OPTUMRx®

Silver State Scripts Board Meeting

SEPTEBMER 24, 2020

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Agenda

NOTICE OF PUBLIC MEETING – SILVER STATE SCRIPTS BOARD

Date of Posting:	August 10, 2020
Date of Meeting:	Thursday, September 24, 2020 at 1:00 PM
Name of Organization:	The State of Nevada, Department of Health and Human Services, Division of Health Care Financing and Policy (DHCFP), Silver State Script Board.
Place of Meeting:	Please use the teleconference/WebEx options provided below. If accommodations are requested, please advise using the information at the end of this agenda. Out of deference to Declaration of Emergency Directive 006 (https://nvhealthresponse.nv.gov/wp-content/uploads/2020/03/Declaration-of-Emergency-Directive-006-re-OML.3-21-20.pdf) from the State of Nevada Executive Department signed by Governor Sisolak as well as Emergency Directive 003 (https://nvhealthresponse.nv.gov/wp-content/uploads/2020/03/2020-03-20.Declaration-of-Emergency-Directive-003.pdf) signed March 20, 2020, a physical location will not be open to the public for attendance at this time.
Webinar Registration:	https://optum.webex.com/optum/onstage/g.php?MTID=e3fc33f7df7b6ca737e3bcd6f0da541b0 Or go to www.webex.com and enter the Event Number listed below. Once you have registered for the meeting, you will receive an email message confirming your registration. This message will provide the information that you need to join the meeting.
Event Number:	161 321 3288 Click "Join Now" Follow the instructions that appear on your screen to join the audio portion of the meeting. Audio will be transmitted over the internet. A password should not be necessary, but if asked use: Medicaid1!

For Audio Only:

Phone: 1-763-957-6300
Event: 161 321 3288

[Please place your phone on mute unless providing public comment.]

Closed Executive Session - 1:00 PM

Open Session/Public Meeting - will begin Upon Completion of the Closed Executive Session

AGENDA

1. Call to Order and Roll Call

2. Public Comment on Any Matter on the Agenda (*Owing to the lack of a physical location for this meeting, public comment is encouraged to be submitted in advance so that it may be included in meeting materials and given attention. No action may be taken upon a matter raised through public comment unless the matter itself has been specifically included on an agenda as an action item. Please provide your name in any comment for record keeping purposes. You may submit comments in writing via e-mail to (rxinfo@dhcfp.nv.gov). There may be opportunity to take public comment via telephone but phone participants should disconnect their call and re-join if they must take another call. Do not place your phone on hold or you may disrupt the meeting for other participants. This guidance applies for all periods of public comment referenced further in the agenda, such as those related to clinical presentations.*)

3. Administrative

a. **For Possible Action:** Review and Approve Meeting Minutes from June 25, 2020.

b. Status Update by the DHCFP.

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

a. **For Possible Action:** Discussion and possible adoption of Biologic Response Modifiers, Immunomodulators, Targeted Immunomodulators, and Multiple Sclerosis Agents, Oral

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

b. **For Possible Action:** Discussion and possible adoption of Cardiovascular Agents, Antihypertensive Agents, Calcium-Channel Blockers

i. Public comment.

ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

c. **For Possible Action:** Discussion and possible adoption of Dermatological Agents, Topical Anti-infectives, Acne Agents: Topical, Benzoyl Peroxide, Antibiotics and Combination Products

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

d. **For Possible Action:** Discussion and possible adoption of Gastrointestinal Agents, Functional Gastrointestinal Disorder Drugs

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

e. **For Possible Action:** Discussion and possible adoption of Hormones and Hormone Modifiers, Antidiabetic Agents, Insulins (Vials, Pens and Inhaled)

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

f. **For Possible Action:** Discussion and possible adoption of Neurological Agents, Anticonvulsants, and Benzodiazepines

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.

v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

g. **For Possible Action:** Discussion and possible adoption of Ophthalmic Agents, Ophthalmic Anti-inflammatory Agents, Ophthalmic Corticosteroids

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

h. **For Possible Action:** Discussion and possible adoption of Respiratory Agents, Long-acting/Maintenance Therapy

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

5. Annual Review - Established Drug Classes Being Reviewed Due to the Release of New Generics

a. **For Possible Action:** Discussion and possible adoption of Anti-infective Agents, Cephalosporins, Third-Generation Cephalosporins

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

b. **For Possible Action:** Discussion and possible adoption of Cardiovascular Agents, Antihypertensive Agents, Vasodilators, Oral

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

c. **For Possible Action:** Discussion and possible adoption of Dermatological Agents, Topical Anti-infectives, Topical Antivirals

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

d. **For Possible Action:** Discussion and possible adoption of Electrolytic and Renal Agents, Phosphate Binding Agents

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

e. **For Possible Action:** Discussion and possible adoption of Genitourinary Agents, Benign Prostatic Hyperplasia (BPH) Agents, Alpha-Blockers and Bladder Antispasmodics

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

f. **For Possible Action:** Discussion and possible adoption of Musculoskeletal Agents, Antigout Agents

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

g. **For Possible Action:** Discussion and possible adoption of Ophthalmic Agents, Ophthalmic Anti-infectives, Ophthalmic Quinolones

i. Public comment.
ii. Drug class review presentation by OptumRx.

iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

6. Annual Review – Established Drug Classes

a. **For Possible Action:** Discussion and possible adoption of Antihistamines, H1 blockers, Non-Sedating H1 Blockers

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

b. **For Possible Action:** Discussion and possible adoption of Cardiovascular Agents, Antilipemics, Cholesterol Absorption Inhibitors, and HMG-CoA Reductase Inhibitors (Statins)

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

c. **For Possible Action:** Discussion and possible adoption of Dermatological Agents, Topical Antineoplastics, Topical Retinoids

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

d. **For Possible Action:** Discussion and possible adoption of Gastrointestinal Agents, Antiemetics, Pregnancy-induced Nausea and Vomiting Treatment, and Gastrointestinal Anti-inflammatory Agents

i. Public comment.
ii. Drug class review presentation by OptumRx.

iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

e. **For Possible Action:** Discussion and possible adoption of Hematological Agents, Platelet Inhibitors

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

f. **For Possible Action:** Discussion and possible adoption of Hormones and Hormone Modifiers, Antidiabetic Agents, Incretin Mimetics; Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

g. **For Possible Action:** Discussion and possible adoption of Monoclonal Antibodies for the treatment of Respiratory Conditions

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

h. **For Possible Action:** Discussion and possible adoption of Musculoskeletal Agents, Restless Leg Syndrome Agents

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.

v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

i. **For Possible Action:** Discussion and possible adoption of Psychotropic Agents, ADHD Agents

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

j. **For Possible Action:** Discussion and possible adoption of Respiratory Agents, Short-Acting/Rescue Therapy

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

k. **For Possible Action:** Discussion and possible adoption of Toxicology Agents, Substance Abuse Agents

i. Public comment.
ii. Drug class review presentation by OptumRx.
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.
iv. Presentation of recommendations for PDL inclusion by OptumRx.
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.

7. Annual Review – Drug Classes Without Proposed Changes

a. Public Comment
b. **For Possible Action**: Discussion and possible adoption of the Preferred Drug List (PDL) as presented by OptumRx and the Division of Health Care Financing and Policy without changes.
   i. Analgesics, Analgesic/Miscellaneous, Neuropathic Pain/Fibromyalgia Agents; Tramadol and Related Drugs; Opiate Agonists; Opiate Agonists - Abuse Deterrent; Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) - Oral
   ii. Anti-infective Agents, Aminoglycosides, Inhaled Aminoglycosides; Antivirals, Alpha Interferons; Antivirals, Anti-hepatitis Agents, Polymerase Inhibitors/Combination Products; Ribavirins; Anti-Herpetic Agents; Influenza

Agents; Cephalosporins, Second-Generation Cephalosporins; Macrolides; Quinolones, Quinolones - 2nd Generation; Quinolones - 3rd Generation;

iii. Autonomic Agents, Sympathomimetics, Self-Injectable Epinephrine

iv. Biologic Response Modifiers, Multiple Sclerosis Agents, Injectable; Specific Symptomatic Treatment

v. Cardiovascular Agents, Antihypertensive Agents, Angiotensin II Receptor Antagonists; Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors); Beta-Blockers; Vasodilators, Inhaled; Antilipemics, Bile Acid Sequestrants; Fibric Acid Derivatives; Niacin Agents; Omega-3 Fatty Acids

vi. Dermatological Agents, Antipsoriatic Agents; Topical Analgesics; Topical Anti-infectives, Impetigo Agents: Topical; Topical Scabicides; Topical Anti-inflammatory Agents, Immunomodulators: Topical;

vii. Gastrointestinal Agents, Antiemetics, Serotonin-receptor antagonists/Combo; Antiulcer Agents, H2 blockers; Proton Pump Inhibitors (PPIs); Gastrointestinal Enzymes

viii. Genitourinary Agents, Benign Prostatic Hyperplasia (BPH) Agents, 5-Alpha Reductase Inhibitors

ix. Hematological Agents, Anticoagulants, Oral; Injectable; Erythropoiesis-Stimulating Agents

x. Hormones and Hormone Modifiers, Androgens; Antidiabetic Agents, Alpha-Glucosidase Inhibitors/Amylin analogs/Misc.; Biguanides; Dipeptidyl Peptidase-4 Inhibitors; Meglitinides; Sulfonylureas; Thiazolidinediones; Anti-hypoglycemic Agents; Pituitary Hormones, Growth hormone modifiers; Progestins for Cachexia

xi. Musculoskeletal Agents, Bone Resorption Inhibitors, Bisphosphonates; Nasal Calcitonins; Skeletal Muscle Relaxants

xii. Neurological Agents, Alzheimer's Agents; Anticonvulsants, Barbiturates; Hydantoins; Anti-Migraine Agents, Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists; Anti-Migraine Agents, Serotonin-Receptor Agonists; Antiparkinsonian Agents, Dopamine Precursors; Antiparkinsonian Agents, Non-ergot Dopamine Agonists

xiii. Ophthalmic Agents, Antiglaucoma Agents; Ophthalmic Antihistamines; Ophthalmic Anti-infectives, Ophthalmic Macrolides; Ophthalmic Anti-infective/Anti-inflammatory Combinations; Ophthalmic Anti-inflammatory Agents, Ophthalmic Nonsteroidal Anti-inflammatory Drugs (NSAIDs); Ophthalmics for Dry Eye Disease

xiv. Otic Agents, Otic Anti-infectives, Otic Quinolones

xv. Psychotropic Agents, Antidepressants, Other; Selective Serotonin Reuptake Inhibitors (SSRIs); Antipsychotics, Atypical Antipsychotics – Oral and Topical; Long-acting Injectable; Anxiolytics, Sedatives, and Hypnotics; Psychostimulants, Narcolepsy Agents

xvi. Respiratory Agents, Nasal Antihistamines; Respiratory Anti-inflammatory Agents, Leukotriene Receptor Antagonists; Nasal Corticosteroids; Phosphodiesterase Type 4 Inhibitors;

xvii. Toxicology Agents, Antidotes, Opiate Antagonists

8. OptumRx Reports: New Drugs to Market and New Line Extensions

9. Closing Discussion

a. Public comments on any subject. (*Owing to the lack of a physical location for this meeting, public comment is encouraged to be submitted in advance so that it may be included in meeting materials and given attention. No action may be taken upon a matter raised through public comment unless the matter itself has been specifically included on an agenda as an action item. Please provide your name in any comment for record keeping purposes. You may submit comments in writing via e-mail to (rxinfo@dhcfp.nv.gov). There may be opportunity to take public comment via telephone, but phone participants should disconnect their call and re-join if they must take another call. Do not place your phone on hold or you may disrupt the meeting for other participants. Public comments may be related to topics on the agenda or matters related to other topics per NRS 241.020(3)(3)(II).*)

b. Date and location of the next meeting.

   i. Discussion of the time of the next meeting.

c. Adjournment.

PLEASE NOTE: **Items may be taken out of order at the discretion of the chairperson. Items may be combined for consideration by the public body. Items may be pulled or removed from the agenda at any time. If an action item is not completed within the time frame that has been allotted, that action item will be continued at a future time designated and announced at this meeting by the chairperson. All public comment may be limited to 3 minutes and written comments are encouraged if possible.**

This notice and agenda have been posted online at http://dhcfp.nv.gov and http://notice.nv.gov as well as Carson City, Las Vegas, and Reno central offices for the Division of Health Care Financing and Policy. E-mail notice has been made to such individuals as have requested notice of meetings (to request notifications please contact tbenitez@dhcfp.nv.gov, or at 1100 East William Street, Suite 101, Carson City, Nevada 89701 or call Tanya Benitez at (775) 684-3730). At this time, in deference to Emergency Directive 006 dated March 22, 2020 and related directives which have discouraged certain in-person activities, notice has not been posted at other physical locations.

If you require a physical copy of supporting material for the public meeting, please contact tbenitez@dhcfp.nv.gov, or at 1100 East William Street, Suite 101, Carson City, Nevada 89701 or call Tanya Benitez at (775) 684-3730). Supporting material will also be posted online as referenced above.

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

Note: We are pleased to make reasonable accommodations for members of the public with a disability and wish to participate. If accommodated arrangements are necessary, notify the Division of Health Care Financing and Policy as soon as possible and at least ten days in advance of the meeting, by e-mail at tbenitez@dhcfp.nv.gov in writing, at 1100 East William Street, Suite 101, Carson City, Nevada 89701 or call Tanya Benitez at (775) 684-3730.

Per Nevada Governor Sisolak's Declaration of Emergency Directive 006; Subsection 3: The requirements contained in NRS 241.020 (4) (a) that public notice agendas be posted at physical locations within the State of Nevada are suspended.

Per Nevada Governor Sisolak's Declaration of Emergency Directive 006; Subsection 4: Public bodies must still comply with requirements in NRS 241.020 (4)(b) and NRS 241.020 (4)(c) that public notice agendas be posted to Nevada's notice website and the public body's website, if it maintains one along with providing a copy to any person who has requested one via U.S. mail or electronic mail.

Per Nevada Governor Sisolak's Declaration of Emergency Directive 006; Subsection 5: The requirement contained in NRS 241.020 (3)(c) that physical locations be available for the public to receive supporting material for public meetings is suspended.

Per Nevada Governor Sisolak's Declaration of Emergency Directive 006; Subsection 6: If a public body holds a meeting and does not provide a physical location where supporting material is available to the public, the public body must provide on its public notice agenda the name and contact information for the person designated by the public body from whom a member of the public may request supporting material electronically and must post supporting material to the public body's website, if it maintains one.

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

Evelyn Chu, Pharm.D.

Mark Crumby, Pharm.D.

Michael Hautekeet, R.Ph

Sapandeep Khurana, MD

Brian Passalacqua, MD

Aditi Singh, MD

Silver State Scripts Board Meeting scheduled for 2020

Date	Time	South Nevada Location	North Nevada Location
September 24, 2020	1:00 PM	On-line	None
December 10, 2020	1:00 PM	On-line	None

Silver State Scripts Board Meeting scheduled for 2021

Date	Time	South Nevada Location	North Nevada Location
March 25, 2021	1:00 PM	TBD	None
June 24, 2021	1:00 PM	TBD	None
September 23, 2021	1:00 PM	TBD	None
December 9, 2021	1:00 PM	TBD	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

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 HORIZANT® QUTENZA®
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® NUCYNTA® ER	**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 OPANA ER® OXYCODONE SR QL OXYMORPHONE SR XARTEMIS XR® QL ZOHYDRO ER® QL
Opiate Agonists - Abuse Deterrent		
EMBEDA® MORPHABOND® XTAMPZA ER®		ARYMO® ER HYSINGLA ER® OXYCONTIN® QL
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) - Oral		
CELECOXIB CAP DICLOFENAC POTASSIUM DICLOFENAC TAB DR FLURBIPROFEN TAB		CAMBIA ® POWDER 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 NAPROXEN TAB ER OXAPROZIN TAB SPRIX® SPR 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 TOBRAMYCIN NEBULIZER		TOBI PODHALER®
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 MAVYRET® SOFOSBUVIR/ VELPATASVIR	**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® SOVALDI® TECHNIVIE® VIEKIRA® PAK VOSEVI® ZEPATIER®
Ribavirins		
RIBAVIRIN		RIBASPHERE RIBAPAK® MODERIBA® REBETOL®
Anti-Herpetic Agents		
ACYCLOVIR FAMCICLOVIR VALCYCLOVIR		FAMVIR®
Influenza Agents		
AMANTADINE OSELTAMIVIR CAP/SUSP RIMANTADINE RELENZA®		RAPIVAB TAMIFLU® XOFLUZA®
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®
Biologic Response Modifiers		
Immunomodulators		
Targeted Immunomodulators		
ACTEMRA® CIMZIA® COSENTYX® ENBREL® ENTYVIO® HUMIRA® ILUMYA® INFLECTRA® KEVZARA® KINERET® OLUMIANT® ORENCIA® OTEZLA® RENFLEXIS® SILIQ® SIMPONI® XELJANZ®	Prior authorization is required for all drugs in this class https://www.medicaid.nv.gov/Downloads/provider/FA-61.pdf	ILARIS® REMICADE® RINVOQ® SKYRIZI® STELARA® TALTZ® TREMFYA®
Multiple Sclerosis Agents		
Injectable		
AVONEX® AVONEX® ADMIN PACK BETASERON® COPAXONE® QL	*Trial of only one agent is required before moving to a non-preferred agent* *PA required*	GLATOPA® GLATIRAMER LEMTRADA® PLEGRIDY®

Preferred Products	PA Criteria	Non-Preferred Products
EXTAVIA® OCREVUS® REBIF® QL TYSABRI®		
Oral		
AUBAGIO® GILENYA® TECFIDERA®	PA required	MAVENCLAD® MAYZENT®
Specific Symptomatic Treatment		
DALFAMPRIDINEQL	PA required	AMPYRA® QL
Cardiovascular Agents		
Antihypertensive Agents		
Angiotensin II Receptor Antagonists		
LOSARTAN LOSARTAN HCTZ VALSARTAN VALSARTAN HCTZ		ATACAND® AVAPRO® BENICAR® CANDESARTAN COZAAR® DIOVAN® DIOVAN HCTZ® EDARBI® EDARBYCLOR® EPROSARTAN HYZAAR® IRBESARTAN MICARDIS® TELMISARTAN TEVETEN®
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 ǂ NONPREFERRED FOR OVER 10 YEARS OLD	ACCURETIC® EPANED® ǂ FOSINOPRIL MAVIK® MOEXIPRIL PERINDOPRIL QUINAPRIL QUINARETIC® QBRELIS® TRANDOLAPRIL UNIVASC®
Beta-Blockers		
ACEBUTOLOL ATENOLOL ATENOLOL/CHLORTH		KAPSPARGO® SOTYLIZE®

Preferred Products	PA Criteria	Non-Preferred Products
BETAXOLOL BISOPROLOL BISOPROLOL/HCTZ		
BYSTOLIC®* CARVEDILOL LABETALOL	*Restricted to ICD-10 codes J40-J48	
METOPROLOL (Reg Release) NADOLOL PINDOLOL PROPRANOLOL PROPRANOLOL/HCTZ SOTALOL TIMOLOL		
Calcium-Channel Blockers		
AFEDITAB CR® AMLODIPINE CARTIA XT® DILTIA XT® DILTIAZEM ER DILTIAZEM HCL EXFORGE® EXFORGE HCT® FELODIPINE ER ISRADIPINE LOTREL® NICARDIPINE NIFEDIPINE ER NISOLDIPINE ER TAZTIA XT® VERAPAMIL VERAPAMIL ER		KATERZIA® MATZIM TAB LA NORVASC®
Vasodilators		
Inhaled		
VENTAVIS® TYVASO®		
Oral		
ORENITRAM® SILDENAFIL TADALAFIL TRACLEER®		ADCIRCA® ADEMPAS® ALYQ® AMBRISENTAN LETAIRIS® OPSUMIT® REVATIO ® TADALAFIL

