerm	dopamine precursor/ dopa-decarboxylase inhibitor	Parkinson's disease (PD)	SC	InTrial	2020	Yes	No
BGF-MDI (PT-010)	budesonide/ glycopyrronium/ formoterol	AstraZeneca	corticosteroid/ long-acting muscarinic receptor antagonist (LAMA)/ long-acting beta 2 adrenergic receptor agonist (LABA)	Chronic obstructive pulmonary diseaser (COPD)/ Asthma	INH	InTrial	2020	No	No
Tivopath (AV-951, KRN-951, ASP-4130)	tivozanib	Aveo/ Astellas/ Kyowa Hakko Kirin	VEGF inhibitor	Renal cell cancer	PO	InTrial	2020	Yes	No
DS-200	DS-200	Eton	undisclosed	Ophthalmological disease	SC	InTrial	2020	unknown	No
QMF-149	indacaterol maleate/ mometasone furoate	Novartis/ Merck	long-acting beta 2 agonist/ corticosteroid	Asthma	INH	InTrial	2020	No	No
BHV-0223	riluzole	Biohaven	glutamate release inhibitor	Amyotrophic lateral sclerosis (ALS)	SL/ Transmucosal	CRL	2020	No	Yes

680

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
MNK-812	oxycodone	Mallinckrodt	opioid agonist	Pain	PO	CRL	2020	No	No
CPP-1X/ sulindac (DFMO)	eflornithine/ sulindac	Cancer Prevention Pharma/ Zeria	ornithine decarboxylase inhibitor/ non-steroidal anti-inflammatory drug (NSAID)	Familial adenomatous polyposis (FAP)/ Colorectal cancer	PO	InTrial	2020	Yes	Yes
GZ-402666 (NeoGAA)	neo-recombinant human acid alpha glucosidase	Sanofi	enzyme therapy	Pompe disease	IV	InTrial	2020	Yes	No
Numbrino	cocaine HCl	Lannett	anesthetic	Anesthesia	TOP	CRL	2020	No	No
cannabidiol	cannabidiol	Insys Therapeutics	cannabinoid product	Seizures/ Prader-Willi	PO	InTrial	Late 2020	Yes	No
skQ1	visomitin	Mitotech	plastoquinone derivative	Dry eyes	OP	InTrial	Late 2020	Yes	No
tanezumab	tanezumab	Pfizer/ Eli Lilly	neurotrophic tyrosine kinase receptor type 1 (TrkA) antagonist (monoclonal antibody)	Osteoarthritis/ Pain	IV/SC	InTrial	Late 2020	Yes	No
BMN-111	vosoritide (vasoritide)	BioMarin/ Chugai	C-type natriuretic peptide (CNP) analog	Achondroplasia	SC	InTrial	Late 2020	Yes	Yes
NS-2 (ALDX-1E1, ALDX-1E2, ADX-102)	reproxalap	Aldeyra Therapeutics	aldehyde antagonist	Uveitis/ Allergic conjunctivitis/ Dry eyes	OP	InTrial	Late 2020	No	No
azacitidine	azacitidine	Celgene	DNA methylation inhibitor	Acute myeloid leukemia (AML)/ Myelodysplastic syndromes	PO	InTrial	Late 2020	Yes	Yes