Preferred Products	PA Criteria	Non-Preferred Products
		UPTRAVI®
Antilipemics		
Bile Acid Sequestrants		
COLESTIPOL CHOLESTYRAMINE WELCHOL®		QUESTRAN®
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 LOVASTATIN PRAVASTATIN SIMVASTATIN		ALTOPREV® AMLODIPINE/ATORVASTATIN CADUET® EZALLOR® EZETIMIBE-SIMVASTATIN FLUVASTATIN FLUVASTATIN XL 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		
OMEGA-3-ACID VASCEPA®		LOVAZA®

Preferred Products	PA Criteria	Non-Preferred Products
Dermatological Agents		
Antipsoriatic Agents		
DOVONEX® CREAM SORILUX® (FOAM) TACLONEX® SUSP VECTICAL® (OINT)		CALCITENE® CALCIPOTRIENE CALCIPOTRIENE OINT/BETAMETHAZONE DUOBRII® LOTION ENSTILAR ® (AER) TACLONEX OINT
Topical Analgesics		
CAPSAICIN FLECTOR® LIDOCAINE LIDOCAINE HC LIDOCAINE VISCOUS LIDOCAINE/PRILOCAINE PENNSAID® VOLTAREN® GEL		DICLOFENAC (gel/sol) EMLA® LICART® LIDODERM® QL LIDAMANTLE® ZTLIDO®
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® DENAVIR® XERESE® CREAM ZOVIRAX®, OINTMENT		ACYCLOVIR OINT

Preferred Products	PA Criteria	Non-Preferred Products
Topical Scabicides		
LINDANE NATROBA® * NIX® PERMETHRIN RID® ULESFIA®	* PA required	EURAX® MALATHION OVIDE® SKLICE® SPINOSAD VANALICE® GEL
Topical Anti-inflammatory Agents		
Immunomodulators: Topical		
ELIDEL® QL EUCRISA® PROTOPIC® QL	Prior authorization is required for all drugs in this class	PIMECROLIMUS 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		
Pregnancy-induced Nausea and Vomiting Treatment		
Diclegis® OTC Doxylamine 25mg/Pyridoxine 10mg		BONJESTA® DOXYLAMINE-PYRIDOXINE TAB 10-10
Serotonin-receptor antagonists/Combo		
GRANISETRON QL ONDANSETRON QL	PA required for all medication in this class	AKYNZEO® ANZEMET® QL KYTRIL® QL SANCUSO® ZOFRAN® QL

Preferred Products	PA Criteria	Non-Preferred Products
		ZUPLENZ® QL
Antiulcer Agents		
H2 blockers		
FAMOTIDINE RANITIDINE RANITIDINE SYRUP*	*PA not required for < 12 years	
Proton Pump Inhibitors (PPIs)		
DEXILANT® NEXIUM® POWDER FOR SUSP* OMEPRAZOLE PANTOPRAZOLE	PA required if exceeding 1 per day *for children ≤ 12 yrs.	ACIPHEX® ESOMEPRAZOLE LANSOPRAZOLE NEXIUM® CAPSULES PREVACID® PRILOSEC® PRILOSEC® OTC TABS PROTONIX® RABEPRAZOLE SODIUM
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 CANASA® PENTASA® SULFASALAZINE DR SULFASALAZINE IR		BALSALAZIDE® COLAZAL® DELZICOL® LIALDA ® MESALAMINE ENEMA SUSP 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®

Preferred Products	PA Criteria	Non-Preferred Products
Alpha-Blockers		
DOXAZOSIN TAMSULOSIN TERAZOSIN		ALFUZOSIN 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 RETACRIT®	PA required Quantity Limit	EPOGEN® QL MIRCERA® QL PROCRIT® QL
Platelet Inhibitors		
AGGRENOX® ANAGRELIDE ASPIRIN BRILINTA® * QL CILOSTAZOL®	* PA required	ASPIRIN/DIPYRIDAMOLE DURLAZA® EFFIENT® * QL PLAVIX® PRASUGREL

Preferred Products	PA Criteria	Non-Preferred Products
CLOPIDOGREL DIPYRIDAMOLE		ZONTIVITY® YOSPRALA®
Hormones and Hormone Modifiers		
Androgens		
ANDRODERM®	**PA required** **PA Form:** https://www.medicaid.nv.gov/Downloads/provider/FA-72.pdf	ANDROGEL® AXIRON® FORTESTA® NATESTO® STRIANT® TESTIM® TESTOSTERONE GEL TESTOSTERONE SOL VOGELXO®
Antidiabetic Agents		
Alpha-Glucosidase Inhibitors/Amylin analogs/Misc.		
ACARBOSE GLYSET® SYMLIN® (PA required)		CYCLOSET® PRECOSE®
Biguanides		
FORTAMET® METFORMIN EXT-REL (Glucophage XR®) METFORMIN EXT-REL (Glucophage XR®) METFORMIN (Glucophage®) METFORMIN ER (GEN GLUMETZA) RIOMET®		GLUCOPHAGE® GLUCOPHAGE XR® GLUMETZA® METFORMIN (GEN FORTAMET)
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® RYBELSUS® SOLIQUA®

Preferred Products	PA Criteria	Non-Preferred Products
		TANZEUM® XULTOPHY®
Insulins (Vials, Pens and Inhaled)		
APIDRA® HUMALOG® HUMULIN® LANTUS® LEVEMIR ® NOVOLIN® NOVOLOG® TOUJEO SOLO® 300 IU/ML TRESIBA FLEX INJ		ADMELOG® AFREZZA® BASAGLAR® FIASP® INSULIN LISPRO INJ 100U/ML HUMALOG® U-200
Meglitinides		
REPAGLINIDE		NATEGLINIDE (Starlix®) PRANDIN® STARLIX®
Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors		
FARXIGA® INVOKANA® INVOKAMET® JARDIANCE® XIGDUO XR®		GLYXAMBI® INVOKAMET® XR QTERN® SEGLUROMET® STEGLATRO® STEGLUJAN™ SYNJARDY® SYNJARDY® XR
Sulfonylureas		
DIABETA® GLIMEPIRIDE (Amaryl®) GLIPIZIDE (Glucotrol®) GLIPIZIDE EXT-REL (Glucotrol XL®) GLYBURIDE MICRONIZED (Glynase®) GLYBURIDE (Diabeta®) METAGLIP®		AMARYL® CHLORPROPAMIDE GLYNASE® GLUCOTROL® GLUCOTROL XL® GLYBURIDE/METFORMIN (Glucovance®) GLUCOVANCE® GLIPIZIDE/METFORMIN (Metaglip®) TOLAZAMIDE TOLBUTAMIDE
Thiazolidinediones		
PIOGLITAZONE		ACTOPLUS MET XR® ACTOPLUS MET® ACTOS® AVANDAMET®

Preferred Products	PA Criteria	Non-Preferred Products
		AVANDARYL® AVANDIA® DUETACT® PIOGLITAZONE/METFORMIN PIOGLITAZONE/GLIMEPR
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		
DUPIXENT® NUCALA® XOLAIR®	PA Required	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 FOSAMAX PLUS D® IBANDRONATE SKELID®
Nasal Calcitonins		
CALCITONIN-SALMON		MIACALCIN®

Preferred Products	PA Criteria	Non-Preferred Products
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® CELONTIN® DEPAKENE® DEPAKOTE ER® DEPAKOTE® DIVALPROEX SODIUM	PA required for members under 18 years old	DIACOMIT® OXTELLAR XR® POTIGA® QUDEXY XR® TROKENDI XR® SPRITAM®

Preferred Products	PA Criteria	Non-Preferred Products
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		
Barbiturates		
LUMINAL® MEBARAL® MEPHOBARBITAL SOLFOTON® PHENOBARBITAL MYSOLINE® PRIMIDONE	PA required for members under 18 years old	
Benzodiazepines		
CLOBAZAM CLONAZEPAM CLORAZEPATE	PA required for members under 18 years old	DIASTAT® KLONOPIN® ONFI® SYMPAZAN® FILM

Preferred Products	PA Criteria	Non-Preferred Products
DIAZEPAM DIAZEPAM rectal soln NAYZILAM® SPRAY* TRANXENE T-TAB® VALIUM®	*PA Required for all ages	
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		
AIMOVIG® AJOVY®	PA required for all products	EMGALITY®
Serotonin-Receptor Agonists		
RIZATRIPTAN ODT SUMATRIPTAN NASAL SPRAY 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® RELPAX® RIZATRIPTAN BENZOATE SUMATRIPTAN INJECTION SUMATRIPTAN/NAPROXEN SUMAVEL® TOSYMRA® TREXIMET® ZEMBRACE SYMTOUCH ZOLMITRIPTAN ZOMIG® ZOMIG® ZMT

Preferred Products	PA Criteria	Non-Preferred Products
Antiparkinsonian Agents		
Dopamine Precursors		
CARBIDOPA/LEVODOPA CARBIDOPA/LEVODOPA ER CARBIDOPA/LEVODOPA ODT STALEVO®	*Trial of only one agent is required before moving to a non-preferred agent*	CARBIDOPA/LEVODOPA/ENTACAPONE DUOPA™ INBRIJA™ (INH) LODOSYN® TAB RYTARY™
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® ROCKLATAN® SIMBRINZA® TIMOLOL DROPS/ GEL SOLN TRAVATAN Z® TRAVATAN®		ALPHAGAN® BETAGAN® BETOPTIC ® BIMATOPROST COSOPT PF® COSOPT® DORZOL/TIMOL SOL PF OCUPRESS® OPTIPRANOLOL® TIMOPTIC XE® TIMOPTIC® TRAVOPROST TRUSOPT® VYZULTA® XALATAN® XELPROS® ZIOPTAN®
Ophthalmic Antihistamines		
BEPREVE® KETOTIFEN PAZEO® ZADITOR OTC®		ALAWAY® AZELASTINE ALOMIDE ALOCRIL ELESTAT® EMADINE®

Preferred Products	PA Criteria	Non-Preferred Products
		EPINASTINE LASTACRAFT® OLOPATADINE (drop/sol) OPTIVAR® PATADAY® PATANOL®
Ophthalmic Anti-infectives		
Ophthalmic Macrolides		
ERYTHROMYCIN OINTMENT		
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		CEQUA®

Preferred Products	PA Criteria	Non-Preferred Products
RESTASIS®		RESTASIS® MULTIDOSE XIIDRA®
Otic Agents		
Otic Anti-infectives		
Otic Quinolones		
CIPRODEX® CIPRO HC® OTIC SUSP OFLOXACIN		CIPROFLOXACIN SOL 0.2% CETRAXAL® OTIPRIO® OTOVEL® SOLN
Psychotropic Agents		
ADHD Agents		
AMPHETAMINE SALT COMBO IR AMPHETAMINE SALT COMBO XR ATOMOXETINE CONCERTA® DEXMETHYLPHENIDATE DEXTROAMPHETAMINE SA TAB DEXTROAMPHETAMINE TAB DAYTRANA® DYANAVEL® FOCALIN XR® GUANFACINE ER METADATE CD® METHYLIN® 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® ADDERALL XR® ADZENYS® APTENSIO XR® CLONIDINE HCL ER COTEMPLA XR®-ODT DESOXYN® DEXEDRINE® DEXTROAMPHETAMINE SOLUTION EVEKEO® EVEKEO® ODT FOCALIN® INTUNIV® JORNAY PM® METADATE ER® METHYLPHENIDATE TAB ER (RELEXXII) METHYLPHENIDATE CHEW MYDAYIS® RELEXXII® MYDAYIS® RITALIN® STRATTERA® ZENZEDI®

Preferred Products	PA Criteria	Non-Preferred Products
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® 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® PAROXETINE ER PAXIL® PROZAC® SARAFEM® ZOLOFT®
Antipsychotics		
Atypical Antipsychotics - Oral		
ARIPIPRAZOLE CLOZAPINE FANAPT® LATUDA® NUPLAZID®* OLANZAPINE QUETIAPINE QUETIAPINE XR REXULTI® RISPERIDONE	**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® ABILIFY MYCITE ® CLOZARIL® FAZACLO® GEODON® INVEGA® PALIPERIDONE RISPERDAL®

Preferred Products	PA Criteria	Non-Preferred Products
SAPHRIS® VRAYLAR® ZIPRASIDONE		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® SOMNOTE®
	PA required for members under 18 years old	SONATA® ZOLPIDEM CR
		ZOLPIMIST®
Psychostimulants		
Narcolepsy Agents		
NUVIGIL® Provigil® *	* (No PA required for ICD-10 code G47.4) **PA Required for all ages	ARMODAFINIL MODAFINIL SUNOSI®** XYREM®
Respiratory Agents		
Nasal Antihistamines		
AZELASTINE DYMISTA® OLOPATADINE		ASTEPRO® PATANASE®
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®

Preferred Products	PA Criteria	Non-Preferred Products
		VERAMYST® XHANCE™ ZETONNA®
Phosphodiesterase Type 4 Inhibitors		
DALIRESP® QL	PA required	
Long-acting/Maintenance Therapy		
ADVAIR HFA® ANORO ELLIPTA® ARNUITY ELLIPTA® ASMANEX® BEVESPI® BUDESONIDE NEBS* DULERA® FLOVENT DISKUS® QL FLOVENT HFA® QL PULMICORT FLEXHALER® RESPULES®* QVAR® SEREVENT DISKUS® QL SPIRIVA® HANDIHALER STIOLTO RESPIMAT® STRIVERDI RESPIMAT® TUDORZA® SYMBICORT®		ADVAIR® DISKUS AEROSPAN HFA® AIRDUO® ALVESCO® ARCAPTA NEOHALER® ARMONAIR® BREO ELLIPTA® BROVANA® INCRUSE ELLIPTA ® LONHALA MAGNAIR® PERFOROMIST NEBULIZER® PULMICORT NEBS QVAR® REDIHALER™ SEEBRI NEOHALER® SPIRIVA RESPIMAT® TRELEGY ELLIPTA® UTIBRON NEOHALER ® WIXELA®
Short-Acting/Rescue Therapy		
ALBUTEROL NEB/SOLN ATROVENT® COMBIVENT RESPIMAT® IPRATROPIUM NEBS IPRATROPIUM/ALBUTEROL NEBS QL LEVALBUTEROL* NEBS PROVENTIL® HFA XOPENEX® HFA* QL		ALBUTEROL AER HFA LEVALBUTEROL* HFA PROAIR RESPICLICK® PROAIR® HFA VENTOLIN HFA® XOPENEX® Solution* QL

	Preferred Products	PA Criteria	Non-Preferred Products
Toxicology Agents			
Antidotes			
Opiate Antagonists			
	EVZIO ® NALOXONE NARCAN® NASAL SPRAY		
Substance Abuse Agents			
	BUPRENORPHINE SUB TAB SUBLOCADE® SUBOXONE® VIVITROL®		BUNAVAIL® BUPRENORPHINE / NALOXONE FILM/TAB ZUBSOLV®

Meeting Minutes

SILVER STATE SCRIPTS BOARD

MEETING MINUTES

Date and Time of Meeting: **Thursday, June 25, 2020 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)**

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

Attendees

Board Members (Present)
Mark Decerbo, Pharm.D., Chair
Joseph Adashek, MD
Evelyn Chu, Pharm.D.
Mark Crumby, Pharm.D.
Michael Hautekeet, RPh
Sapandeep Khurana, MD
Brian Passalacqua, MD
Kate Ward, Pharm.D.

Board Members (Absent)
Aditi Singh, MD

DHCFP:
Holly Long, Social Services Program Specialist III
Gabriel Lither, DAG
Ellen Flowers, Program Officer I
Antonio Gudino-Vargas, Social Services Program Specialist II
Tammy Moffitt, Social Services Chief III
DuAne Young, Deputy Administrator

DXC:
Jovanna Leid, Pharm.D.

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

Public:

Maria Agapoval
Karen Beattie, Carson City Community Counseling Center
Jeanette Belz, J. K Belz and Associates
Kenneth Berry, Alkermes
Josh Bishop
Lorraine Bonaldi, Renovations Mental Health
Jeana Colabianchi, Sunovion
Dana Conell
Christa Cooper
David Cram, Takeda
Ashley Cruz, Carrara Nevada
Leslie Dixon, Nevada Psychiatric Association
Ben Droese, Amgen
Mark Duerre
Michelle Duke, Genentech
Dawn Dynak
Georgette Dzwilewski, INDIVIOR
David Freilich
Jenna Gianninoto, AbbVie
Sharron Glass, Alimera Sciences
Suzann Gordon
Shannon Groppenbacher, JJHCS
Deron Grothe, Teva
Penny Higashi, Boehringer Ingelheim
Lee Hochner, Amneal Pharmaceuticals
Anthony Hoovler
Greg Horikoshi, Novo Nordisk
Steve Isaki, Lundbeck
Chi Kohlhoff, Viela Bio
William Lai, Xeris Pharmaceuticals
David Large, Biohaven Pharmaceuticals
Jimmy Lau
Jennifer Lauper
Chelsea Leroue, Biohaven Pharmaceuticals
Lori McDermott, Supernus
Melisa McEwen, OAPI
Hector Mobine
Dan Musgrove, Strategies 360
Valerie Ng, Indivior
Joanne Nguyen
Gary Okano, BMS
Carmen Oliver, Biohaven Pharmaceuticals
Valerie Padovani
Hiten Patadia, Otsuka Pharmaceuticals
Deborah Profant
Warner Quon, Ascendis
Leon Ravin, DPBH
Robin Reedy, NAMI
Carol Ricciotti
Lovell Robinson, ABBVIE
Nicole Robling
Amy Rodenburg
William Rowe, Intra-Cellular Therapies, Inc.
Erin Shaal
Alice Swett
Trent Taylor, Johnson & Johnson
Ashlie Temple, Albertsons/Safeway Pharmacies
Stephanie Yamamoto
Kelvin Yamashita
Michael Zarob, Alkermes
David Zimmerman

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

Attendance:

Mark Crumby
Kate Ward
Brian Passalacqua
Mark Decerbo
Michael Hautekeet
Joseph Adashek
Sapandeep Khurana
Evelyn Chu
Holly Long, DHCFP
Gabriel Lither, DHCFP
Jovanna Leid, DXC
Kevin Whittington, OptumRx
Carl Jeffery, OptumRx

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

AGENDA

1. Call to Order and Roll Call

Meeting called to order at 2:00 PM.

Mark Decerbo, Chair: Good afternoon. I would like to call the meeting to order for the Silver State Script Board. We do have seven of the nine members in attendance, so we do have a quorum. We will start with a roll call.

Evelyn Chu

Mark Crumby

Mark Decerbo, Chair

Mike Hautekeet

Sapandeep Khurana

Kate Ward

Joseph Adashek

2. Public Comment on Any Matter on the Agenda

Mark Decerbo, Chair: We will start with general public comments. I would ask that if you are here to provide testimony on a specific agent, please hold your public comment until your therapeutic class is presented.

Robin Reedy: This is Robin Reedy. I have a general comment and a comment for later in the meeting.

Mark Decerbo, Chair: Ok, before I turn it over to you, I just want to remind everyone that we have three minutes for public comment. We will have a timer on the screen so you can see how much time you have left.

Robin Reedy: I am the Executive Director for NAMI Nevada. Distinguished members of the board, on behalf of NAMI, Nevada, the state chapter of the National Alliance on Mental Illness. I would like to offer our views on the impact of your decisions on our members, families and all those that live with a mental health condition. The current healthcare crisis and our corresponding economic crisis has only exacerbated the effect that you have. As a matter of principle, NAMI is in support of open access to all safe and effective medications for mental health conditions as prescribed by qualified health care professionals. We support excluding anti-psychotic medication from any non-clinically based restrictive formulary measures. Access to meds is crucial. Without the right medications at the right time, they may struggle, have worsening conditions and experience dramatic negative consequences. Effectiveness and side effects vary for every person being put on one med may map the brain and another med that may have worked well before will not work now. Various levels of severity, different levels of effectiveness and the flexibility needed in drug policy and access to all drugs, shows improvement in treatment and outcomes. NAMI believes that the decision to prescribe medication to patients with a mental health condition should be based on the clinical judgment of the treatment providers. Research has shown that prior authorizations, denials for psychiatric populations, results or outcomes, which include increased utilization of ER, higher incarceration and higher usage of mental health inpatient hospitalizations. Thank you.

3. Administrative

a. **For Possible Action:** Review and Approve Meeting Minutes from March 26, 2020.

Mark Decerbo, Chair: Thank you. Do we have any other general public comment? I am not seeing any other comment or comments in the chat box. We will move to review and approval of the meeting minutes from our last meeting. Do we have additions, edits, clarification or deletions from the minutes? Hearing none, by unanimous consent, the minutes will stand as approved. Next we will have an update by the DHCFP.

b. **Status Update by the DHCFP**

Holly Long: Thank you Dr. Decerbo, this is Holly Long, I am the supervising Social Services Program Specialist for Pharmacy Services at the DHCFP. I just have a couple of quick announcements. The DHCFP recently received approval from CMS for the Disaster Relief SPA submitted to address COVID-19 response efforts. This relief State Plan Amendment provides Nevada Medicaid approval to make specific changes related to the National Emergency declared due to COVID-19 outbreak. And the DHCFP has also created a COVID Billing Guide, which is posted with other provider billing guides on the DHHS Medicaid provider site. There is a general COVID Billing Guide. And in addition to that, there is one specific to COVID Community-Based Testing. This concludes the DHCFP updates, thank you.

Mark Decerbo, Chair: Thank you. We will start our presentations today. Some housekeeping first. We will be unmuting lines for public comments, so please mute your line if you are not speaking. Public comment is limited to three minutes. Optum will be displaying their recommendation for preferred and non-preferred, so please take a look at that prior to your testimony. I will turn it over to Carl.

Holly Long: This is Holly. Not only will Carl and Kevin be presenting the information, we will be posting the letters and emails that were provided to the State prior to the meeting to the DHCFP public notices site. These were also shared with the board prior to the meeting today.

4. Proposed New Drug Classes

a. **For Possible Action:** Discussion and possible adoption of hormones and hormone modifiers, anti-hypoglycemic agents

Carl Jeffery: Good afternoon, thank you for joining us today. Our first class is the Hormones and Hormone Modifiers, anti-hypoglycemic agents. This is a new class of medications and as you can see here, we have our proposed list shown with the glucagon emergency kit recommended as preferred and Baqsimi and Gvoke recommended as non-preferred. We have some written testimony; I am showing that now. The letter is from the manufacturer of Gvoke and there is a lot of information in here. This was sent to the board and will be posted publicly after the meeting. Do we have other comment for this class?

Mark Decerbo, Chair: Do we have any public comment?

William Lai: My name is William Lai with Xeris Pharmaceuticals. I'm here on behalf of the company to represent Gvoke, a liquid stable glucagon that received FDA approval in September 2019. I am here to present some clinical data, and some thought as to why this should be included on the preferred drug list. Over 30 million adults and children in the US have diabetes, and approximately 7.4 million Americans are treated with insulin annually. In 2014, approximately 14.2 million emergency department visits for ages 18 years and older for hypoglycemia. Currently the standard of care is the glucagon emergency kit. These kits are a multistep process to prepare and administer, usually eight to 11 steps. Handling difficulties as well as inaccuracies in administering these doses have been recorded in the literature. Approximately only one-third of these patients and their families are able to successfully administer the full dosage. If left untreated, severe hypoglycemia can worsen to conditions such as seizures or coma or death. The American Diabetes Associates standard of care states glucagon should be prescribed for all individuals at an increased risk of level two hypoglycemia, that is defined as blood glucose levels of less than 54 milligrams per deciliter. In September 2019, the FDA approved the first and only premixed, prefilled

and pre-measured liquid glucagon in both the prefilled syringe as well as the auto injector. The auto injector is very similar to an EpiPen with the two-step process. You open the cap and then inject perpendicular to the skin. It is approved for adults and pediatric patients aged two and above. It can be stored at room temperature and has a shelf-life of approximately 40 months. In terms of clinical data, this has been evaluated in two adult trials and a pediatric trial. All the clinical endpoints were met. In terms of adverse events, it is similar to other products with nausea and vomiting. In addition, there have been some usability studies done whereby 99% of patients who are using this product to administer a full rescue dosage. In summary, I want to ask the board to consider adding Gvoke to the formulary.

Mark Decerbo, Chair: Thank you. Do we have any Board members with questions? Do we have any other public comment?

Carl Jeffery: This is a new class. I will give a quick refresher of hypoglycemia because not everyone deals with this day-in and day-out. Diabetics are vulnerable to hypoglycemic events. Normally that is defined as blood sugar of less than 70 milligrams per deciliter, but clinically important hypoglycemia is defined as blood glucose less than 54 milligrams per deciliter. But many of you may know that work with diabetics frequently, their glucose can drop well below. This can lead to disastrous consequences. The treatment is to normalize the glucose. The easiest is glucose tablet or juice or milk to get their blood sugar back up. For more severe hypoglycemia, intravenous dextrose is effective. The third option is to administer glucagon. With the Gvoke we just heard about, this is an autoinjector for subcutaneous administration. There were two studies that demonstrate noninferiority to subcutaneous glucagon. There were also two usability studies. I think this is where it really stands out. Eighty-eight percent of the users of Gvoke were able to successfully administer glucagon versus the 31% of the standard kit. A validation study demonstrated that almost 99% of patients successfully administered the rescue injection with the Gvoke auto-injector. The other new medication is a nasal powder. It is the first nasally administered glucagon approved. It is delivered by placing the tip of the device in one nostril and push the plunger to get the medication. It should act within 15 minutes. There are three efficacy studies, two adult and one pediatric study demonstrated noninferiority to intramuscular glucagon. They also had a usability study that demonstrated 95% of the Baqsimi users successfully administered the dose compared to 13% for the product that requires reconstitution. Looking at the indications, they are all very similar with severe hypoglycemia in patients with diabetes. There are some slight age differences, Gvoke is indicated down to two years of age and Baqsimi is approved down to four years of age. Optum recommends the board consider this class clinically and therapeutically equivalent.

Mark Decerbo, Chair: I need a motion to consider clinically and therapeutically equivalent.

Motion and second to accept the class as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends the standard glucagon emergency kit be listed as preferred. I think there is a good argument for trying this first. With good training for the patient and their family this can be safely and effectively used. Baqsimi and Gvoke would be listed as non-preferred.

Mark Decerbo, Chair: Ok Board, we see the recommendations here. Certainly, two new novel agents with a clearly more convenient, easier administration. Do we have any motions with the recommendation?

Motion and second to approve the preferred drug list as presented.

Voting: Ayes are unanimous, the motion carries.

b. **For Possible Action:** Discussion and possible adoption of neurological agents (anti-migraine agents, acute treatment of migraine, preventative treatment of migraine)

Carl Jeffery: Our next class is the Neurological Agents, Antimigraine Agents, Serotonin-Receptor Agonists. We have a few recommended changes, moving Zomig Nasal Spray to preferred and the Sumatriptan Nasal Spray to non-preferred and a new medication in the class, Reyvow as non-preferred. Do we have any public comment?

Lee Hochner: This is Lee Hochner from Amneal pharmaceuticals. It looks like you have done my work for me already since you are recommending Zomig nasal spray as preferred. I will defer comment at this point.

Carl Jeffery: Any other public comment? Not hearing any, I will start with some information about Reyvow. We had this agenized on a past meeting but was bypassed because it didn't really fit anywhere. Reyvow is similar to the others in the class because technically it is a serotonin receptor blocker, but different receptors. This is a 5-HT_{1F} receptor agonist referred to as a "ditan". It lacks the vasoconstrictor activity associated with the triptans, so it may be an option for those who are higher risk of cardiovascular problems. Two placebo-controlled trials demonstrate its efficacy. The SPARTAN trial included patients with known coronary artery disease, clinically significant arrhythmia and uncontrolled hypertension. The rate of serious adverse events with potential CV etiology was low, occurring in about 0.4% of patients compared to 0.1% in placebo. When looking at the comparative trials, all the values are significant versus the placebo. We look at pain free at two hours and the most bothersome symptoms or MBS, we are seeing some good results compared to placebo. I will pause for a second to see if there are any questions. With this class we have the serotonin receptor agonists, Optum recommends the board consider this class clinically and therapeutically equivalent.

Motion and second to accept the class as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends moving Zomig Nasal Spray to preferred and move sumatriptan nasal spray to non-preferred and make the new medication, Reyvow, non-preferred. We will also clarify the brand Zomig on the non-preferred side will just be the tabs.

Mark Decerbo, Chair: We have multiple dosage forms preferred now.

Motion and second to accept the preferred drug list as presented.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Our next class is the CGRP, or calcitonin gene-related peptide receptor antagonists. We discussed the categorization during the previous meeting, and I think this might come back in the future. But right now, we had some ideas to switch Emgality to preferred and Aimovig to non-preferred. The two new medications we will be hearing about today, Nurtec ODT and Ubrelvy, we recommend adding those as non-preferred. We have a lot of public comment submitted and I will share that now. These letters were sent to the board prior to the meeting and will be posted after the meeting. We have several for Ubrelvy, Emgality, Nurtec ODT, and Ajovy. Do we have any public comment on the line today?

Josh Bishop: Hi, this is Josh Bishop, I would like to speak on behalf of Ubrelvy. I'm a clinical pharmacist with Abbvie, formerly Allergan. It was the first CGRP receptor antagonist approved for the acute treatment of migraine not for the prevention. I will first speak to the patient populations who should have access to Ubrelvy and then I want to describe four differentiators between Ubrelvy and the other agents. At Abbvie, we believe that triptans will continue to be the standard of care for the acute treatment of migraine attacks. However, there are patients with vasospastic and ischemic cardiovascular conditions who should not be prescribed triptans. That represents approximately 25% of your migraine population, and those patients should have first-line access to Ubrelvy. There is robust data confirming that many patients prescribed oral triptans have side effects that we did this continuation. Approximately 30% of patients on triptans have an insufficient clinical response. There have been multiple studies confirming that nearly half of patients never actually refill their triptans and very few move to a

second. Those who do have an inadequate response. Approximately 30% of patients on triptans have an inefficient response. Of those with an inadequate response, approximately 53% of patients fill an opioid. Of those patients that do not respond accrue about $6000 per in additional expenses. Ubrelvy is a different treatment option and has differentiated itself from the treatments for cardiovascular and insufficient or standard populations. There are four differentiators from the other new acute agents that I will highlight for you. First, Ubrelvy has been proven to be safe and effective, the tolerability profile similar to that of placebo. The most common adverse events were nausea and somnolence. Second, the phase three studies with Ubrelvy should be more representative of your migraine population because we included patients with cardiovascular disease and depression. Third, Ubrelvy is only being studied for acute treatment of migraines. This should lead to predicable utilization patters in your population. The last thing, Ubrelvy did achieve the FDA co-primary endpoints of two-hour pain freedom and absence of the most bothersome symptoms. However, Ubrelvy is the only medication to achieve pain freedom in rates up to 55% of patients who chose to take an optional second dose. I request first-line access to Ubrelvy for migraine patients with cardiovascular disease and those patients who had an inadequate response to triptans.

Chelsea Leroue: This is Chelsea Leroue from Biohaven Pharmaceuticals. Thank you for allowing me to present information on Nurtec ODT. Nurtec ODT is indicted for the acute or abortive treatment of migraine with or without aura in adults. Nurtec ODT is available in 75mg orally disintegrating tablet formulation. Nurtec represents a novel mechanism of action that targets the underlying pathophysiology of migraine, treats migraine without the vasoconstrictive effects of the triptans and is not associated with addiction potential or medication overuse headache. One dose of Nurtec ODT provides rapid release that lasts through 48 hours. Nurtec treated patients achieved rapid pain relief within 60 minutes as well as freedom from pain and freedom from most bothersome symptoms by 90 minutes. All these endpoints were sustained through 48 hours with a single dose. After taking Nurtec, patients returned to normal function by 60 minutes. Repeat dosing and rescue medications need is reduced. Nurtec has minimal or no adverse events, the most common being nausea. I respectfully ask the board to add Nurtec ODT as a preferred agent.

Holly Long: I just want to remind everyone; we do function off an open formulary PDL. So even though a drug or drug class is not included on our PDL, it does not mean that it cannot be covered. There is the opportunity for coverage.

Carl Jeffery: We have two new CGRP's to discuss today, Ubrelvy and Nurtec ODT. I have the breakdown of the different products displayed on the screen. They really fall into two categories, preventative treatments like Aimovig, Ajovy and Emgality or acute treatments like Nurtec ODT and Ubrelvy. With Nurtec, it has an indication for acute treatment of migraine with or without aura in adults. There were few studies I will highlight. A phase three study with about 1500 patients. About 21% were pain-free at two hours compared to about 11% in the placebo group. The most bothersome symptoms free at 35% vs about 27% in the placebo group. There were three additional trials that support the approval all showing significant improvement versus placebo. With Ubrelvy, it has the same indication with the acute treatment of migraine with or without aura in adults. It was evaluated in two phase three trials versus placebo. Both trials demonstrated significant improvement with ubrogepant compared to placebo for pain freedom at two hours and most bothersome symptom free at two hours. Optum recommends the board consider this class clinically and therapeutically equivalent.

Motion and second to accept as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends a few changes in this class. We propose moving Aimovig to non-preferred and Emgality to preferred and the two new agents Nurtec ODT and Ubrelvy added as non-preferred. To remind the board, the DUR Board added prior authorization criteria for all the medications in this class.

Mark Decerbo, Chair: Thank you. We have in front of us the proposed PDL. We had some discussion on how to classify these drugs, do you do it by structure or indication or mechanism of action? I think we are certainly sensitive to a class of meds here with different indications.

Carl Jeffery: We have some providers that want to offer comment, but they were seeing patients. If you can just wait a minute for them to get on the line.

Mark Decerbo, Chair: While we are waiting, I just want to offer some thoughts on the classification of drugs. There are different groups that have taken shots of it outside of this committee. I think the United States Pharmacopoeia Drug Classification system that has been through Medicare model guidelines and others is a good, interesting system.

Joseph Adashek: I am always sensitive when I see letters from physician who take time out to write a letter and ask us to make something preferred. Ubrelvy was cited by several letters, I am curious to hear what the pharmacists and provider who use this medication think.

Josh Bishop: This is Josh Bishop. I can offer some insight if that is ok. They do have different indications and within the CGRP class generally two different mechanism, those that block the receptor and those that bind to the ligand. The monoclonal antibodies have a long half-life by their nature. The medications indicated for acute treatment are both receptor antagonists in contract to the ligand binders. I would advocate for a different therapeutic category given the very different use of these products on migraine patients.

Mark Decerbo, Chair: Just because we have a drug on the non-preferred side does not mean it can never be covered. It is a matter of how many preferred agents do they need to pass through before getting a non-preferred product. The member has to try one or two preferred products before getting a non-preferred for most classes.

Carl Jeffery: You are right, most classes require trial of two agents. But there is an allowance for unique indications or legitimate reason none of the preferred agents are appropriate, they can get a non-preferred first line.

Joseph Adashek: Given the letters from the physicians for Ubrelvy, I make the motion to make Ubrelvy preferred.

Motion seconded.

Mark Decerbo, Chair: Just adding a comment, is it reasonable to ask the providers to try a triptan before moving to Ubrelvy? That is my thought process.

Kate Ward: They would have to fail two products to get Ubrelvy, but not fail two to get Ajovy?

Carl Jeffery: The DUR Board did add criteria for trying a triptan before getting one of these agents.

Sapandeep Khurana: That would be the criteria to meet to get into this class, and then to get a non-preferred agent, they would have to try a preferred agent?

Dr. Anserina: This is Dr. Anserina calling regarding the panel's discussion on a triptan trial. I was listening and your points are valid. The only problem is that a lot of these patients have cardiovascular risk factors. In those cases, the non-triptan based therapies are the best choice. I would like to see Ubrelvy available for first line for these patients. The other scenario we see is patients that fail other abortive treatments. Having this available allows us to at least combine the two and get added benefit.

Dr. Patterson: I would like to second that; this is Dr. Patterson in Reno. Triptan medications are not good for the cardiovascular population and patients who have that should not have to try and fail a triptan in order to move to Ubrelvy. The other thing I would like to point out as a pain specialist, I see patients with migraine that have been treated by other providers. When they fail a triptan they end up on a barbiturate or opioid and those are not really

helping the situation. I think we need another option to treat these patients regardless of their cardiovascular situation.

Mark Decerbo, Chair: Do we know the PA criteria for Ubrelvy from the DUR committee?

Carl Jeffery: Those changes have not been implemented yet.

Mike Hautekeet: I really agree with the points the two physicians just made. I think the cardiovascular point is relevant. Could we add for Ubrelvy for cardiovascular concerns that it would be preferred? So, making Ubrelvy preferred if the patient has GI or cardiovascular problems.

Carl Jeffery: We have a motion and second already and I think you are getting into the realm of the DUR committee. We can take a recommendation back to the DUR Board if necessary. I don't have the approved criteria handy, but I believe there was an exception for cardiovascular concerns.

Kate Ward: I think our choice right now is what is on the preferred list. Are we going to have Ajovy and Emgality only? Or are we going to add Ubrelvy?

Mark Decerbo, Chair: The motion on the floor is to move Ubrelvy from the non-preferred side to preferred. I think we have heard some good commentary and taking into account the clinical criteria, which is not necessarily in our purview. Any further discussion on moving Ubrelvy to preferred? I will open the voting to move Ubrelvy to preferred right now, no other changes are being considered right now.

Voting: Four Ayes, Four Nays, the motion does not carry.

Mark Decerbo, Chair: We are back to the originally presented list with Ajovy and Emgality as our preferred products.

Motion and Second to accept the presented list with Ajovy and Emgality as preferred.

Voting: Ayes are unanimous, the motion carries.

c. **For Possible Action:** Discussion and possible adoption of psychotropic agents, antipsychotics, atypical antipsychotics – long-acting injectable

Carl Jeffery: Our next topic is the antipsychotics, atypical antipsychotics, long-acting injectable products. This is a new proposed class. As you can see on the screen, Optum is recommending all the medications in this class be made preferred. We do have some letters that I will display for the board and public. Many ask for open access for all antipsychotics. We can open it up for public comment.

Robin Reedy: This is Robin Reedy from NAMI Nevada. I would like to make a more personal plea. We have heard a lot of statistics, but there is more than just numbers, it is about family and friends and children from those families. I'm involved with NAMI Nevada because my mother had been diagnosed with manic depressive disorder. I mostly remember when my mom was on her meds, which were not that great at that time verses when she was not. A long-acting injectable would have created a greatly improved childhood for myself and my brothers. This was at a time when quite literally men in white coats came and took her away, or she was arrested. While many may think those effects go away with adulthood, I would argue that many of the effects continue into adulthood and are a contributing factor that affect my children, nieces and nephews and how my brothers and I react to trauma even into our 60s. Now more than ever, the people of Nevada deserve the opportunity to health and productivity. Removing barriers to getting the ability to use long-acting injectables in detention, correctional facilities and for those on Medicaid, Medicare and private insurance without arbitrary regulation not only affect our current population, but future generations. In support of this goal, NAMI Nevada urges public policies that ensure all people have access to the right treatments at the right time. We urge the Board to encourage policies

that continue our path to improving the lives of our citizens who through no fault of their own need your help. Thank you.