681

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
MVA-MUC1-IL2	TG-4010	Transgene	vaccine	Non-small cell lung cancer (NSCLC)	SC	InTrial	Late 2020	No	No
QAW-039 (NVP-QAW-039)	fevipiprant	Novartis	chemoattractant receptor-homologous molecule (CRTH2) antagonist	Asthma/ Atopic dermatitis	PO	InTrial	Late 2020	Yes	No
Molgradex	molgramostim	Savara	granulocyte macrophage-colony stimulating factor	Pulmonary alveolar proteinosis (PAP)	INH	InTrial	Late 2020	Yes	Yes
Translarna	ataluren	PTC Therapeutics	gene transcription modulator	Duchenne muscular dystrophy/ Mucopolysaccharidosis (MPS)	PO	CRL	Late 2020	Yes	Yes
BIVV-009 (TNT-009)	sutimlimab	Sanofi	complement C1s subcomponent inhibitor	Cold agglutnin disease	IV	InTrial	Late 2020	Yes	Yes
RG-3477 (ACT-128800)	ponesimod	Johnson & Johnson	sphingosine 1 phosphate receptor agonists	Multiple sclerosis	PO	InTrial	Late 2020	Yes	No
Lucassin	terlipressin	Orphan Therapeutics/ Ikaria	V-1 (vasopressin) agonist	Hepato-renal syndrome (HRS)	IV	CRL	Late 2020	Yes	Yes
HuMax-TF ADC	tisotumab vedotin	Genmab/ Seattle Genetics	tissue factor antibody	Solid tumors	Undisclosed	InTrial	Late 2020	Yes	No
RE-024	fosmetpantotenate	Retrophin	phosphopantothenate replacement therapy	Neurodegeneration	IV	InTrial	Late 2020	Yes	Yes

0682

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
MK-0594 (VPD-737)	serlopitant	Menlo	NK-1 receptor antagonist	Atopic dermatitis/ Cough	PO	InTrial	Late 2020	Yes	No
Linhaliq	ciprofloxacin	Aradigm/ Grifols	fluoroquinolone	Non-cystic fibrosis bronchiectasis/ Cystic fibrosis	INH	CRL	Late 2020	Yes	Yes
MEDI-551	inebilizumab	AstraZeneca	CD-19 antagonist	Neuromyelitis optica (NMO)	IV	InTrial	Late 2020	Yes	Yes
TSR-042	dostarlimab	AnaptysBio	PD-1 checkpoint inhibitor	Endometrial cancer	IV	InTrial	Late 2020	Yes	No
LY-900014 (URLi)	LY-900014	Eli Lilly	insulins	Diabetes mellitus	SC	InTrial	Late 2020	No	No
SHP-621	budesonide	Shire	corticosteroid	Eosinophilic esophagitis	PO	InTrial	Late 2020	Yes	Yes
iclaprim	iclaprim	Motif Bio	tetrahydrofolate dehydrogenase inhibitor	Bacterial infections	IV	CRL	Late 2020	Yes	Yes
GFT-505	elafibranor	Genfit	selective peroxisome proliferator-activated receptor (PPAR) modulator	Non-alcoholic steatohepatitis (NASH)/ Primary biliary cirrhosis	PO	InTrial	Late 2020	No	No
BIM-22493 (RM-493)	setmelanotide	Rhythm/ Camurus/ Ipsen	melanocortin 4 receptor (MC4R) agonist	Obesity/ Bardet-Biedl syndrome	SC	InTrial	Late 2020	Yes	Yes
SCY-078 (MK-3118)	ibrexafungerp	Scynexis/ R-Pharm JSC/ Merck	glucan synthase inhibitors	Fungal infections	IV/PO	InTrial	Late 2020	No	Yes