Sapandeep Khurana: Could you explain to the board and the public the difference between open access and being preferred on the PDL?

Carl Jeffery: Yes, Holly alluded to this earlier. We do have a formulary from CMS that says all products need to be listed as rebatable and has to be approved by the FDA. The preferred drug list allows us to list products as preferred and we can request providers and patients try those first before moving to a non-preferred medication. All the medications listed as non-preferred are still available, they just have to try a preferred or justify why none of the preferred agents would work. Medicaid has a rule that says only one preferred product needs to be tried for anti-psychotics. So even if down the road we make some products non-preferred, only a single agent is required to be tried first.

Leslie Dixon: This is Dr. Leslie Dixon with the Nevada Psychiatric Association. I believe you saw our letter. I want to support what Robin Reedy just said. It is important to realize that trying one drug before going to another is not always a good idea with these long-acting injectables. Most of us will try an oral drug first if we have a new patient to find what works. But if they have a history of doing well on one, we would rather stick with that. Having to back up and do a trial first is a very bad idea with a patient with schizophrenia because there is time involved. Patients can decompensate very rapidly or disappear or end up in the hospital. We want open access to allow the physician, patient and family to make the decision. I do want to add that the long-acting injectable products have really turned around psychiatric treatment of the seriously mentally ill. They are working well with drug courts, the criminal justice system and outpatient treatment. It is important we have good access and payment for these drugs. Thank you.

Hiten Patadia: Hi this is Hiten Patadia, I would just like to make a statement. I am the Managed Markets Liaison with Otsuka Pharmaceuticals. I would just like to say we appreciate what Optum has recommended here. We support open access to allow individualized and appropriate treatment with patients with serious mental illness. These patients are heterogeneous in nature and given the open access that Optum has proposed is something we support. Thank you.

Carl Jeffery: Any other public comment? Hearing none, we will move ahead. This is a big class and a complex list of medications. Most of the medications are indicated for schizophrenia. There are a couple that have schizoaffective disorder or bipolar mania disorder. All these medications have been out for several years. There are a number of meta-analysis and systemic reviews that have been conducted trying to compare them. But this is really an individual treatment and disease and different antipsychotics work differently for different people. It is difficult to show one medication is better than another. The guidelines suggest a long-acting injectable if the patient is having trouble with adherence, or if they are just having chronic relapses. The dosing interval is where they may stand out. Some have more flexibility or longer duration, from two weeks to monthly to every two months. Optum recommends the board consider the medications in this class be considered clinically and therapeutically equivalent.

Motion and second to accept as clinically and therapeutically equivalent.

Sapandeep Khurana: How will this vote affect what was presented from the audience in regard to open access?

Carl Jeffery: The board is voting on if these medications are all loosely interchangeable and are recognizing the products have similar indications or are in the same class of medications. And there is not one product that has a significant advantage over another.

Sapandeep Khurana: As a psychiatrist, while their mechanisms of action might make them similar and therapeutically equivalent, their effect is extremely different for what they do for patients. I want to add a comment that it is no longer a recommendation that we have to wait for people to fail multiple trials and have multiple episodes of non-adherence before trying a long-acting. There is evidence that starting long-acting prevents relapses and improve the life of people with mental illness.

Carl Jeffery: The board could make the recommendation that if there were one or two agents that were clearly superior to the rest of them, then you could call those out. That would document that statement where you go into the next vote for preferred or non-preferred. If you identify a product with a clinical advantage, but we recommend it added as non-preferred, that would have an impact in your voting.

Mark Decerbo, Chair: I think it also comes in is how the drugs are classified. For example, if we were trying to include older agents like Haldol Decanoate with this class, we might say they are not the same. In my mind it comes down to how they are classified.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends all the products in this class, the long-acting injectable atypical antipsychotics be added as preferred.

Motion and second to accept the list as presented.

Sapandeep Khurana: With all the agents being preferred, does this class come in to play after any PA requirements?

Carl Jeffery: The only medication in this class with PA requirements is Invega Trinza.

Sapandeep Khurana: So, an oral is not needed first?

Carl Jeffery: That is correct.

Voting: Ayes are unanimous, the motion carries.

5. Established Drug Classes

a. **For Possible Action:** Discussion and possible adoption of biologic response modifiers, multiple sclerosis agents, oral

Carl Jeffery: We will move to the Established Drug Classes and our first class is the Biologic Response Modifiers, Multiple Sclerosis Agents, Oral. We have a new medication in the class, Vumerity. Is there any public comment? I will start with a brief description of Vumerity or diroximel fumarate. It is indicated for the relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease. This is similar to Tecfidera and is actually a line extension. It is rapidly converted to its active metabolite monomethyl fumarate. This monomethyl fumarate was just approved by the FDA, we will see this again at a future meeting. The efficacy was established through bioavailability studies of Tecfidera. Two other studies were also added, EVOLVE-MS-1, which was a phase three study showing fewer GI side effects. The EVOLVE-MS-2 study also demonstrated significantly fewer GI issues. Looking at the indications for the different agents, the only one that has something different is Mavenclad. This is the treatment with the funny dosing and is not recommended first-line. The other thing that stands out is the dosage. Most of them are once or twice daily except for Mavenclad that has a unique dosing cycle. Optum recommends the board consider this class clinically and therapeutically equivalent.

Motion and second to accept the class as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends the new product, Vumerity, be added as non-preferred and the rest of the class remain the same.

Motion and second to accept the list as presented.

Voting: Ayes are unanimous, the motion carries.

b. **For Possible Action:** Discussion and possible adoption of cardiovascular agents, antihypertensive agents, calcium-channel blockers

Carl Jeffery: The next class is calcium channel blockers and Optum requests the chair to bypass this class. A new medication was supposed to be available, but it is not on the market yet.

Mark Decerbo, Chair: Yes, unless there are objections. Hearing none, by unanimous consent, we will move along to the next item on the agenda.

c. **For Possible Action:** Discussion and possible adoption of hormones and hormone modifiers, antidiabetic agents (sodium-glucose co-transporter 2 (SGLT2) inhibitors, antidiabetic agents, insulins (vials, pens and inhaled))

Carl Jeffery: The next class is the Antidiabetic Agents, SGLT-2's. There is a new medication, Trijardy XR. Do we have any public comment?

Penny Higashi: This Penny Higashi with Boehringer-Ingelheim, I have a quick question about the combinations not being covered? It looks like just the monotherapy agents.

Carl Jeffery: Historically we usually stick with the single-agent products. Many guidelines suggest stabilizing on a single agent before moving to the combination products. That has changed recently, we do have a couple combination agents so that is not a hard and fast rule anymore. The board can add combinations as preferred as they may see fit.

Mark Decerbo, Chair: I agree with that, there is no hard and fast rule that states combo products are definitively not allowed to be on the preferred list. We consider each one on a case-by-case basis.

Penny Higashi: If I can just add one comment. Boehringer-Ingelheim relative to Jardiance does have a lot of new data coming out shortly. On May 26, 2020, Boehringer-Ingelheim and Eli Lilly Company announced an academic research collaboration with Duke Clinical Research Institute on a new trial called EMPACT for the prevention of chronic heart failure and mortality after acute myocardial infarction. There was a lot of data coming out specifically around other disease states. This is part of a broader empower program, EMPEROR-Reduced is another study that is ongoing in patients with chronic heart failure with reduced ejection fraction. EMPEROR-Preserved is in patients with chronic heart failure with preserved ejection fraction. And EMPULSE trial in patients hospitalized for acute heart failure. That is all ongoing.

Carl Jeffery: Do we have any other public comment? No, I will go ahead. The new agent in this class is Trijardy, a combination of three medications, empagliflozin, linagliptin and metformin. It is approved on the individual components. Nothing landmark about this agent, just a combination of the existing agents. I am showing the indications for the single-agent products. It gets too big if I try to include all the different combinations. They all have the indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes. There is some new data coming out about the cardiovascular disease indications and we may see that more in the future. I am displaying all the products and the combo products that are currently available. Optum recommends the board consider this class clinically and therapeutically equivalent.

Motion and second to accept the class as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends the new agent Trijardy XR be added as non-preferred and the rest of the class remain the same.

Motion and second to accept the preferred drug list as presented.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Our next class is Insulin products. We are proposing a couple changes here. To clarify, the Humulin listed before included all the different strengths, so we will list those now. Do we have any public comment? I don't hear any. There are two new products available now, Insulin Aspart and Insulin Aspart Mix, both authorized generics for Novolog and Novolog Mix. I have the different products broken down on the screen now by rapid-acting to long-acting and combinations. Optum recommends the board consider this class clinically and therapeutically equivalent.

Motion and second to accept the class as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends just a few changes. We will keep the Humulin 70/30 and U-500 as preferred as well as the Insulin Lispro 100 and make the Humulin N and R non-preferred and the two new authorized generics Insulin Aspart and Insulin Aspart Mix non-preferred.

Mark Decerbo, Chair: Could we also break out the different products for the Novolin to reduce confusion?

Carl Jeffery: I think that is a good idea and we can make that update.

Motion and second to accept the preferred drug list as presented.

Voting: Ayes are unanimous, the motion carries.

d. **For Possible Action:** Discussion and possible adoption of ophthalmic agents, antiglaucoma agents, ophthalmic antihistamines

Carl Jeffery: The next class should be easy, Antiglaucoma agents. Do we have any public comment? There is a new generic available for Travatan Z which is a benzalkonium-free travoprost. It has the same indication as the brand. In this class we have several different classes included and I had to spread out the list over two pages. Under the prostaglandin analogues, you can see the updated generic availability for Travatan Z now. Optum recommends the board consider this class clinically and therapeutically equivalent.

Motion and second to accept as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends the new generic travoprost BAK-free be added as non-preferred and the rest of the class remain the same.

Motion and second to accept the preferred drug list as presented.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Our next class is ophthalmic antihistamines. Do we have any public comment? There is a new medication in this class, Zerviate which is cetirizine. This has an indication for the treatment of ocular itching

associated with allergic conjunctivitis. There were two phase three studies showing significantly reduced ocular itching compared to the vehicle alone in both studies. I have not seen information on a clinical advantage over other products in the class. I'm showing the list of the products on the screen, some have been out for quite some time. Optum recommends the board consider this class clinically and therapeutically equivalent.

Motion and second to accept the class as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends the new agent, Zerviate, be added as non-preferred and the rest of the class remain the same.

Motion and Second to accept the preferred drug list as presented.

Voting: Ayes are unanimous, the motion carries.

e. **For Possible Action:** Discussion and possible adoption of psychotropic agents (ADHD agents, antipsychotics, atypical antipsychotics – oral, psychostimulants, narcolepsy agents)

Carl Jeffery: The next class is ADHD agents. We have one new medication and one new generic. Do we have any public comment? There are two new medications. The first is a different dosage form of methylphenidate, Adhansia XR, indicated for ADHD. There were four studies, two in adults, one in children age 12 to 17 and one in children age six to 12 years of age. When all the dose groups are combined, there was significant improvement over placebo. The other new agent is an amphetamine ER suspension, it is a generic for Adzenys ER Suspension. I have all the different products on the screen and you can see the different stimulants and non-stimulants. Optum recommends the board consider this class clinically and therapeutically equivalent.

Motion and second to accept the class as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum is proposing just a few minor changes, swapping the brand and generic Adderall XR to make the brand preferred and the generic non-preferred. Strattera brand would be made preferred and the generic atomoxetine non-preferred. The two new agents Adhansia XR and amphetamine ER suspension added as non-preferred.

Motion and second to accept the preferred drug list as presented.

Sapandeep Khurana: When we move products from preferred to non-preferred, is there a way to notify the pharmacy or recipients a month or so prior or the medical offices so they can adjust when writing the next prescription?

Carl Jeffery: Notifications for change in the formulary is not something we normally do.

Mark Decerbo, Chair: Holly, can you speak to what is done operations-wise as to what is done for the prescribers in the state?

Holly Long: After the meeting today, we will get started on the meeting minutes and then they go through the approval process to get posted. In the meantime, we are also drafting all the changes that are approved during the meeting. Once you see the meeting minutes posted, you are going to see the implementation come up pretty soon. The implementation information will come up on the DHHS Medicaid Pharmacy Services site with a web announcement. Everyone is always welcome to email me if they need to know where we are in the process.

Sapandeep Khurana: I can imagine there is a lot of effort on the back end. But as a provider or recipient, there is no way to know when things have changed. The next time I may need to prescribe differently.

Holly Long: You really have to watch those web announcements that come up on the DHHS Medicaid site for providers and pharmacy services. It is not consistent enough to give an exact date or process that would speak to a date. I wish it were easier.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: The next class is the Atypical Antipsychotics – Oral and Topical. We had to add topical because we now have a patch, Secuado. We have a few written comments I am showing now. Many of the letters support Caplyta as preferred. Is there any public comment?

Hiten Patadia: Hi this is Hiten Patadia with Otsuka Pharmaceuticals. I just wanted to make a quick comment. Abilify MyCite public testimony was given on September 2019, I just want to offer to answer any questions.

William Rowe: This is William Rowe with Intra-Cellular. I would like to talk about Caplyta. I am a nurse practitioner and a Senior Medical Science Liaison with Intra-Cellular here to talk about Caplyta, an atypical antipsychotic indicated for the treatment of schizophrenia in adults. I am not going to belabor the burden of schizophrenia; I think we are all familiar with that. But there is certainly an unmet need in the class of antipsychotics. Typically, there is a trade-off between metabolic side effects and weight gain and prolactin effects and motoric side effects and extrapyramidal symptoms. Caplyta was approved for the treatment of schizophrenia in adults in two positive controlled studies, very similar in design. Both statistically separated from placebo at the 42-milligram dose on the total positive symptom score. In short-term studies, the most common adverse effects were somnolence and sedation and dry mouth. All metabolic changes, changes in prolactin, EPS, akathisia were similar to placebo in these four-week studies. In the open-label studies, one of them being up to one year, over 90% of patients if they were in a normal class on glucose, total cholesterol, etc., they remained in that normal range at the end of the study. Three times as many people lost weight in a clinically significant way. The mechanism is unique, as the neurobiology of the disease is unknown, the exact mechanism of how it treats schizophrenia is also unknown. We respectfully request preferred status.

Sapandeep Khurana: Do you have any data on the metabolic side effects of this medicine as compared to how it stacks up with other agents?

William Rowe: There is no head-to-head data, risperidone was used as the active control in the short-term studies. In the package insert risperidone is listed as an active comparator, but we believe this is an error as it was only used for assay sensitivity. You can kind of see the changes in prolactin changes, changes in glucose and cholesterol. But you cannot make the head-to-head comparison.

Carl Jeffery: Any other public comment? We just heard about Caplyta. It is indicated for the treatment of schizophrenia in adults. It has a very complex list of receptors and I'm not going to read through all of these. The central activity is the 5-HT_{2A} receptor and a little bit of the D_2 receptor. It is different than the standard atypical antipsychotic. It was evaluated in three studies, one phase two and two phase three studies. The phase two study demonstrated superiority versus placebo in the PANSS total score. The first phase three study did show 42mg demonstrated superiority versus placebo. The second phase three study did not demonstrate any statistical benefit over placebo. The next agent is Secuado, or asenapine transdermal system. It was approved based on the sublingual formulation of asenapine and one unpublished clinical trial. It had a six-week, phase three study showing some statistical improvement in PANSS total score and CGI-S. Looking at the different indications for these products, most of them have a schizophrenia indication. There are a few other specialty indications. I have all the products shown here, they are all a little unique in what receptors they hit and different agents are most

appropriate for different recipients depending on symptoms and side effects. Optum recommends the board consider the class clinically and therapeutically equivalent.

Motion and second to accept the class as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends the board add Caplyta and Secuado as non-preferred and the rest of the class remain the same.

Mark Decerbo, Chair: Any thoughts from the board? I think it is worth pointing out, most classes require two preferred products prior to moving to the non-preferred agents. With antipsychotics, only one preferred product is required.

Motion and second to approve the preferred drug list as presented.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Ok, this is the last class, the Narcolepsy Agents. There is a new medication, Wakix. We do have a couple letters here. Do we have any public comment? Wakix is a new medication indicated to improve wakefulness in adults with excessive daytime sleepiness associated with narcolepsy. It has a little different mechanism of action as it is an H_3 antagonist/inverse agonist. The advantage with this one is it has no abuse potential and is the only unscheduled agent indicated for the treatment of narcolepsy. Two studies shown here, HARMONY 1 compared to modafinil and placebo. Wakix was demonstrated superior to placebo but not non-inferior to modafinil. The other study, HARMONY 1bis compared to modafinil and placebo. Wakix demonstrated significantly greater ESS score improvement from baseline versus placebo but again non-inferiority to modafinil could not be concluded. The screen is displaying the different indications for the different agent. On this screen I have them broken down by the different mechanisms, stimulants and dopamine and norepinephrine reuptake inhibitors and the new class histamine H_3-receptor antagonists/inverse agonists and finally the anti-cataplectic agents. Optum recommends the board consider this class clinically and therapeutically equivalent.

Motion and second to accept the class as clinically and therapeutically equivalent.

Voting: Ayes are unanimous, the motion carries.

Carl Jeffery: Optum recommends a couple changes, moving the generic armodafinil to preferred and the new product Wakix added as non-preferred.

Motion and second to move Wakix to preferred.

Sapandeep Khurana: This is the only agent without abuse potential. There is an overlap in the patient population and you run out of options for treatment when someone has a substance use disorder or that unique profile. I think it makes sense to make this preferred.

Mark Decerbo, Chair: Has the DUR Board added criteria?

Carl Jeffery: They have, but I think it is just a diagnosis requirement, no other step therapy involved.

Mark Crumby: Is it just the ICD-10 code that just needs to be on the script?

Carl Jeffery: I don’t have that information handy.

Sapandeep Khurana: That is a good question because some of these medications are restricted to sleep medicine doctors.

Mark Decerbo, Chair: The other agents in the class are either C-III or C-IV. I think the PA criteria would factor into play here.

Carl Jeffery: I am presenting what was proposed to the DUR Board. I am not sure if they made any changes to the proposed criteria. It just has a diagnosis of narcolepsy as confirmed by a sleep study.

Antonio Gudino-Vargas: The other addition that was added to Wakix was the recipient has to be at least 18 years of age or older.

Sapandeep Khurana: Could we make the recommendation to the DUR Board to consider if someone has a substance abuse disorder and controlled substances are not the preferred modality of treatment then we could in that case be considered preferred?

Mark Decerbo, Chair: Any other input for the board? I see it does present an advantage for those individuals with an abuse disorder but does come at a highly divergent cost to the State. I would feel better if there was some better DUR criteria to capture those really appropriate for it.

Joseph Adashek: In the meantime, we can make it preferred and move it to non-preferred, I would rather take it in that direction.

Sapandeep Khurana: I agree with you. Mark, your point is well taken. The DUR Board could add additional criteria.

Holly Long: The DUR Board just reviewed this at the April 30, 2020 Board Meeting. The policy we just spoke about has not been implemented yet. That is going to take a few months. I would recommend you either provide a letter or if you can call into the DUR Board meeting to participate.

Mark Decerbo, Chair: We have a motion on the floor. Do we know when the next DUR Board meeting is?

Holly Long: The next DUR Board meeting is July 23, but that agenda has already been set. I don't think it would be appropriate to suggest that anyone speak about Wakix until it is implemented. The next meeting after that is October 29. I would recommend some feedback be provided for that meeting.

Mark Decerbo, Chair: We have the motion on the floor. We have the timeline and a good thought process and another mechanism by which to address some of our concerns. Any further discussion strictly on the motion to move Wakix to preferred?

Voting: Ayes – 6, Nays – 1, the motion carries.

Carl Jeffery: We still have the recommendation to move armodafinil to preferred.

Mark Decerbo, Chair: So now that we have Wakix as preferred, we would have four preferred products. Any discussion or motions with this amendment carrying? We need to act on the rest of the recommendation.