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
2021 Possible launch date									
Furoscix	furosemide	scPharmaceuticals	diuretic	Heart failure	SC	CRL	1Q2021	Yes	No
MK-4618 (KRP-114V, RVT-901)	vibegron	Roivant Sciences/ Urovant/ Kissei/ Kyorin/ Merck	selective beta 3 adrenergic receptor agonist	Overactive bladder	PO	InTrial	1Q2021	No	No
ALNG-01 (ALN-G-01)	lumasiran	Alnylam	glycolate oxidase antagonist	Hyperoxaluria	Intranasal	InTrial	1Q2021	Yes	Yes
SDP-037, SDN-037	SDP-037, SDN-037	Sun Pharma Advanced Research Company (SPARC)	Corticosteroid	Ocular inflammation/pain	OP	InTrial	2Q2021	No	No
UCB-4940 (CDP-4940)	bimekizumab	UCB	interleukin-17 (IL-17) receptor inhibitor	Psoriasis(Ps)/ Psoriatic arthritis (PsA)/ Ankylosing spondylitis (AS)/ Rheumatoid arthritis (RA)	IV	InTrial	1H2021	Yes	No
RGN-259 (GBT-201; RGN-352)	thymosin beta 4	RegeneRx	actin regulating peptide	Neurotrophic keratitis (NK)/ Dry eyes	OP	InTrial	1H2021	No	Yes
WVE-210201	WVE-210201	Wave Life Sciences	oligonucleotide	Duchenne muscular dystrophy (DMD)	IV	InTrial	1H2021	Yes	Yes
ACER-001	sodium phenylbutyrate	Acer Therapeutics	BCKDC kinase inhibitor	Maple Syrup Urine Disease	PO	InTrial	1H2021	No	Yes
AXS-05	dextromethorphan/ bupropion	Axsome	N-methyl-D-aspartate (NMDA) antagonist/ antidepressant	Treatment-resistant depression/ Alzheimer's disease	PO	InTrial	1H2021	No	No

684

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
ACP-001	TransCon Growth Hormone	Ascendis	growth hormone prodrug	Short stature/ Growth hormone deficiency	SC	InTrial	1H2021	Yes	No
CCX-168	avacopan	ChemoCentryx/ Galencia	C5a receptor (C5aR) antagonist	Vasculitis/ Glomerulopathy	PO	InTrial	1H2021	Yes	Yes
GSK-2894512 (WBI-1001)	tapinarof	GSK/ Celestial/ Roivant Sciences/ Welichem Biotech	therapeutic aryl hydrocarbon receptor modulating agent (TAMA)	Atopic dermatitis (AD)/ Psoriasis	TOP	InTrial	1H2021	Yes	No
TadFin	tadalafil and finasteride	Veru	phosphodiesterase type 5 inhibitor /5-alpha-reductase inhibitor	Benign prostatic hyperplasia (BPH)	PO	InTrial	Mid-2021	No	No
EBV-CTL (ATA-129)	tabelecleucel	Atara Biotherapeutics/ Memorial Sloan-Kettering Cancer Center	cell therapy	Lymphoproliferative disorder	IV	InTrial	Mid-2021	Yes	Yes
RSV-F (ResVax)	respiratory syncytial virus vaccine	Novavax	vaccine	Respiratory syncytial virus (RSV) infection	IM	InTrial	Mid-2021	Yes	No
Recorlev	levoketoconazole	Strongbridge Biopharma	azole antifungal	Cushing's syndrome	PO	InTrial	3Q2021	No	Yes
PDP-716	brimonidine	Sun Pharma Advanced Research Company (SPARC)	alpha-2 agonist	Glaucoma	OP	InTrial	3Q2021	No	No
Otividex	dexamethasone sustained-release	Otonomy	corticosteroid	Meniere's disease	Intratympanic	InTrial	2H2021	Yes	No