Motion and second to approve the preferred drug list as voted and modified.

Voting: Ayes are unanimous, the motion carries.

6. OptumRx Reports: New Drugs to Market and New Line Extensions

Carl Jeffery: Optum has the RxOutlook with some new drugs. The first is filgotinib, a JAK1 inhibitor for moderate to severe rheumatoid arthritis, I think we will see this one soon. The other one that caught my eye is the gene therapy for hemophilia A. It is getting close to being approved as a gene therapy. It is a one-time dose and we are getting more information about it. It has been shown to decrease the annualized bleeding rate by 96%. But the problem is it is limited to patients with severe disease without factor inhibitors and not having existing antibodies to the AAV vector. The manufacturer suggests this could last up to eight years in durability. But we are looking at

a price tag of two to three million dollars. There are also a few generics I want to call out like Ciprodex and Byetta and a couple antipsychotics we may see about the end of the year, Risperdal Consta and Saphris. That is all I had.

7. Closing Discussion

Mark Decerbo, Chair: Thank you everyone for hanging in. Do we have any closing comments from the public? I'm not hearing any public comment. Our next meeting is scheduled for September 24. I will move to adjourn, thank you.

Meeting adjourned at 4:33 PM.

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

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 numerous biosimilar TNF inhibitors: Amjevita (adalimumab-atto), Abrilada (adalimumab-afzb), Cyltezo (adalimumab-adbm), Hadlima (adalimumab-bwwd), Hyrimoz (adalimumab-adaz), Erelzi (etanercept-szzs), Eticovo (etanercept-ykro), Avsola (infliximab-axxq), Inflectra (infliximab-dyyb), Ixifi (infliximab-qbtx), and Renflexis (infliximab-abda). Other immunomodulators targeting different cells and cytokines in the inflammatory and immune process are also FDA-approved. 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, 2 biosimilar products have been approved: Truxima (rituximab-abbs) and Ruxience (rituximab-pvvr). Oral agents on the market, Xeljanz and Xeljanz XR (tofacitinib), Rinvoq (upadacitinib), 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 and UC. Cosentyx (secukinumab) and Taltz (ixekizumab) bind and neutralize IL-17A and are indicated for the treatment of PsO, PsA, and AS. Siliq (brodalumab), an IL-17 receptor antagonist, as well as Tremfya (guselkumab), Skyrizi (risankizumab), and Ilumya (tildrakizumab-asmn), 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 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).
    - Cimzia for non-radiographic axial spondyloarthritis (NRAS) with objective signs of inflammation.
    - Otezla for treatment of adults with oral ulcers associated with Behçet disease.
- 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 2019*). 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 Abrilada (adalimumab-afzb), Amjevita (adalimumab-atto), Erelzi (etanercept-szzs), Eticovo (etanercept-ykro), Cyltezo (adalimumab-adbm), Hadlima (adalimumab-bwwd), Hyrimoz (adalimumab-adaz), Avsola (infliximab-axxq), and Ixifi (infliximab-qbtx) 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	Biosimilar or Generic Availability	Type of Agent
Actemra (tocilizumab)	-	Human monoclonal antibody targeting the IL-6 receptor
Cimzia (certolizumab)	-	TNFα inhibitor
Cosentyx (secukinumab)	-	Human monoclonal antibody to IL-17A
Enbrel (etanercept)	-*	sTNFR fusion protein, TNFα inhibitor
Entyvio (vedolizumab)	-	Human monoclonal antibody binds to the α4β7 integrin
Humira (adalimumab)	-*	TNFα inhibitor
Ilaris (canakinumab)	-	Human monoclonal antibody that binds to IL-1ß
Ilumya (tildrakizumab-asmn)	-	Human monoclonal antibody to IL-23
Inflectra (infliximab-dyyb)	N/A†	TNFα inhibitor
Kevzara (sarilumab)	-	Human monoclonal antibody targeting IL-6 receptor
Kineret (anakinra)	-	IL-1 receptor antagonist
Olumiant (baricitinib)	-	Small molecule Janus kinase (JAK) inhibitor
Orencia (abatacept)	-	sCTLA-4-Ig recombinant fusion protein
Otezla (apremilast)	-	Small-molecule phosphodiesterase 4 inhibitor
Remicade (infliximab)	-†	TNFα inhibitor
Renflexis (infliximab-abda)	N/A†	TNFα inhibitor
Rinvoq (upadacitinib)	-	Small molecule Janus kinase (JAK) inhibitor
Rituxan (rituximab)	-*	Anti-CD20 monoclonal antibody
Ruxience (rituximab-pvvr)	N/A†	Anti-CD20 monoclonal antibody
Siliq (brodalumab)	-	Human monoclonal antibody directed against the IL-17 receptor A (IL-17RA)
Simponi/ Simponi Aria (golimumab)	-	TNFα inhibitor
Skyrizi (risankizumab-rzaa)	-	Human monoclonal antibody to IL-23
Stelara (ustekinumab)	-	Human monoclonal antibody targeting the IL-12 and IL-23 cytokines
Taltz (ixekizumab)	-	Human monoclonal antibody to IL-17A
Tremfya (guselkumab)	-	Human monoclonal antibody to IL-23 cytokine
Truxima (rituximab-abbs)	N/A†	Anti-CD20 monoclonal antibody
Xeljanz/Xeljanz XR (tofacitinib)	-	Small molecule Janus kinase (JAK) inhibitor

*Erelzi (etanercept-szzs) and Eticovo (etanercept-ykro) have been FDA-approved as biosimilars to Enbrel (etanercept). Abrilada (adalimumab-afzb), Amjevita (adalimumab-atto), Cyltezo (adalimumab-adbm), Hadlima (adalimumab-bwwd), and Hyrimoz (adalimumab-adaz) have been FDA-approved as biosimilars to Humira (adalimumab). Two biosimilars are FDA-approved for Rituxan (rituximab), but Truxima (rituximab-abbs) only carries indications for the treatment of adult patients

with NHL or CLL, while Ruxience (rituximab-pvvr) is approved for adult patients with NHL, CLL, and GPA/MPA. Further information on Erelzi, Eticovo, Abrilada, Amjevita, Cyltezo, Hadlima, and Hyrimoz will be included in this review after these products have launched.
†Inflectra (infliximab-dyyb), Renflexis (infliximab-abda), Avsola (infliximab-axxq), and Ixifi (infliximab-qbtx) have been FDA-approved as biosimilar agents to Remicade (infliximab) and Truxima (rituximab-abbs) and Ruxience (rituximab-pvvr) have been FDA-approved as biosimilar agents to Rituxan (rituximab). However, none of these agents is FDA-approved as an interchangeable biologic.

(Drugs@FDA, 2020; Prescribing information: Actemra, 2019; Cimzia, 2019; Cosentyx, 2020; Enbrel, 2019; Entyvio, 2019; Humira, 2019; Ilaris, 2016; Ilumya 2018; Inflectra, 2019; Kevzara, 2018; Kineret, 2018; Olumiant 2019; Orencia, 2019; Otezla, 2019; Remicade, 2018; Renflexis, 2019; Rinvoq, 2019; Rituxan, 2020; Ruxience, 2019; Siliq, 2018; Simponi, 2019; Simponi Aria, 2019; Skyrizi, 2019; Stelara, 2020; Taltz, 2019; Tremfya, 2019; Truxima, 2019; Xeljanz/Xeljanz 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.

INDICATIONS

Table 2. Food and Drug Administration Approved Indications (see footnotes for less common indications: oral ulcers associated with Behçet disease, CAPS, CRS, FMF, GCA, HIDS/MKD, NRAS, 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˅ (tocilizumab)	✔ *		✔ **	✔ **						
Cimzia˜˜ (certolizumab)	✔	✔			✔ ‡	✔	✔			
Cosentyx (secukinumab)					✔ ‡	✔	✔			
Enbrel (etanercept)	✔ †			✔ **	✔ ‡	✔ †	✔			
Entyvio (vedolizumab)		✔						✔		
Humira (adalimumab)	✔ ‡‡	✔ ⌐		✔ ∫	✔ ‡	✔ ∫∫	✔	✔	✔ ↑	✔ ▼

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)
Ilaris" (canakinumab)			✔ **							
Ilumya (tildrakizumab-asmn)					✔ ‡					
Inflectra (infliximab-dyyb)	✔ ⊥	✔ ⌐⌐			✔ ‡‡‡	✔	✔	✔ ⊥⊥		
Kevzara (sarilumab)	✔ *									
Kineret▼▼ (anakinra)	✔ ∞									
Olumiant (baricitinib)	✔ *									
Orencia (abatacept)	✔ ∞∞			✔ ⌂		✔				

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)
Otezla~~~ (apremilast)					✔ ‡	✔				
Remicade (infliximab)	✔ ⊥	✔ ⌐⌐			✔ ‡‡‡	✔	✔	✔ ⊥⊥		
Renflexis (infliximab-abda)	✔ ⊥	✔ ⌐⌐			✔ ‡‡‡	✔	✔	✔ ⊥⊥		
Rinvoq (upadacitinib)	✔ †									
Rituxan''' (rituximab)	✔ ⫩									
Siliq (brodalumab)					✔ ⫩					
Simponi (golimumab)	✔ ⫞					✔ ⫞⫞	✔	✔ ~		

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)
Simponi Aria (golimumab)	✔┤					✔	✔			
Skyrizi (risankizumab-rzaa)					✔ ‡					
Stelara (ustekinumab)		✔ ⌐⌐⌐			✔ ‡	✔		✔		
Taltz (ixekizumab)					✔ ‡	✔	✔			
Tremfya (guselkumab)					✔ ‡					
Xeljanz/ Xeljanz XR (tofacitinib)	✔╪					✔		✔		

ϓActemra 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) or [≥ 1 TNF antagonists (Olumiant)].
**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.
‡‡‡ 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, Inflectra, Renflexis).
'''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.
¯Cimzia also indicated for treatment of adults with active non-radiographic axial spondyloarthritis (NRAS) with objective signs of inflammation.
~~~Otezla also indicated for treatment of adults with oral ulcers associated with Behçet disease.
†Indicated for treatment of adults with moderately to severely active disease who have had an inadequate response or intolerance to MTX.
***Ruxience is indicated for NHL, CLL, GPA (Wegener’s Granulomatosis) and MPA. Truxima is indicated for NHL and CLL.
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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 ($p \leq 0.001$).
- Approval of Rinvoq (upadacitinib) was based on clinical trials from the SELECT program in patients with RA. In SELECT-EARLY (n = 947), 52% of MTX-naïve patients treated with upadacitinib 15 mg daily achieved ACR 50 vs 28% treated with MTX at week 12, and at week 24, significantly more patients treated with upadacitinib 15 mg daily had no radiographic progression (87.5% vs 77.7%; $p < 0.01$) *(van Vollenhoven et al 2018)*. In SELECT-MONOTHERAPY (n = 648), 68% of patients with an inadequate response or intolerance to MTX (MTX-IR) treated with upadacitinib 15 mg daily achieved ACR 20 vs 41% treated with continued MTX at week 14 *(Smolen et al 2019)*. In SELECT-COMPARE, which evaluated MTX-IR patients (n = 1629), ACR 20 was significantly more frequent with upadacitinib 15 mg daily vs placebo and vs adalimumab at week 12 (70.5% vs 36.4% and 63%, respectively; $p < 0.001$ and $p < 0.05$) and at week 26 (67.4% vs 35.6% and 57.2%, respectively; $p <0.001$ and $p <0.01$). At week 26, significantly more patients treated with upadacitinib had no radiographic progression vs placebo (83.5% vs. 76.0%; $p < 0.001$) *(Fleischman et al 2018)*. In SELECT-BEYOND (n = 499), 65% of biologic-IR patients treated with upadacitinib 15 mg daily plus conventional DMARDs achieved ACR 20 vs 28% treated with placebo plus conventional DMARDs at week 12 ($p <0.0001$) *(Genovese et al 2018)*.
- 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 (QoL).
- 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 2016[b]*). 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 that 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 were 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*).
- The efficacy and safety of Taltz (ixekizumab) were evaluated in the phase 3 randomized, double-blind, placebo-controlled COAST-V and COAST-W trials. In total, 657 patients were studied in these trials, incuding biologic DMARD-naïve patients in COAST-V and patients with previous inadequate response or intolerance to TNF inhibitors in COAST-W. The primary endpoint in both trials, ASAS 40 response at week 16, was significantly improved with ixekizumab every 4 weeks vs placebo (48% vs 18% in COAST-V, $p < 0.0001$; 25% vs 13% in COAST-W, $p < 0.017$). Common adverse events included nasopharyngitis, upper respiratory tract infection, neutropenia, and infection *(van der Heijde et al 2018[a]; Deodhar et al 2019[a])*. The efficacy and safety of ixekizumab were also recently evaluated in

non-radiographic AS in the 52 week, randomized, double-blind, placebo-controlled, parallel-group, multicenter COAST-X trial (*Deodhar et al 2020*). In COAST-X, 303 adults with non-radiographic AS and an inadequate response or intolerance to NSAIDs were randomly assigned to ixekizumab 80 mg SQ every 4 weeks (n = 96), every 2 weeks (n = 102), or placebo (n = 105). Both primary endpoints were met with ixekizumab: ASAS 40 at week 16 (35% every 4 weeks vs 40% every 2 weeks vs 19% placebo; p = 0.0094 and p = 0.0016, respectively) and ASAS 40 at week 52 (30% every 4 weeks vs 31% every 2 weeks vs 13% placebo; p = 0.0045 and p = 0.0037, respectively). The most common treatment-emergent adverse events were nasopharyngitis and injection site reaction.

- 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*). More recently, an international, randomized, double-blind, phase 3, study revealed biosimilar infliximab (Inflectra) to be non-inferior to infliximab in patients with active CD with similar response rates (*Ye et al 2019*).
- 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 HRQoL, 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, NAVIGATE, and ECLIPSE 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 blinded 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 ($p \leq 0.001$).
  - In ECLIPSE (n = 1048), patients with moderate-to-severe plaque PsO were randomly assigned to Tremfya (guselkumab) 100 mg SQ at weeks 0 and 4 and then every 8 weeks (n = 534) or Cosentyx (secukinumab) 300 mg SQ at weeks 0, 1, 2, 3, and 4, and then every 4 weeks (n = 514) (*Reich et al 2019[a]*). Results revealed that the proportion of patients with a PASI 90 response at week 48 was greater in the guselkumab group as compared to the secukinumab group (84% vs 70%; $p < 0.0001$). The proportion of patients with adverse events, infections, and serious adverse events were similar between the treatments.

- 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 PsO 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[a]*).
    - 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; $p = 0.0663$).
- The approval of Skyrizi (risankizumab-rzaa) was based on 4 randomized, double-blind, multicenter trials. In two replicate placebo- and active-controlled trials (UltIMMa-1 and -2), patients with moderate to severe chronic PsO (n = 997) assigned to risankizumab 150 mg every 12 weeks experienced significantly higher rates of PASI 90 response at week 16 (75.3% and 74.8% in UltIMMa-1 and -2, respectively) vs patients assigned to placebo (4.9% and 2.0% in UltIMMa-1 and -2, respectively) and Stelara (ustekinumab) 45 or 90 mg (42.0% and 47.5% in UltIMMa-1 and -2, respectively; $p < 0.0001$ for both comparisons from both trials) *(Gordon et al 2018)*. In an active controlled trial (IMMvent) in patients with moderate-to-severe chronic PsO (n = 605), PASI 90 was achieved by 72% of patients receiving risankizumab-rzaa vs 47% receiving Humira (adalimumab) ($p < 0.0001$) at week 16 (*Reich et al 2019[b]*). In a trial with a randomized withdrawal and retreatment design (IMMhance) (n = 507), PASI 90 was achieved by 73.2% of risankizumab-rzaa-treated patients vs 2.0% of placebo-treated patients ($p < 0.001$) at week 16 (*Langley et al 2019)*
- 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 140 studies (*Sbidian E et al 2020*). The network meta-analysis showed that compared to placebo, the biologics infliximab, ixekizumab, risankizumab, guselkumab, secukinumab, and brodalumab were the best choices for achieving PASI 90 in patients with moderate-to-severe PsO on the basis of moderate- to high-certainty evidence.

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 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 ≤ 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[b]*).
- 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 2016[bj*]). 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.
- In a network meta-analysis of 8 randomized trials (N = 3086), the efficacy and safety of apremilast were compared with tofacitinib in patients with active PsA, including treatment with tofacitinib 10 mg or 5 mg, apremilast 20 or 30 mg, and placebo *(Song et al 2019)*. Tofacitinib 10 mg and apremilast 30 mg were among the most effective treatments, followed by tofacitinib 5 mg and apremilast 20 mg. Tofacitinib 10 mg was most likely to be most effective in ACR 20 response (SUCRA = 0.785), followed by apremilast 30 mg (SUCRA = 0.670), tofacitinib 5 mg (SUCRA = 0.596), and apremilast 20 mg (SUCRA = 0.448). There were no significant differences in adverse event rates.

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*).
- Entyvio (vedolizumab) was directly compared to Humira (adalimumab) in the double-blind, double-dummy, randomized, multicenter, VARSITY trial (*Sands et al 2019[a]*). VARSITY enrolled 769 adults with moderate-to-severe UC and randomized them to vedolizumab (n = 383) 300 mg IV on day 1 and at weeks 2, 6, 14, 22, 30, 38, and 46 (plus placebo injections) or adalimumab (n = 386) 160 mg SQ at week 1, 80 mg at week 2, and 40 mg every 2 weeks thereafter (plus placebo infusions) until week 50. Results revealed that clinical remission at week 52 occurred in significantly more patients in the vedolizumab group (31.3% vs 22.5%; difference, 8.8%; 95% CI, 2.5 to 15; $p = 0.0006$). Endoscopic improvement was also significantly improved with vedolizumab (39.7% vs 27.7%; difference, 11.9%; 95% CI, 5.3 to 18.5; $p < 0.001$). However, corticosteroid-free clinical remission was better with adalimumab (12.6% vs 21.8%; difference, -9.3%; 95%, -18.9 to 0.4).
- The efficacy of Xeljanz (tofacitinib) for UC 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*).
- The efficacy of Stelara (ustekinumab) as induction and maintenance therapy in 961 patients with moderate-to-severe UC was evaluated in the UNIFI study (*Sands et al 2019[b]*). The study involved 8 week induction and 44 week maintenance phases. Patients were randomly assigned to receive an IV induction dose of either ustekinumab 130 mg (n = 320), a weight-range-based ustekinumab dose that approximated 6 mg/kg (n = 322), or placebo (n = 319). Patients with an induction response were then randomly assigned to ustekinumab 90 mg SQ every 12 weeks (n = 172), every 8 weeks (n = 176), or placebo (n = 175) for maintenance. Results revealed a significantly higher clinical remission at week 8 with ustekinumab 130 mg (15.6%) or 6 mg/kg (15.5%) as compared to placebo (5.3%; $p < 0.001$ for both comparisons). At the end of maintenance, the percentage of patients who had clinical remission was also significantly increased in both ustekinumab groups (38.4% every 12 weeks vs 43.8% every 8 weeks vs 24% placebo; $p = 0.002$ and $p < 0.001$, respectively).
- 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 UV. 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.

Behçet disease, CAPS, CRS, FMF, GCA, HIDS/MKD, NOMID, NRAS, and TRAPs

- The efficacy of Otezla (apremilast) for Behçet disease was evaluated in a randomized, double-blind, placebo-controlled trial in 207 adults with Behçet disease with active oral ulcers who were previously treated with at least one nonbiologic therapy (*Hatemi et al 2019*). At week 12, apremilast 30 mg twice daily was associated with a 42.7 point mean reduction from baseline in oral ulcer pain on a visual analog scale (VAS), compared with an 18.7 point reduction with placebo. The area under the curve (AUC) of the total mean number of ulcers during the 12 week period was 129.5 in the apremilast vs 222.1 in the placebo group ; p < 0.001). The proportion of patients who were oral ulcer-free at week 12 was 53% and 22% with apremilast vs placebo, respectively. Adverse events with apremilast included diarrhea, nausea, and headache.
- 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 of Cimzia (certolizumab) was evaluated in a phase 3, randomized, double-blind, placebo-controlled trial in 317 patients with NRAS. Patients were randomized to certolizumab (400 mg at weeks 0, 2, and 4, followed by 200 mg every 2 weeks) or placebo in addition to nonbiologic background medication. At week 52, treatment with certolizumab was associated with a significantly higher proportion of patients achieving major improvement (≥ 2 point decrease in Ankylosing Spondylitis Disease Activity Score; 47.2% vs 7.0%; p < 0.0001) *(Deodhar et al 2019[b]).*
- 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*). The ACR updated guideline on RA management is currently underway with final publication anticipated in early 2020.
    - EULAR guidelines for RA management were recently updated (*Smolen et al 2020*). EULAR recommends that therapy with DMARDs should be initiated as soon as the RA diagnosis is made with treatment aimed at reaching a target of sustained remission or low disease activity in every patient. If the treatment target is not achieved with the first conventional synthetic DMARD strategy, in the absence of poor prognostic factors, others should be considered. If poor prognostic factors are present with treatment failure, a biological or targeted synthetic DMARD should be added. If a biological or targeted synthetic DMARD has failed, treatment with another should be considered. If one TNF inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF inhibitor.
    - 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:
    - According to the American College of Rheumatology (ACR) JIA guidelines focusing on the management of SJIA, 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*).
    - The ACR and Arthritis Foundation published a guideline for the treatment of JIA in 2019 focusing on therapy for non-systemic polyarthritis, sacroiliitis, and enthesitis. In children and adolescents with JIA and polyarthritis with moderate to high disease activity, addition of a biologic (TNF inhibitor, abatacept, or tocilizumab) is conditionally recommended. Patients with continued disease activity and primary TNF inhibitor failure are conditionally recommended to receive abatacept or tocilizumab over a second TNF inhibitor. Children and adolescents with JIA and active sacroiliitis despite treatment with NSAIDs are strongly recommended to add TNF inhibitor therapy over continuing NSAID monotherapy. In children and adolescents with JIA and active enthesitis, TNF inhibitor therapy is conditionally recommended over methotrexate or sulfasalazine *(Ringold et al 2019)*. The ACR is developing a new clinical practice guideline for the management of JIA, specifically covering pharmacologic and non-pharmacologic treatments that were not addressed in the 2019 guidelines; final publication is anticipated in early 2021.
- UC:
    - For the treatment of UC, 2019 guidelines from the American College of Gastroenterology (ACG) recommend 5-aminosalicylate (5-ASA) therapy for induction of remission in mildly active UC, and budesonide, systemic corticosteroids, TNF inhibitor therapy (adalimumab, golimumab, or infliximab), vedolizumab, and tofacitinib for induction of remission in moderately to severely active disease. Vedolizumab and tofacitinib are recommended for induction of remission in patients who have failed previous TNF inhibitor therapy. For maintenance of remission in patients with previously mildly active disease, 5-ASA therapy is recommended, and in patients with previously moderately to severely active disease, continuation of anti-TNF therapy, vedolizumab, or tofacitinib is recommended after induction of remission with these agents (*Rubin et al 2019*).
    - 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 adult outpatients with moderate to severe UC, the AGA strongly recommends using infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or ustekinumab over no treatment (*Feuerstein et al 2020*).
    - 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*).
    - In 2020, ECCO released a guideline on medical treatment in CD (*Torres et al 2020*). Regarding immunomodulators, these guidelines recommend the use of TNF inhibitors (infliximab, adalimumab, and certolizumab pegol) to induce remission in patients with moderate-to-severe CD who have not responded to conventional therapy. Other immunomodulator-related recommendations within the guideline include:
        - Suggesting against the combination of adalimumab and thiopurines over adalimumab alone to achieve clinical remission and response.
        - Recommending combination therapy with a thiopurine when starting infliximab to induce remission in patients with moderate-to-severe CD, who have had an inadequate response to conventional therapy.
        - Recommending ustekinumab for induction of remission in patients with moderate-to-severe CD with inadequate response to conventional therapy and/or to anti-TNF therapy.
        - Recommending vedolizumab for induction of response and remission in patients with moderate-to-severe CD with inadequate response to conventional therapy and/or to anti-TNF therapy.
        - Equally suggesting the use of either ustekinumab or vedolizumab for the treatment of moderate-to-severe active luminal CD in patients who have previously failed anti-TNF therapy.
- 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 2016[b]*).
    - 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 (*Elmets et al 2019, Menter et al 2008, Menter et al 2009a, Menter et al 2009b, 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 address 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, risankizumab, 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 QoL 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:
  - The American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network joint recommendations for treatment of AS and NRAS were updated in 2019. Patients with active AS or NRAS who do not respond to initial NSAID therapy are conditionally recommended to be treated with sulfasalazine, MTX, or tofacitinib; sulfasalazine or methotrexate should be considered only in patients with prominent peripheral arthritis or when TNF inhibitors are not available. Patients who do not respond to NSAID therapy are strongly recommended to receive treatment with a TNF inhibitor, although no particular TNF inhibitor is preferred. Treatment with a TNF inhibitor is conditionally recommended over tofacitinib, secukinumab, and ixekizumab in these patients. In patients with active disease who have primary nonresponse with a TNF inhibitor, treatment with secukinumab or ixekizumab is strongly recommended, and treatment with tofacitinib is conditionally recommended. Patients with secondary nonresponse to treatment with a TNF inhibitor are conditionally recommended to receive treatment with an alternative TNF inhibitor. In patients with AS and inflammatory bowel disease or recurrent iritis, TNF inhibitors are conditionally recommended over treatment with other biologics. In patients with stable disease who are treated with an originator TNF inhibitor, the guideline strongly recommends continuing the originator TNF inhibitor over mandated switching to its biosimilar *(Ward et al 2019).*
  - Joint recommendations for the management of axial spondyloarthritis are available from ASAS and EULAR. (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[b]*).
- 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.
    - A 2019 guideline by the ACR and Arthritis foundation focusing on children with JIA-associated UV conditionally recommended starting a monoclonal antibody TNF inhibitor over etanercept in children and adolescents with chronic anterior UV. Children and adolescents with inadequate response to one monoclonal TNF inhibitor are conditionally recommended to be treated with an escalated dose and/or frequency of the TNF inhibitor over switching to another TNF inhibitor; patients failing dose escalation are conditionally recommended to switch to another monoclonal TNF inhibitor. Children and adolescents failing MTX and 2 monoclonal TNF inhibitors are conditionally recommended to receive abatacept or tocilizumab as biologic DMARD options *(Angeles-Han et al 2019).*
- 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*).
    - For the management of HS, the US and Canadian Hidradenitis Suppurativa Foundation recommend adalimumab to improve disease severity and QoL in patients with moderate-to-severe disease (*Alikhan et al, 2019*). Additionally, infliximab is recommended for moderate-to-severe disease; however, the optimal dose is not currently known. Anakinra and ustekinumab may be effective agents for HS as well.
    - 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 CD 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), Rinvoq (upadacitinib), 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), Rinvoq (upadacitinib), Simponi / Simponi Aria (golimumab), and Xeljanz (tofacitinib) all have warnings for increased risk of malignancies.
    - Xeljanz and Xeljanz XR (tofacitinib) have warnings for increased risk of thrombosis and death with the 10 mg twice daily dose, which is used in patients with UC. Rinvoq (upadacitinib) and Olumiant (baricitinib), other JAK inhibitors, also carry a boxed warning for this risk.
    - 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)
  - Embryo-fetal toxicity with Rinvoq (upadacitinib)
  - Hepatotoxicity with Actemra (tocilizumab)
  - Cardiovascular and cerebrovascular reactions during and after infusion (infliximab)
  - 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*).

o 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.

o 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.

o 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*).

o 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 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	**RA:** Can give with MTX or other DMARDs. **PJIA and SJIA:** Can give with MTX. **GCA:** Can use alone after discontinuation of	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

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		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.	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, infection, and low ANC.	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. **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 (for body weight ≤ 90 kg) **AS, NRAS:** 400 mg SQ initially and at weeks 2 and 4. Maintenance	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
		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 or AS continues, consider 300 mg dose every 4 weeks.	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/0.5 mL and 50 mg/mL Prefilled SureClick autoinjector: 50 mg/mL Multiple-use vial: 25 mg lyophilized powder Solution: 50 mg/mL in Enbrel Mini® cartridge for use with reusable autoinjector only	**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 IV infusion at time 0, 2, and 6 weeks, and then every 8 weeks 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 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	**RA, AS, PsA**: 40 mg SQ every other week. For RA, may increase to 40 mg every week if not on MTX. **PJIA or pediatric uveitis:** 10 kg to <15	**RA, AS, PsA:** MTX, other non-biologic DMARDS, glucocorticoids, NSAIDs, and/or analgesics may be continued.	Patients may be taught to self-inject. Injections should occur at separate sites in the thigh or abdomen. Rotate injection sites. May bring to room

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	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	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 1, 80 mg on day 15, 40 mg on day 29;	**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).	temperature prior to injecting.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		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 (≥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 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	**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.		
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: 1 mg, 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		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
		infusion and every 4 weeks thereafter. >75 kg, follow adult RA IV 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, Behçet's:** 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	**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.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		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.		Infuse over 2 hours. Do not administer with other drugs.
Renflexis (infliximab-abda)	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 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.
Rinvoq (upadacitinib)	Extended release tablet: 15 mg	**RA:** 15 mg once daily.		May be administered with or without food.
Rituxan (rituximab)	Vial: 100 mg/10 mL 500 mg/50 mL	**RA:** Two 1,000 mg IV infusions separated by 2 weeks (one course). Additional doses should be given every 24 weeks or based on clinical evaluation but no sooner than every 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.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
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/0.5 mL and 100 mg/mL Prefilled syringe: 50 mg/0.5 mL and 100 mg/mL Aria, Vial: 50 mg/4 mL	**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. **Aria (RA, PsA, and AS)**: 2 mg/kg IV at weeks 0 and 4, then every 8 weeks.	**RA:** give with MTX. **PsA and AS**: may give with or without MTX or other DMARDs. 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.	Patients may be taught to self-inject the SQ dose. For SQ, injection sites should be rotated. 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.
Skyrizi (risankizumab-rzaa)	Prefilled syringe: 75 mg/0.83 mL	**PsO:** 150 mg (two 75 mg injections) SQ at week 0, week 4, and every 12 weeks thereafter.	Product is not made with natural rubber latex.	Each dose must be administered in different anatomic locations. Patients may be taught to self-inject using the prefilled syringes.
Stelara (ustekinumab)	Prefilled syringe: 45mg/0.5 mL and 90 mg/mL Vial: 45 mg/0.5 mL and 130 mg/26 mL	**PsO**: ≤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	**Co-existent moderate-to-severe PsO with PsA weighing >100 kg**: 90 mg SQ initially and 4 weeks later,	Patients may be taught to self-inject using the prefilled syringes. Stelara for IV infusion must be diluted, prepared and infused by a healthcare