685

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
VBP-15	vamorolone	Santhera	corticosteroid	Duchenne muscular dystrophy (DMD)	PO	InTrial	2H2021	Yes	Yes
PL-56	budesonide	Calliditas/ Kyowa Hakko Kirin	corticosteroid	Nephropathy	PO	InTrial	2H2021	No	No
TWIN (S6G5T-1; S6G5T-3)	benzoyl peroxide/ tretinoin	Sol-Gel Technologies	retinoid	Acne vulgaris	TOP	InTrial	2H2021	No	No
177Lu-PSMA-617	Lutetium	Endocyte	Radiopharmaceutical	Prostate cancer	IV	InTrial	2H2021	Yes	No
LN-145	lifileucel	Iovance Biotherapeutics	tumor infiltrating lymphocyte	Cervical Cancer	IV	InTrial	2H2021	Yes	No
GS-010	GS-010	GenSight Biologics	gene therapy	Optic neuropathy	Intraocular	InTrial	2H2021	Yes	Yes
AMAG-423	digoxin immune fab (DIF)	AMAG/ Velo	digitalis-like factor antagonist	Preeclampsia	IV	InTrial	2H2021	Yes	Yes
SPN-810	molindone	Supernus	atypical antipsychotic	Attention deficit hyperactivity disorder (ADHD)	PO	InTrial	2H2021	No	No
R-1658 (RG-1658, JTT-705, RO-4607381)	dalcetrapib	DalCor/ Japan Tobacco/ Roche	cholesteryl ester transfer protein inhibitor	Acute coronary syndrome (ACS)	PO	InTrial	2021	Yes	No
Korsuva	difelikefalin	Cara Therapeutics/ Vifor/ Fresenius	opioid receptor agonist	Pruritus/ Pain/ Osteoarthritis	IV/PO	InTrial	2021	No	No
OTL-101	ADA-transduced autologous stem cell therapy	Orchard Therapeutics	gene therapy	Adenosine deaminase (ADA)-deficient severe combined immunodeficiency (SCID)	Undisclosed	InTrial	2021	Yes	Yes

686

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
BMS-986089 (RG-6206)	BMS-986089 (RG-6206)	Roche/ Bristol-Myers Squibb	anti-myostatin adnectin	Duchenne muscular dystrophy (DMD)	SC	InTrial	2021	Yes	Yes
AZD-6094 (HMPL-504)	savolitinib (volitinib)	AstraZeneca (Hutchison MediPharma)	c-Met receptor tyrosine kinase inhibitor	Renal cell cancer (RCC)/ Non-small cell lung cancer (NSCLC)	PO	InTrial	2021	Yes	No
CT-100	corticotrophin	Eton	adrenocorticotropic hormone (ACTH)	Rheumatoid arthritis (RA)	INJ	InTrial	2021	No	No
SHP-647 (PF-00547659)	SHP-647 (PF-00547659)	Shire	MAdCAM-1 antagonist	Irritable bowel disease (IBD)/ Crohn's disease (CD)/ Ulcerative colitis (UC)	IV/SC	InTrial	2021	Yes	Yes
ABL-001	asciminib	Novartis	allosteric Bcr-Abl inhibitor	Chronic myelogenous leukemia (CML)	PO	InTrial	2021	Yes	Yes
CMX-001	brincidofovir hexadecyloxypropyl ester	Chimerix	DNA-directed DNA polymerase inhibitor	Adenovirus/ Cytomegalovirus (CMV)/ Smallpox	PO	InTrial	2021	No	Yes
S5G4T-1 (DER-45-EV)	benzoyl peroxide	Sol-Gel Technologies	benzoyl peroxide	Rosacea	TOP	InTrial	2021	No	No
POL-6326	balixafortide	Polyphor	chemokine (CXCR4) antagonist	Transplant/ Breast cancer	IV	InTrial	2021	Yes	No
DS-100	DS-100	Eton	undisclosed	Ophthalmological disease	SC	InTrial	2021	unknown	No
Qizenday	MD-1003	MedDay	biotin	Multiple sclerosis	PO	InTrial	2021	Yes	No
ATI-5923	tecarfarin	ARYx Therapeutics/ Armetheon	vitamin K epoxide reductase enzyme inhibitor	Anticoagulation	PO	InTrial	2021	No	No

687

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
RG-7314 (RO-5285119)	balovaptan	Roche	V1A vasopressin receptor antagonist	Autism spectrum disorder	PO	InTrial	2021	Yes	No
Edsivo	celiprolol HCl	Acer Therapeutics	alpha-2/beta-1 adrenergic agent	vascular Ehlers-Danlos Syndrome (vEDS)	PO	CRL	2021	Yes	Yes
OSE-2101 (IDM-2101, EP-2101)	tedopi	OSE Pharma/ Takeda	vaccine	Non-small cell lung cancer (NSCLC)	SC	InTrial	2021	Yes	Yes
LY-686017	tradipitant	Vanda Pharmaceuticals	neurokinin 1 receptor (NK-1R) antagonist	Motion sickness	PO	InTrial	2021	No	No
IMO-2125	tilsotolimod	Idera	toll-like receptor 9 (TLR-9) agonist	Melanoma	SC/ intratumoral	InTrial	2021	Yes	Yes
gantenerumab	gantenerumab	Roche	beta-amyloid (Abeta) inhibitor	Alzheimer's disease	SC	InTrial	Late 2021	Yes	No
Ultomiris SC	ravulizumab-cwvz	Alexion	C5 complement inhibitor	paroxysmal nocturnal hemoglobinuria (PNH); Hemolytic uremic syndrome (HUS)	SC	InTrial	Late 2021	Yes	Yes
ONS-5010	bevacizumab	Outlook Therapeutics	anti-VEGF antibody	wet age-related macular degeneration	Intravitreal	InTrial	Late 2021	Yes	No
PF-06482077	multivalent group B streptococcus vaccine	Pfizer	vaccine	Bacterial infection	IM	InTrial	Late 2021	Yes	No
CAT-1004	edasalonexent	Catabasis	NF-kB inhibitor	Duchenne muscular dystrophy (DMD)	PO	InTrial	Late 2021	Yes	Yes
Humacyl	human acellular vessel	Humacyte	cellular therapy	End-stage renal disease (ESRD)/ Peripheral artery disease (PAD)	Implant	InTrial	Late 2021	Yes	No
AMT-061	AMT-061	uniQure	gene therapy	Hemophilia B	IV	InTrial	Late 2021	Yes	No

Drug name	Generic name	Company	Drug class	Therapeutic use	Route of administration	Regulatory status	Estimated release date	Specialty drug	Orphan drug
PW-4142 (T-111)	nalbuphine ER	Trevi Therapeutics/ Endo	opioid agonist/ antagonist	Prurigo nodularis	PO	InTrial	Late 2021	No	No
NNZ-2566	trofinetide	Neuren	insulin-like growth factor 1 (IGF-1) derivative	Rett syndrome/ Fragile X syndrome/ Brain injury	IV/PO	InTrial	Late 2021	Yes	Yes
GSK-2696274 (OTL-200)	GSK-2696274 (OTL-200)	GlaxoSmithKline	gene therapy	Leukodystrophy	IV	InTrial	Late 2021	Yes	Yes

IM = intramuscular, INH = inhalation, INJ = injection, IUD = intrauterine device, IV = intravenous, OP = ophthalmic, PO = oral, SC = subcutaneous, SL = sublingual, SPR = spray, TOP = topical, VG = vaginal, NSCLC = Non-small cell lung cancer

689

Key pending indication forecast

OptumRx key pending indication forecast

Brand name	Generic name	Company	Drug class	Therapeutic use	Proposed new indication	Route of administration	Estimated approval date
Tecentriq	atezolizumab	Genentech	PD-L1 monoclonal antibody	Non-small cell lung cancer (NSCLC)	In combination with Abraxane (albumin-bound paclitaxel; nab-paclitaxel) and carboplatin for the initial (first-line) treatment of people with metastatic non-squamous non-small cell lung cancer (NSCLC) who do not have EGFR or ALK genomic tumour aberrations	IV	9/2/2019
Ofev	nintedanib	Boehringer Ingelheim	tyrosine kinase inhibitor	Systemic sclerosis	Treatment of systemic sclerosis associated with interstitial lung disease	PO	9/7/2019
Nucala	mepolizumab	GlaxoSmithKline	IL-5 antagonist monoclonal antibody	Eosinophilic asthma	Add-on treatment for severe eosinophilic asthma in pediatric patients aged six to 11 years	SC	9/19/2019
Pifeltro	doravirine	Merck	non-nucleoside reverse transcriptase inhibitor (NNRTI)	HIV infection	Use in people living with HIV-1 who are switching from a stable antiretroviral regimen and whose virus is suppressed (HIV-1 RNA < 50 copies/mL)	PO	9/20/2019
Delstrigo 691	doravirine/ lamivudine/ tenofovir disoproxil fumarate	Merck	non-nucleoside reverse transcriptase inhibitor (NNRTI)/ nucleoside reverse transcriptase inhibitor (NRTI)/ NRTI	HIV infection	Use in people living with HIV-1 who are switching from a stable antiretroviral regimen and whose virus is suppressed (HIV-1 RNA < 50 copies/mL)	PO	9/20/2019