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		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. **PsA:** 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. **CD and UC**: 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).	followed by 90 mg every 12 weeks. Needle cover of the syringe contains dry rubber (latex).	professional; it is diluted in 0.9% sodium chloride or 0.45% sodium chloride for a final volume of 250 mL and infuse over at least 1 hour. Rotate injection sites.
Taltz (ixekizumab)	Prefilled syringe: 80 mg/mL Autoinjector: 80 mg/mL	**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. **PsA, AS:** 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.		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.
Tremfya (guselkumab)	Prefilled syringe or single-dose patient-controlled autoinjector: 100 mg/mL	**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, 22 mg	**RA:** 5 mg PO twice daily or 11 mg PO once daily **PsA:** 5 mg PO twice daily or 11 mg once daily used in	Patients may switch from Xeljanz 5 mg twice daily to Xeljanz XR 11 mg once daily the day following the last	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
		combination with nonbiologic DMARDs **UC (induction):** 10 mg PO twice daily or 22 mg PO once daily for 8 weeks, then, if needed, continue 10 mg twice daily or 22 mg once daily for a maximum of 16 weeks. Discontinue therapy after 16 weeks if an adequate therapeutic response is not achieved. **UC (maintenance):** 5 mg PO twice daily or 11 mg PO once daily; for patients with loss of response during maintenance, 10 mg twice daily or 22 mg once daily may be considered and limited to the shortest duration.	dose of Xeljanz 5 mg. Patients may switch from Xeljanz 10 mg twice daily to Xeljanz XR 22 mg once daily the day following the last dose of Xeljanz 10 mg. Use as monotherapy or in combination with MTX or other nonbiologic DMARDs in RA. Dose adjustment needed in patients taking CYP450 inhibitors and in lymphopenia, neutropenia, and anemia.	

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; NRAS=nonradiographic axia spondyloarthritis; 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	Safety and effectiveness have not been	No data	No data	Unclassified† Limited data from

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	was not sufficient to determine whether they responded differently from younger subjects. Use caution.	established.			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 not sufficient to determine whether they responded differently from younger subjects.	Safety and efficacy have not been established.	No data	No data	Unclassified† Available and ongoing data have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Available data suggest presence in milk; use with caution.
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	No data	No data	Unclassified† Available studies do not reliably support association with major birth defects.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
		older), and HS (12 years and older).			Present in low levels in breast milk; consider risks and benefits.
Ilaris (canakinumab)	The number of patients ≥65 years in clinical trials was not sufficient to determine whether they responded differently from younger subjects.	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 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; 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 or UC.	No data	No data	Unclassified† Available data have not reported a clear association with adverse pregnancy outcomes. Unknown whether excreted in breast milk; consider risks and benefits.
Kevzara (sarilumab)	Frequency of serious infection is greater in ≥ 65 years. Use caution.	Safety and efficacy have not been 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.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Kineret (anakinra)	Use caution as there is a higher incidence of infections in the elderly in general.	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 < 30 mL/min/1.73 m^2; for estimated glomerular filtration rate between 30 and 60 mL/min/1.73m^2: administer 1 mg once daily.	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; avoid use.
Orencia (abatacept)	Frequency of serious infection and malignancies is greater in ≥65 years. Use caution.	Not recom-mended in <2 years old. 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 impairment (CrCl<30	No dosage adjustment necessary.	Unclassified† Available data have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
			mL/min).		Unknown whether excreted in breast milk; consider risks and benefits.
Remicade (infliximab)	Frequency of serious infection is greater in ≥65 years. Use caution.	Not recommended 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 recommended in < 6 years in children with CD or UC.	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.
Rinvoq (upadacitinib)	No differences in safety or efficacy were observed between older and younger patients; however, there was a higher rate of overall adverse events in elderly patients.	Safety and efficacy have not been established.	No dose adjustment required.	No dose adjustment required in mild or moderate hepatic impairment; not recommended in severe hepatic impairment.	Unclassified† Animal data suggest potential for fetal harm; females of reproductive potential should use effective contraception during treatment and for 4 weeks following completion of therapy. Unknown whether excreted in human breast milk, but excreted in animal milk; breastfeeding not recommended during treatment and for 6 days after last dose.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Rituxan (rituximab)	Rates of serious infections, malignancies, and cardiovascular events were higher in older patients.	Indicated for the treatment of GPA and MPA in children ≥2 years of age; safety and efficacy not established in children with NHL, CLL, PV, or RA.	No data	No data	Unclassified† May potentially cause B-cell lymphocytopenia due to in-utero exposure; advise women to use effective contraception during treatment and for at least 12 months after the last dose. Unknown whether excreted in breast milk; advise women not to breastfeed during treatment and for at least 6 months after the last dose.
Siliq (brodalumab)	No differences in safety or efficacy were observed between older and younger patients, but the number of patients ≥65 years in clinical trials 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. IV Aria: Use caution.	Effectiveness in <18 years has not been established (Simponi). Safety and effectiveness in < 18 years have not been established (Aria).	No data	No data	Unclassified† No adequate and well-controlled trials in pregnant women. Unknown whether excreted in breast milk. Consider risks and benefits.
Skyrizi (risankizumab-rzaa)	No differences observed between older and younger patients. Use caution.	Safety and efficacy have not been established.	No data	No data	Unclassified† Limited data in pregnant women are insufficient to inform risks.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
					Unknown whether excreted in breast milk; consider risks and benefits.
Stelara (ustekinumab)	No differences observed between older and younger patients. Use caution.	Safety and effectiveness have been established in children 12 to 17 years with moderate to severe PsO; safety and effectiveness not established in children with PsA, CD, or UC.	No data	No data	Unclassified† Limited data in pregnant women are insufficient to inform risks. Unknown whether excreted in breast milk; systemic exposure to breastfed 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 in clinical trials 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 in clinical trials 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 Xeljanz and reduce dose to 5 mg once daily and those receiving Xeljanz 5 mg twice daily should reduce to 5 mg once daily. Patients with UC on Xeljanz should switch to 5 mg twice daily (if on 10 mg twice daily) or 5 mg once daily (if on 5 mg twice daily). Patients with UC on Xeljanz XR 22 mg once daily, should reduce to 11 mg once daily; if taking 11 mg once daily, reduce to Xeljanz 5 mg once daily.	Moderate impairment: Patients with RA or PsA receiving Xeljanz XR should switch to Xeljanz and reduce dose to 5 mg once daily and those receiving Xeljanz 5 mg twice daily should reduce to 5 mg once daily. Patients with UC on Xeljanz should switch to 5 mg twice daily (if on 10 mg twice daily) or 5 mg once daily (if on 5 mg twice daily). Patients with UC on Xeljanz XR 22 mg once daily, should reduce to 11 mg once daily; if taking 11 mg once daily, reduce to Xeljanz 5 mg once daily. Not recom-mended in severe hepatic impairment.	Unclassified† Available data are insufficient to inform a drug-associated risk; consider pregnancy planning and prevention for females of reproductive potential. Unknown whether excreted in breast milk; advise women to avoid breastfeeding during treatment and for at least 18 hours after the last dose of Xeljanz or 36 hours after the last dose of Xeljanz XR.

CLL=chronic lymphocytic leukemia; CrCl=creatinine clearance; CD=Crohn's disease; CAPS=cryopyrin-associated periodic syndromes; CRS=cytokine release syndrome; FMF=familial Mediterranean fever; GPA=granulomatosis with polyangiitis; HS=hidradenitis suppurative; HIDS/MKD=hyperimmunoglobulin D syndrome/mevalonate kinase deficiency; MPA=microscopic polyangiitis; NHL=non-Hodgkin's lymphoma; NOMID= Neonatal-Onset Multisystem Inflammatory Disease; PJIA=polyarticular juvenile idiopathic arthritis; PsA=psoriatic arthritis; PsO=plaque psoriasis; PV=pemphigus vulgaris; RA=rheumatoid arthritis; SJIA=systemic juvenile idiopathic arthritis; TRAPS=tumor necrosis factor receptor associated periodic syndrome; UC=ulcerative colitis; XR=extended-release.
*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.

†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 patients with RA and inadequate response or intolerance to MTX, upadacitinib was associated with significantly greater ACR 20 response compared with adalimumab at weeks 12 and 26 *(Fleischman et al 2018).*
    - 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 and 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]*).
    - In two trials of patients with moderate to severe chronic PsO, risankizumab was associated with significant improvement in PASI 90 response at week 16 vs ustekinumab *(Gordon et al 2018)*.

  - In ECLIPSE, patients with moderate-to-severe plaque PsO were randomly assigned to Tremfya (guselkumab) or Cosentyx (secukinumab) (*Reich et al 2019[a]*). Results revealed that the proportion of patients with a PASI 90 response at week 48 was greater in the guselkumab group as compared to the secukinumab group (84% vs 70%; p < 0.0001).
  - 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*).
  - Entyvio (vedolizumab) was directly compared to Humira (adalimumab) in the VARSITY trial (*Sands et al 2019*). Results revealed that clinical remission at week 52 occurred in significantly more patients in the vedolizumab group (31.3% vs 22.5%; difference, 8.8%; 95% CI, 2.5 to 15; p = 0.0006). Endoscopic improvement was also significantly improved with vedolizumab (39.7% vs 27.7%; difference, 11.9%; 95% CI, 5.3 to 18.5; p < 0.001). However, corticosteroid-free clinical remission was better with adalimumab (12.6% vs 21.8%; difference, -9.3%; 95%, -18.9 to 0.4).
  - 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 per ACR guidance (*Singh et al 2016c*). EULAR guidelines for RA management were recently updated (*Smolen et al 2020*). EULAR recommends that therapy with DMARDs should be initiated as soon as the RA diagnosis is made with treatment aimed at reaching a target of sustained remission or low disease activity in every patient. If the treatment target is not achieved with the first conventional synthetic DMARD strategy, in the absence of poor prognostic factors, others should be considered. If poor prognostic factors are present with treatment failure, a biological or targeted synthetic DMARD should be added. If a biological or targeted synthetic DMARD has failed, treatment with another should be considered. If one TNF inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF inhibitor. EULAR has also 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 produce 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 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, risankizumab, 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*).
- The ACR 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*). Patients with JIA and active sacroiliitis or enthesitis are recommended to receive TNF inhibitor therapy, and patients with non-systemic polyarthritis are recommended to

receive TNF inhibitor therapy, abatacept, or tocilizumab. Patients with continued disease activity and primary TNF inhibitor failure are recommended to receive abatacept or tocilizumab *(Ringold et al 2019)*.

- According to the ACG, for induction of remission in moderately to severely active UC, TNF inhibitor therapy, vedolizumab, or tofacitinib are recommended, and should be continued to maintain remission. Vedolizumab and tofacitinib are recommended in patients with previous failure to TNF inhibitor therapy (*Rubin et al 2019*). For adult outpatients with moderate to severe UC, the AGA strongly recommends using infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or ustekinumab over no treatment (*Feuerstein et al 2020*). 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*). In 2020, ECCO released a guideline on medical treatment in CD (*Torres et al 2020*). Regarding immunomodulators, these guidelines recommend the use of TNF inhibitors (infliximab, adalimumab, and certolizumab pegol) to induce remission in patients with moderate-to-severe CD who have not responded to conventional therapy, among other recommendations.
- 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 2016[b]*).
- 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[b]*). The 2019 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. Secukinumab or ixekizumab are recommended in patients with active disease who have primary nonresponse with a TNF inhibitor (*Ward et al 2019*).
- 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, tofacitinib, sarilumab, baricitinib, and upadacitinib have boxed warnings regarding a risk of serious infections. TNF inhibitors, tofacitinib, baricitinib, and upadacitinib also have boxed warnings regarding an increased risk of malignancies. Brodalumab has a boxed warning regarding the risk of suicidal ideation and behavior. Tofacitinib (10 mg twice daily dose), upadacitinib, and baricitinib also have boxed warnings regarding thrombosis risk.
- Warnings, precautions, and AE profiles vary in this class.
- All of the biologic agents with the exception of apremilast, baricitinib, tofacitinib, and upadacitinib are given by subcutaneous injection and/or intravenous infusion. Administration schedule varies among the injectable agents in the class. Apremilast, baricitinib, tofacitinib, and upadacitinib 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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Publication Date:

INTRODUCTION

- Multiple Sclerosis (MS), a chronic, immune-mediated disease of the central nervous system (CNS), is among the most common causes of neurological disability in young adults *(MS Coalition 2019; National Institutes of Health MS 2019)*. Multiple sclerosis is characterized by inflammation, demyelination, and degenerative changes. Most patients with MS experience relapses and remissions of neurological symptoms, usually early in the disease process, with clinical events that are generally associated with CNS inflammation. There are 4 clinical subtypes of MS:
  - Relapsing-remitting MS (RRMS), which is characterized by acute attacks followed by partial or full recovery. This is the most common form of MS, accounting for an estimated 85% of cases.
  - Secondary progressive MS (SPMS) begins as RRMS; however, the attack rate declines over time. Patients experience a gradual deterioration. Patients with RRMS for more than 10 years may transition to SPMS.
  - Primary progressive MS (PPMS) occurs in approximately 15% of patients with MS. Patients have a continuous and gradual decline in function without evidence of acute attacks.
  - Clinically isolated syndrome (CIS) refers to the first episode of neurologic symptoms that lasts at least 24 hours and is caused by inflammation or demyelination in the CNS. Patients who experience a CIS may or may not develop MS *(Sanvito et al 2011, National MS Society 2020[a])*.
- A more recent revision of the MS clinical course descriptions recommended that the core MS phenotype descriptions of relapsing and progressive disease be retained with some of the following modifications: (1) an important modifier of these core phenotypes is an assessment of disease activity, as defined by clinical assessment of relapse occurrence or lesion activity detected by CNS imaging; (2) the second important modifier of these phenotypes is a determination of whether progression of disability has occurred over a given time period; and (3) the historical category of progressive-relapsing multiples sclerosis (PRMS) can be eliminated since subjects so categorized would now be classified as PPMS patients with disease activity *(Lublin et al 2014)*.
- An estimated 1 million adults in the United States are affected by MS. Most patients are diagnosed between the ages of 20 and 50 years, and MS is at least 2 to 3 times more common in women than in men *(National MS Society 2020[b])*.
- Diagnosis of MS requires evidence that demonstrates lesions in the CNS showing “dissemination in space” (ie, suggestions of damage in > 1 place in the nervous system) and “dissemination in time” (ie, suggestions that damage has occurred more than once). It is a diagnosis of exclusion, after consideration of and elimination of more likely diagnoses *(Thompson et al 2018)*.
- The patient evaluation includes an extensive history, neurological examination, laboratory tests to rule out other possible causes, magnetic resonance imaging (MRI) to evaluate for new disease and signs of more chronic damage, and possibly lumbar puncture (*Thompson et al 2018*).
- Exacerbations, also known as flares, relapses, or attacks of MS are caused by inflammation in the CNS that lead to damage to the myelin and slowing or blocking of transmission of nerve impulses. A true MS exacerbation must last at least 24 hours and be separated from a previous exacerbation by at least 30 days. Exacerbations can be mild or severe. Intravenous (IV) corticosteroids may be used to treat severe exacerbations of MS. Corticosteroids decrease acute inflammation in the CNS but do not provide any long-term benefits *(Frohman et al 2007)*.
- The approach to treating MS includes the management of symptoms, treatment of acute relapses and utilization of disease-modifying therapies (DMTs) to reduce the frequency and severity of relapses, reduce lesions on MRI scans, and possibly delay disease and disability progression *(Rae-Grant et al 2018)*. The American Academy of Neurology (AAN), the European Committee for Research and Treatment of Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) guidelines recommend initiation of DMTs early on in the patient’s disease course (*Rae Grant et al 2018[b], Montalban et al 2018*). These therapies may delay the progression from CIS to clinically definite MS (CDMS) *(Miller et al 2012, Armoiry et al 2018)*.The MS Coalition, the AAN, and the Association of British Neurologists guidelines support access to available DMTs for patients with MS. While there are no precise algorithms to determine the order of product selection, therapy should be individualized and patients’ clinical response and tolerability to medications should be monitored (*MS Coalition 2019, Rae-Grant et al 2018, Scolding et al 2015*).

- Pediatric-onset MS is rare, with the vast majority of cases demonstrating a relapsing-remitting disease course (*Otallah et al 2018*). Gilenya (fingolimod) is the first FDA-approved agent for pediatric patients. Its approval was based on the PARADIGMS trial (*Chitnis et al 2018*).
- Cladribine injection is indicated for the treatment of active hairy-cell leukemia (*Clinical Pharmacology 2020*). This oncology indication is not related to the treatment of MS and will not be discussed in this review.
- A recently approved agent in this review, Vumerity (diroximel fumarate), is rapidly converted to monomethyl fumarate (MMF), which also is the active metabolite of Tecfidera (dimethyl fumarate). Diroximel fumarate may offer improved gastrointestinal (GI) tolerability as compared to dimethyl fumarate (*Naismith et al 2019, Selmaj et al 2019*). In April 2020, the FDA approved another agent in this class, Bafiertam (monomethyl fumarate). This drug is considered a "bioequivalent alternative" to dimethyl fumarate since dimethyl fumarate is a prodrug, and monomethyl fumarate is its active ingredient. Since the drug is already in its active form, it is administered at a lower dose than dimethyl fumarate, and it is thought that it may lead to fewer GI adverse effects (*Drugs@FDA 2020*).

- All agents in this class review are listed as Multiple Sclerosis Agents in Medispan; the exceptions are mitoxantrone (listed as an antineoplastic antibiotic) and Ampyra (dalfampridine) (listed as a potassium channel blocker).

Table 1. Medications Included Within Class Review§

Drug	Generic Availability
Ampyra (dalfampridine)	✔
Aubagio (teriflunomide)	✔ *
Avonex (interferon β-1a)	-
Bafiertam (monomethyl fumarate)	-
Betaseron (interferon β-1b)	-
Copaxone, Glatopa† (glatiramer acetate)	✔
Extavia (interferon β-1b)	-
Gilenya (fingolimod)	✔ *
Lemtrada (alemtuzumab)	-
Mavenclad (cladribine)	-
Mayzent (siponimod)	-
mitoxantrone‡	✔
Ocrevus (ocrelizumab)	-
Plegridy (peginterferon β-1a)	-
Rebif (interferon β-1a)	-
Tecfidera (dimethyl fumarate)	-
Tysabri (natalizumab)	-
Vumerity (diroximel fumarate)	-
Zeposia (ozanimod)	-

*Generics have received FDA-approval; however, settlement agreements will delay launch.
†Glatopa by Sandoz is an FDA-approved generic for Copaxone (glatiramer acetate).
‡Although brand Novantrone has been discontinued, generic mitoxantrone remains available.
§As of April 30, 2018, the manufacturer has voluntarily withdrawn Zinbryta (daclizumab) from the market; cases of encephalitis and meningoencephalitis have been reported in patients treated with Zinbryta.

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020, Purple Book 2020*)

INDICATIONS

- In 2019, the FDA requested all manufacturers of drugs indicated for treatment of MS to revise the language of the indications to conform to contemporary nomenclature. As of May 22, 2020, all drugs have received revised FDA-approved indications except mitoxantrone (*Drugs@FDA 2020*).

Table 2. Food and Drug Administration Approved Indications

Drug	Improve walking in MS	Relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease	Relapsing forms of MS, to include relapsing-remitting disease and active secondary progressive disease in adults	Primary Progressive MS in adults	Reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary progressive, progressive relapsing, or worsening relapsing-remitting MS
Ampyra (dalfampridine)	✔ *	-	-	-	-
Aubagio (teriflunomide)	-	✔	-	-	-
Avonex (interferon β-1a)	-	✔	-	-	-
Bafiertam (monomethyl fumarate)	-	✔	-	-	-
Betaseron/Extavia (interferon β-1b)	-	✔	-	-	-
Copaxone (glatiramer acetate)	-	✔	-	-	-
Gilenya (fingolimod)	-	✔ †	-	-	-
Lemtrada (alemtuzumab)	-	-	✔ ‡ (3rd line)	-	-
Mavenclad (cladribine)	-	-	✔ §	-	-
Mayzent (siponimod)	-	✔	-	-	-
mitoxantrone	-	-	-	-	✔ ‖
Ocrevus (ocrelizumab)	-	✔	-	✔	-
Plegridy (peginterferon β-1a)	-	✔	-	-	-
Rebif (interferon β-1a)	-	✔	-	-	-
Tecfidera (dimethyl fumarate)	-	✔	-	-	-
Tysabri (natalizumab)	-	✔ ¶	-	-	-
Vumerity (diroximel fumarate)	-	✔	-	-	-
Zeposia (ozanimod)	-	✔	-	-	-

*Ampyra is indicated as a treatment to improve walking in adult patients with MS. This was demonstrated by an increase in walking speed.
†Approved in patients 10 years of age and older.
‡Because of its safety profile, Lemtrada should generally be reserved for patients who have had an inadequate response to 2 or more drugs indicated for the treatment of MS. Lemtrada is not recommended for use in patients with CIS because of its safety profile.
§ Because of its safety profile, use of Mavenclad is generally recommended for patients who have had an inadequate response, or are unable to tolerate, an alternate drug indicated for the treatment of MS. Mavenclad is not recommended for use in patients with CIS because of its safety profile.

‖Mitoxantrone is indicated for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening RRMS (ie, patients whose neurologic status is significantly abnormal between relapses). Mitoxantrone is not indicated for the treatment of patients with PPMS. The product has additionally been approved for several cancer indications including pain related to advanced hormone-refractory prostate cancer and initial therapy of acute nonlymphocytic leukemia (includes myelogenous, promyelocytic, monocytic, and erythroid acute leukemias).
¶Tysabri increases the risk of Progressive Multifocal Leukoencephalopathy (PML). When initiating and continuing treatment with Tysabri in patients with MS, physicians should consider whether the expected benefit of Tysabri is sufficient to offset this risk. Tysabri is also indicated for inducing and maintaining clinical response and remission in adult patients with moderately to severely active Crohn's disease (CD) with evidence of inflammation who have had an inadequate response to, or are unable to tolerate, conventional CD therapies and inhibitors of TNF-α. In CD, Tysabri should not be used in combination with immunosuppressants or inhibitors of TNF- α.

(Prescribing information: Ampyra 2019, Aubagio 2020, Avonex 2020, Bafiertam 2020, Betaseron 2019, Copaxone 2020, Extavia 2019, Gilenya 2019, Glatopa 2019, Lemtrada 2020, Mavenclad 2019, Mayzent 2019, mitoxantrone 2018, Ocrevus 2020, Plegridy 2020, Rebif 2019, Tecfidera 2020, Tysabri 2020, Vumerity 2020, Zeposia 2020)