Brand name	Generic name	Company	Drug class	Therapeutic use	Proposed new indication	Route of administration	Estimated approval date
Invokana	canagliflozin	Janssen	sodium-dependent glucose transporter 2 (SGLT-2) inhibitor	Diabetes mellitus	To reduce the risk of end-stage kidney disease (ESKD), the doubling of serum creatinine, which is a key predictor of ESKD, and renal or cardiovascular death in adults with type 2 diabetes and chronic kidney disease	PO	9/22/2019
Darzalex	daratumumab	Janssen	CD 38 molecule agonist	Multiple myeloma	in combination with bortezomib, thalidomide and dexamethasone (VTd) for newly diagnosed patients with multiple myeloma who are eligible for autologous stem cell transplant (ASCT)	IV	9/26/2019
Xarelto	rivaroxaban	Janssen	factor Xa inhibitor	Anticoagulation	Prevention of venous thromboembolism (VTE), or blood clots, in medically ill patients.	PO	10/14/2019
Nplate	romiplostim	Amgen	thrombopoietin receptor agonist	Immune thrombocytopenia (ITP)	Treatment of adult patients with immune thrombocytopenia (ITP) who have had ITP for 12 months or less and an insufficient response to corticosteroids, immunoglobulins or splenectomy	SC	10/15/2019
Eylea	aflibercept	Regeneron	vascular endothelial growth factor-A (VEGF-A) inhibitor/ placental growth factor (PlGF) inhibitor	Macular degeneration	Prefilled-syringe formulation	INJ	10/15/2019

692

Brand name	Generic name	Company	Drug class	Therapeutic use	Proposed new indication	Route of administration	Estimated approval date
Zilretta	triamcinolone acetonide	Flexion Therapeutics	corticosteroids	Osteoarthritis	Label update: Repeat administration of Zilretta for treatment of osteoarthritis (OA) knee pain was safe and well tolerated with no deleterious impact on cartilage or joint structure observed through X-ray analysis.	Intra-articular	10/17/2019
Ultomiris	ravulizumab-cwvz	Alexion	C5 complement inhibitor	Hemolytic uremic syndrome (HUS)	Treatment of atypical hemolytic uremic syndrome	IV	10/19/2019
Stelara	ustekinumab	Janssen	human interleukin-12 and -23 antagonist	Ulcerative colitis	Treatment of ulcerative colitis (UC)	SC	10/20/2019
Baxdela	delafloxacin	Melinta Therapeutics	fluoroquinolone	Community Acquired Pneumonia (CAP)	Treatment of adult patients with community acquired pneumonia (CAP)	PO/IV	10/24/2019
Zejula	niraparib	Tesaro	poly (ADP-ribose) polymerase (PARP) inhibitor	Ovarian cancer	Treatment of advanced ovarian, fallopian tube, or primary peritoneal cancer patients who have been treated with three or more prior chemotherapy regimens and whose cancer	PO	10/24/2019
Erleada	apalutamide	Janssen	androgen receptor antagonist	Prostate cancer	Treatment of patients with metastatic castration-sensitive prostate cancer (mCSPC).	PO	10/26/2019
Belviq XR	lorcaserin	Arena/Eisai	5-HT-2C receptor agonist	Obesity	Label update: to include long-term efficacy and safety data and remove the limitation of use related to the effect of Belviq on CV morbidity and mortality	PO	10/31/2019
Botox	onabotulinumtoxinA	Allergan	botulinum toxin analog	Lower spasticity	Treatment of pediatric patients (2 years of age and older) with lower limb spasticity	IM	11/1/2019

693

Brand name	Generic name	Company	Drug class	Therapeutic use	Proposed new indication	Route of administration	Estimated approval date
Xofluza	baloxavir	Genentech/ Shionogi	polymerase acidic (PA) endonuclease inhibitor	Influenza	Treatment of influenza in individuals at high-risk for influenza-related complications 12 years of age or older	PO	11/4/2019
Farxiga	dapagliflozin	AstraZeneca	sodium glucose cotransporter-2 (SGLT-2) inhibitor	Diabetes mellitus	Addition of cardiovascular outcomes trial data for Farxiga for type 2 diabetes.	PO	12/1/2019
Rituxan	rituximab	Roche/ Genentech	CD-20 antagonist	Granulomatosis with polyangiitis (GPA) and microscopic polyangiitis	In combination with glucocorticoids, for the treatment of granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA) in children two years of age and older	IV	12/11/2019
Vascepa	icosapent ethyl	Amarin	ethyl ester of eicosapentaenoic acid	Hyperlipidemia	Adjunct to diet in the treatment of adults with high triglycerides (≥ 200 mg/dL and < 500 mg/dL) and mixed dyslipidemia	PO	12/28/2019
Fiasp	insulin aspart	Novo Nordisk	insulins	Diabetes mellitus	To improve glycemic control in children and adolescents with type 1 diabetes	SC	1/1/2020
Ozempic	semaglutide	Novo Nordisk	glucagon-like peptide-1 (GLP-1) receptor agonist	Cardiovascular risk reduction	Cardiovascular risk reduction in adults with type 2 diabetes	SC	1/20/2020

694

Brand name	Generic name	Company	Drug class	Therapeutic use	Proposed new indication	Route of administration	Estimated approval date
Keytruda	pembrolizumab	Merck	anti-PD-1 inhibitor	Melanoma, classical Hodgkin lymphoma, primary mediastinal large B-cell lymphoma, gastric cancer, hepatocellular carcinoma and Merkel cell carcinoma	Updated dosing frequency: every-six-weeks (Q6W) dosing schedule option.	IV	2/18/2020
luspatercept	luspatercept	Celgene	modified type II activin receptor recombinant fusion protein	Myelodysplastic syndromes (MDS)	Treatment of adult patients with very low to intermediate risk myelodysplastic syndromes (MDS)-associated anemia who have ring sideroblasts and require red blood cell (RBC) transfusions	SC	4/4/2020
Otezla	apremilast	Celgene	phosphodieasterase 4 inhibitor	Scalp psoriasis	Treatment of moderate to severe scalp psoriasis	PO	4/15/2020
Nerlynx	neratinib	Puma Biotechnology	irreversible pan-ErbB receptor tyrosine kinase inhibitor	Breast cancer	In combination with capecitabine for the treatment of patients with HER2-positive metastatic breast cancer who have failed two or more prior lines of HER2-directed treatment (third-line disease)	PO	5/1/2020
Xtandi	enzalutamide	Astellas/ Pfizer	androgen receptor inhibitor	Prostate cancer	Treatment of metastatic hormone-sensitive prostate cancer (mHSPC)	PO	5/30/2020

695

Brand name	Generic name	Company	Drug class	Therapeutic use	Proposed new indication	Route of administration	Estimated approval date
Orilissa	elagolix	AbbVie	gonadotropin-releasing hormone (GnRH) receptor antagonist	Uterine fibroids	Management of heavy menstrual bleeding (HMB) associated with uterine fibroids in women	PO	6/5/2020

IM = intramuscular, IV = intravenous, OPH = ophthalmic, PO = oral, SC = subcutaneous

699

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