- 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 the management of MS, numerous clinical trials have established the safety and efficacy of the biological response modifiers in reducing the frequency of relapses, lesions on MRI scans, and possibly delaying disease progression and disability.

Interferons and glatiramer acetate

- Pivotal clinical trials demonstrating efficacy in reducing the rate of relapses, burden of disease on MRI, and disability progression for the interferons (IFNs) and glatiramer acetate were published in the 1990's *(Jacobs et al 1996, Johnson et al 1995, The interferon beta [IFNβ] Multiple Sclerosis Study Group 1993, The IFNβ Multiple Sclerosis Study Group 1995)*. Long-term follow-up data for IFN β-1b show that overall survival in MS is improved *(Goodin et al 2012)*.
- Head-to-head trials have found Copaxone (glatiramer acetate), Rebif (IFNβ-1a SC), and Betaseron (IFNβ-1b) to be comparable in terms of relapse rate reduction and disease and disability progression *(PRISMS 1998, Kappos et al 2006, Mikol et al 2008, Flechter et al 2002, Cadavid et al 2009, O'Connor et al 2009)*. Results from several studies suggest that lower dose Avonex (IFNβ-1a 30 mcg IM once weekly) may be less efficacious while being more tolerable compared to Rebif (IFNβ-1a SC 3 times weekly) or Betaseron (IFNβ-1b every other day) or glatiramer acetate *(Barbero et al 2006, Durelli et al 2002, Khan et al 2001[a], Khan et al 2001[b], Panitch et al 2002, Panitch et al 2005, Schwid et al 2005, Schwid et al 2007, Traboulsee et al 2008)*.
- In a meta-analysis of 5 randomized studies comparing IFNs with glatiramer acetate, there were no significant differences between IFNs and glatiramer acetate in terms of the number of patients with relapses, confirmed progression, or discontinuation due to adverse events at 24 months *(La Mantia et al 2016)*.
  - At 36 months, however, evidence from a single study suggested that relapse rates were higher in the group given IFNs than in the glatiramer acetate group (risk ratio [RR] 1.40, 95% confidence interval [CI]: 1.13 to 1.74; p = 0.002). While a MRI outcomes analysis showed that effects on newer enlarging T2 or new contrast-enhancing T1 lesions at 24 months were similar, the reduction in T2- and T1-weighted lesion volume was significantly greater in the groups given IFNs than in the glatiramer acetate groups (mean difference [MD] −0.58, 95% CI: −0.99 to −0.18; p = 0.004, and MD −0.20, 95% CI: −0.33 to −0.07; p = 0.003, respectively).
- In a network meta-analysis of 24 studies comparing IFNs and glatiramer acetate, both drugs were found to reduce the annualized relapse rate (ARR) as compared to placebo but did not differ statistically from each other (*Melendez-Torres et al 2018*). Ranking of the drugs based on SUCRA (surface under the cumulative ranking curve) indicated that glatiramer acetate 20 mg once daily had the highest probability for superiority, followed by peginterferon β-1a 125 mcg every 2 weeks.
- A meta-analysis of 6 placebo-controlled trials failed to find a significant advantage of Avonex (IFNβ-1a) 30 mcg IM once weekly compared to placebo in the number of relapse-free patients after 1 year of therapy (*Freedman et al 2008*). In contrast, other studies found Avonex (IFNβ-1a) 30 mcg IM once weekly to be comparable to the other IFNβ products in terms of relapse rate reduction, disability progression, and SPMS development *(Carra et al 2008, Limmroth et al 2007, Minagara et al 2008, Rio et al 2005, Trojano et al 2003, Trojano et al 2007)*. Moreover, IFN therapy, especially the higher dose products, is associated with the production of neutralizing antibodies (NAb), which may result in decreased

radiographic and clinical effectiveness of treatment *(Goodin et al 2007, Sorensen et al 2005)*. Exploratory post-hoc analyses of the PRISMS trial linked the development of NAb with reduced efficacy *(Alsop et al 2005)*. Development of NAb among patients (N = 368) randomized to receive Rebif (IFNβ-1a) 44 or 22 mcg SC 3 times weekly for 4 years was associated with higher relapse rates (adjusted relapse rate ratio, 1.41; 95% CI: 1.12 to 1.78; p = 0.004), a greater number of active lesions, and percentage change in T2 lesion burden from baseline on MRI scan (p < 0.001).

- In a systematic review of 40 studies of MS agents including IFNβ-1a and IFNβ-1b, the primary outcome measure was the frequency of IFN NAb *(Govindappa et al 2015)*. NAb development was most frequent with IFN β-1b, followed by IFN β-1a SC, and lowest with IFN β-1a IM. Higher doses were associated with a higher rate of NAb development.
- The CombiRx trial evaluated the combination of Copaxone (glatiramer acetate) and Avonex (IFNβ-1a IM) over 3 years. The ARR for the combination therapy (IFNβ-1a + glatiramer) was not statistically superior to the better of the 2 single treatment arms (glatiramer) (p = 0.27). The ARRs were 0.12 for the combination therapy, 0.16 for IFNβ-1a, and 0.11 for glatiramer acetate. Glatiramer acetate performed significantly better than IFNβ-1a, reducing the risk of exacerbation by 31% (p = 0.027), and IFNβ-1a + glatiramer acetate performed significantly better than IFNβ-1a, reducing the risk of exacerbation by 25% (p = 0.022). The 3 treatment groups did not show a significant difference in disability progression over 6 months. Combination therapy was superior to either monotherapy in reducing new lesion activity and accumulation of total lesion volume *(Lublin et al 2013)*.
- It is estimated that within a few years of initiating treatment, at least 30 and 15% of patients discontinue MS biological response modifiers due to perceived lack of efficacy or side effects, respectively *(Coyle 2008, Portaccio et al 2008)*. According to several observational studies, switching patients who have failed to adequately respond to initial treatment to another recommended therapy is safe and effective *(Caon et al 2006, Carra et al 2008, Zwibel 2006,)*. Patients switching to glatiramer acetate after experiencing an inadequate response to IFNβ-1a therapy had a reduction in relapse rates and disability progression. Likewise, switching to IFNβ-1a therapy after suboptimal efficacy with glatiramer acetate increased the number of relapse-free patients in 1 study *(Carra et al 2008)*. The smallest reduction in the ARR was seen in patients who had switched from one IFNβ-1a preparation to another.
- The GALA study evaluated glatiramer acetate SC 40 mg 3 times weekly compared to placebo in 1404 patients with relapsing MS over 12 months. Results demonstrated that glatiramer acetate 40 mg 3 times weekly, compared to placebo, reduced the ARR and MRI endpoints *(Khan et al 2013)*.
- A Phase 3 dose comparison study evaluated glatiramer acetate 20 mg and 40 mg each given daily in 1155 patients with MS. The primary endpoint, mean ARR, was similar in both groups: ARR = 0.33 (20 mg group) vs ARR = 0.35 (40 mg group). For patients from both groups who completed the entire 1-year treatment period, the mean ARR = 0.27 *(Comi et al 2011)*.
- The efficacy and safety of Plegridy (peginterferon β-1a) in adult patients with MS (n = 1516) were evaluated in ADVANCE, a Phase 3, multicenter, randomized, placebo-controlled trial. Eligible adult patients had RRMS with a baseline Expanded Disability Status Scale (EDSS) score ≤ 5 and 2 clinically documented relapses in the previous 3 years with at least 1 relapse in the previous 12 months. Patients were randomized to placebo or SC peginterferon β-1a 125 mcg every 2 weeks or every 4 weeks for 48 weeks. Approximately 81% of patients were treatment naïve.
  - At week 48, ARRs were significantly lower in the peginterferon β-1a every 2 week group (ARR = 0.256; p = 0.0007) and peginterferon β-1a every 4 week group (ARR = 0.288; p = 0.0114) compared to placebo (ARR = 0.397).
  - There were also significant differences between the peginterferon β-1a every 2 weeks and every 4 weeks groups compared to placebo in the proportion of patients with relapse at week 48 (p = 0.0003 and p = 0.02, respectively). The proportions of patients with 12 weeks of sustained disability progression at the end of the 48 week study period were significantly lower in the peginterferon β-1a groups (both 6.8%; p = 0.0383 for every 2 weeks group; p = 0.038 for every 4 weeks group) compared to placebo (10.5%).
  - The mean number of new or newly enlarging T2 hyperintense lesions on MRI were significantly reduced in the peginterferon β-1a every 2 weeks group compared to placebo (3.6 lesions vs 10.9 lesions, respectively; p < 0.0001). Significant beneficial effects on the mean number of Gadolinium (Gd)-enhancing lesions were also observed with peginterferon β-1a every 2 weeks compared to placebo (p < 0.0001).
  - During the 48 weeks of treatment, the most commonly reported adverse effects included influenza-like illness and injection site erythema. Discontinuations due to adverse effects were higher in the peginterferon β-1a groups compared to placebo *(Calabresi et al 2014b)*.
  - NAb to interferon β-1a were identified in < 1% of all groups after 1 year (peginterferon β-1a every 2 weeks, 4 patients; peginterferon β-1a every 4 weeks, 2 patients; placebo, 2 patients) *(Calabresi et al 2014b)*. Preliminary data on NAb development to peginterferon β-1a over 2 years showed < 1% for all groups *(White et al 2014)*.

- The ADVANCE study continued into a second year. Patients originally randomized to placebo were re-randomized to peginterferon β-1a (the "placebo-switch group"). Peginterferon β-1a patients were continued on their original assigned therapy. A total of 1332 patients entered the second year of the study. After 96 weeks, the ARR was significantly lower in the peginterferon β-1a every 2 weeks group (ARR 0.221; p = 0.0001 vs placebo-switch group; p = 0.0209 vs every 4 week regimen) compared to both the placebo-switch group (ARR 0.351) and the peginterferon β-1a every 4 week group (ARR 0.291). The peginterferon β-1a every 4 week group (ARR 0.291; p = NS vs placebo-switch group) was not significantly different from the placebo-switch group (ARR 0.351) after 96 weeks based on the intent-to-treat (ITT) analysis. Peginterferon β-1a every 2 weeks was also associated with a lower proportion of patients who had relapse and a lower proportion of patients who had disability progression. Mean number of new or newly enlarging T2-weighted hyperintense MRI lesions over 2 years was numerically lower with the peginterferon β-1a every 2 weeks group compared to the placebo-switch group *(Calabresi et al 2014b, Kieseier et al 2015)*.
- The ATTAIN study was an open-label extension of the ADVANCE study, where patients were followed for an additional 2 years (*Newsome et al 2018*). Of the original ADVANCE patients, 71% continued into the ATTAIN study, and 78% of those patients completed the extension study. The primary objective of the study was to evaluate the long-term safety of peginterferon β-1a. During the study, the common adverse events were influenza-like illness (43%), injection site erythema (41%), and headache (29%). The rate of treatment-related serious adverse events was 1%. The adjusted ARR and risk of relapse was reduced significantly with the every 2 weeks compared to the every 4 weeks dosing group (0.188 vs 0.263 and 36% vs 49%, respectively).

Gilenya (fingolimod)

- Gilenya (fingolimod) has been evaluated in 2 large, randomized controlled trials (RCTs) in adults against placebo and against Avonex (IFNβ-1a IM). In FREEDOMS, a 24-month placebo-controlled trial, fingolimod (0.5 and 1.25 mg once daily) was associated with significant reductions in ARR compared to placebo (54 and 60%, respectively; p < 0.001 for both). Moreover, fingolimod was associated with reductions in disability progression and a prolonged time to first relapse compared to placebo *(Kappos et al 2010)*. In the 12-month TRANSFORMS trial, fingolimod 0.5 and 1.25 mg once daily significantly reduced ARR by 52 and 40%, respectively, compared to IFNβ-1a 30 mcg IM once weekly (p < 0.001 for both) *(Cohen et al 2010)*. In a 12-month extension of TRANSFORMS, patients initially randomized to IFNβ-1a IM were switched to either dose of fingolimod for 12 additional months and experienced significant reductions in ARR compared to initial treatment with IFNβ-1a IM. Patients switched from IFNβ-1a IM to fingolimod experienced fewer adverse events compared to treatment with IFNβ-1a IM in the core study (86 vs 91% and 91 vs 94% for the 0.5 and 1.25 mg groups, respectively; p values not reported). Fewer patients continuing fingolimod from the core study reported adverse events in the extension period compared to the core study (72 vs 86% and 71 vs 90% for the 0.5 and 1.25 mg doses, respectively; p values not reported) *(Khatri et al 2011)*. The TRANSFORMS extension study followed patients for up to 4.5 years with results consistent with those observed in the first 12 months of the extension study; however, there was significant attrition bias with very few patients enrolled past 36 months *(Cohen et al 2015)*.
- In the FREEDOMS II study, a 24-month placebo-controlled study, fingolimod (0.5 mg and 1.25 mg) significantly reduced ARR compared to placebo (48 and 50%, respectively; both p < 0.0001) *(Calabresi et al 2014a)*. Mean percentage brain volume change was lower with both fingolimod doses compared to placebo. Fingolimod did not show a significant effect on time to disability progression at 3 months compared to placebo.
- Fingolimod has also been evaluated in pediatric patients with relapsing MS (*Chitnis et al 2018*). The PARADIGMS trial randomized patients between 10 and 17 years of age to fingolimod 0.5 mg daily (0.25 mg for patients ≤ 40 kg) or IFNβ-1a IM 30 mcg weekly for up to 2 years. Fingolimod significantly reduced ARR compared to IFNβ-1a IM (adjusted rates, 0.12 vs 0.67; relative difference of 82%; p < 0.001). Fingolimod was also associated with a 53% relative reduction in the annualized rate of new or newly enlarged lesions on MRI. However, serious adverse events occurred more frequently with fingolimod than IFNβ-1a IM (16.8% vs 6.5%, respectively).

Aubagio (teriflunomide)

- Efficacy and safety of Aubagio (teriflunomide) were evaluated in two Phase 3, double-blind, placebo-controlled, RCTs – the TEMSO trial (*O'Connor et al, 2011*) and the TOWER trial *(Confavreux et al 2014)*. In the TEMSO trial, 1088 patients with relapsing MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for a total of 108 weeks. Results demonstrated that compared to placebo, teriflunomide at both doses, reduced the ARR.
  - The percentage of patients with confirmed disability progression (CDP) was significantly lower only in the teriflunomide 14 mg group (20.2%) compared to placebo (27.3%; p = 0.03) *(O'Connor et al 2011)*.

- Teriflunomide has demonstrated beneficial effects on MRI scans in a Phase 2, randomized, double-blind, clinical trial. A total of 179 patients with MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for 36 weeks and were followed every 6 weeks with MRI scans during the treatment period. The teriflunomide groups had significant reductions in the average number of unique active lesions per MRI scan *(O'Connor et al 2006)*.
- In the TOWER trial, 1165 patients with relapsing MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for at least 48 weeks of therapy. The study ended 48 weeks after the last patient was randomized. Results demonstrated that, compared to placebo, teriflunomide 14 mg significantly reduced the ARR and the risk of sustained accumulation of disability *(Confavreux et al 2014)*.
- Teriflunomide and Rebif (IFNβ-1a SC) were compared in the 48-week TENERE study evaluating 324 patients with relapsing MS. The primary outcome, time to failure defined as a confirmed relapse or permanent discontinuation for any cause, was comparable for teriflunomide 7 mg and 14 mg and Rebif *(Vermersch et al 2014)*.

Tecfidera (dimethyl fumarate)

- Tecfidera (dimethyl fumarate) was evaluated in two Phase 3 studies: DEFINE and CONFIRM *(Gold et al 2012, Fox et al 2012, Xu et al 2015)*. DEFINE was a multicenter RCT that compared 2 dosing regimens of dimethyl fumarate (240 mg twice daily and 240 mg 3 times daily) to placebo in 1237 patients with RRMS over 96 weeks. Results demonstrated that, compared to placebo, treatment with both doses of dimethyl fumarate reduced the proportion of patients with a relapse within 2 years, the ARR, the number of lesions on MRI, and the proportion of patients with disability progression *(Gold et al 2012)*.
- CONFIRM was a multicenter RCT that compared 2 dosing regimens of dimethyl fumarate (240 mg twice daily and 240 mg 3 times daily) to placebo, with an additional, open-label study arm evaluating glatiramer acetate 20 mg SC daily. Glatiramer acetate was included as a reference comparator, but the study was not designed to test the superiority or non-inferiority of dimethyl fumarate vs glatiramer acetate. There were 1430 patients enrolled, and the trial duration was 96 weeks. Results of CONFIRM were similar to DEFINE, with the exception that there was no significant difference between groups in the likelihood of disability progression. The CONFIRM trial demonstrated that, compared to placebo, treatment with both doses of dimethyl fumarate reduced the proportion of patients with a relapse within 2 years, the ARR, and the number of lesions on MRI *(Fox et al 2012)*.

Bafiertam (monomethyl fumarate)

- The efficacy of monomethyl fumarate, the active moiety of dimethyl fumarate, is based on bioavailability studies in healthy patients comparing oral dimethyl fumarate delayed-release capsules to monomethyl fumarate delayed-release capsules. Analyses compared the blood levels of monomethyl fumarate to establish bioequivalency and support the FDA approval (*Bafiertam Prescribing Information 2020*).

Tysabri (natalizumab)

- Tysabri (natalizumab) reduced the risk of experiencing at least 1 new exacerbation at 2 years and reduced the risk of experiencing progression at 2 years *(Polman et al 2006, Pucci et al 2011, Rudick et al 2006)*. The AFFIRM trial compared natalizumab to placebo in patients with MS with less than 6 months of treatment experience with any DMT. Natalizumab reduced the ARR at 1 and 2 years compared to placebo. The cumulative probability of sustained disability progression and lesion burden on MRI were significantly reduced with natalizumab compared to placebo *(Polman et al 2006)*. In the SENTINEL trial, natalizumab was compared to placebo in patients who were receiving IFNβ-1a IM 30 mcg once weekly for at least 1 year. The combination of natalizumab plus IFNβ-1a IM resulted in a significant reduction in ARR at year 1 and 2 and significant reduction in cumulative probability of sustained disability progression at year 2. Lesion burden on MRI was also significantly reduced with the combination therapy. Two cases of PML were reported in the SENTINEL patient population resulting in the early termination of the trial *(Rudick et al 2006)*.

Lemtrada (alemtuzumab)

- The efficacy and safety of alemtuzumab were compared to Rebif (IFNβ-1a SC) in two Phase 3, open-label RCTs in patients with relapsing forms of MS – CARE-MS I and CARE-MS II (*Cohen et al 2012, Coles et al 2012)*. In the 2-year studies, patients were randomized to alemtuzumab infused for 5 consecutive days followed by a 3 consecutive day treatment course 12 months later or to Rebif (IFNβ-1a SC) 44 mcg 3 times weekly after an initial dosage titration. All patients received methylprednisolone 1 g IV for 3 consecutive days at the initiation of treatment and at month 12.
  - The CARE-MS I trial enrolled treatment-naïve patients with MS (n = 581) who were high functioning based on the requirement of a score of 3 or lower on the EDSS.

- Patients (n = 840) enrolled in the CARE-MS II trial had experienced at least 1 relapse while on IFNβ or glatiramer acetate after at least 6 months of treatment. Patients were required to have an EDSS score of ≤ 5.
- The co-primary endpoints for both trials were the relapse rate and the time to 6-month sustained accumulation of disability.
- In the CARE-MS I trial, alemtuzumab reduced the risk of relapse by 55% compared to IFNβ-1a SC ($p < 0.0001$). Relapses were reported in 22% of alemtuzumab-treated patients and 40% of IFNβ-1a SC patients over 2 years. The proportion of patients having sustained accumulation of disability over 6 months was not significantly different between alemtuzumab (8%) vs IFNβ-1a SC (11%) ($p = 0.22$).
- In the CARE-MS II trial, alemtuzumab significantly reduced the relapse rate and sustained accumulation of disability compared to IFNβ-1a SC. The relapse rate at 2 years was reduced by 49% with alemtuzumab ($p < 0.0001$). The percent of patients with sustained accumulation of disability confirmed over 6 months was 13% with alemtuzumab and 20% with IFNβ-1a SC, representing a 42% risk reduction with alemtuzumab ($p = 0.0084$).
- Both studies evaluated MRI outcomes, specifically the median percent change in T2 hyperintense lesion volume from baseline. Neither study found a significant difference between the 2 drugs for this measure.
- During extension studies of CARE-MS I and CARE-MS II, approximately 80% of patients previously treated with alemtuzumab did not require additional treatment during the first year of the extension study *(Garnock-Jones 2014)*.

- A Cochrane review by Zhang et al (2017) that compared the efficacy, tolerability, and safety of alemtuzumab vs IFNβ-1a in the treatment of RRMS identified 3 RCTs in 1694 total patients from the CARE-MS I, CARE-MS II, and CAMMS223 studies. In the alemtuzumab 12 mg/day group, the results showed statistically significant differences in reducing relapses (RR = 0.60, 95% CI: 0.52 to 0.70); preventing disease progression (RR = 0.60, 95% CI: 0.45 to 0.79); and developing new T2-weighted lesions on MRI (RR = 0.75, 95% CI: 0.61 to 0.93) after 24 and 36 months' follow-up, but found no statistically significant difference in the changes of EDSS score (MD = -0.35, 95% CI: -0.73 to 0.03). In the alemtuzumab 24 mg/day group, the results showed statistically significant differences in reducing relapses (RR = 0.38, 95% CI: 0.23 to 0.62); preventing disease progression (RR = 0.42, 95% CI: 0.21 to 0.84); and the changes of EDSS score (MD = -0.83, 95% CI: -1.17 to -0.49) after 36 months' follow-up. The most frequently reported adverse effects with alemtuzumab were infusion-associated reactions, infections, and autoimmune events.

Ocrevus (ocrelizumab)

- The Phase 3 clinical development program for ocrelizumab (ORCHESTRA) included 3 studies: OPERA I, OPERA II, and ORATORIO *(Hauser et al 2017, Montalban et al 2017)*.
  - OPERA I and OPERA II were 2 identically-designed, 96-week, Phase 3, active-controlled, double-blind, double-dummy, multicenter, parallel-group, RCTs that evaluated the efficacy and safety of ocrelizumab (600 mg administered as an IV infusion given as 2-300 mg infusions separated by 2 weeks for dose 1 and then as a single 600 mg infusion every 6 months for subsequent doses) compared with Rebif (IFNβ-1a 44 mcg SC 3 times weekly) in 1656 patients with relapsing MS *(Hauser et al 2017, ClinicalTrials.gov Web site, Ocrevus Formulary Submission Dossier 2017)*.
    - Across both studies, the majority of patients had not been treated with a DMT in the 2 years before screening (range: 71.4% to 75.3%); of those patients that had received a previous DMT as allowed by the protocol, most received IFN (18.0% to 21.0%) or glatiramer acetate (9.0% to 10.6%). Two patients previously treated with natalizumab for < 1 year were included, while 5 patients previously treated with fingolimod and 1 patient previously treated with dimethyl fumarate (both not within 6 months of screening) were also included.
    - Ocrelizumab achieved statistically significant reductions in the ARR vs Rebif (IFNβ-1a SC) across both trials (primary endpoint).
      - OPERA I (0.16 vs 0.29; 46% lower rate with ocrelizumab; $p < 0.001$)
      - OPERA II (0.16 vs 0.29; 47% lower rate; $p < 0.001$)
    - In pre-specified pooled analyses (secondary endpoints), the percentage of patients with disability progression confirmed at 12 weeks was statistically significantly lower with ocrelizumab vs Rebif (9.1% vs 13.6%; hazard ratio [HR] = 0.60, 95% CI: 0.45 to 0.81; $p < 0.001$). The results were similar for disability progression confirmed at 24 weeks: 6.9% vs 10.5%; HR = 0.60, 95% CI: 0.43 to 0.84; $p = 0.003$. The percentages of patients with disability improvement confirmed at 12 weeks were 20.7% in the ocrelizumab group vs 15.6% in the Rebif group (33% higher rate of improvement with ocrelizumab; $p = 0.02$).
    - The mean numbers of Gd-enhancing lesions per T1-weighted MRI scan were statistically significantly reduced with ocrelizumab vs Rebif (secondary endpoint).

- OPERA I: 0.02 vs 0.29 (rate ratio = 0.06, 95% CI: 0.03 to 0.10; 94% lower number of lesions with ocrelizumab; p < 0.001)
- OPERA II: 0.02 vs 0.42 (rate ratio = 0.05, 95% CI: 0.03 to 0.09; 95% lower number of lesions; p < 0.001)

▪ The most common adverse events were infusion-related reactions and infections.

o No opportunistic infections, including PML, were reported in any group over the duration of either trial.

▪ An imbalance of malignancies was observed with ocrelizumab; across both studies and through 96 weeks, neoplasms occurred in 0.5% (4/825) of ocrelizumab-treated patients vs 0.2% (2/826) of Rebif-treated patients.

▪ Among the ocrelizumab-treated patients that developed neoplasms, there were 2 cases of invasive ductal breast carcinoma, 1 case of renal-cell carcinoma, and 1 case of malignant melanoma. Rebif-treated patients with neoplasms included 1 case of mantle-cell lymphoma and 1 case of squamous-cell carcinoma in the chest.

- Between the clinical cutoff dates of the 2 trials (April 2, 2015 [OPERA I] and May 12, 2015 [OPERA II]) and June 30, 2016, 5 additional cases of neoplasm (2 cases of breast cancer, 2 cases of basal-cell skin carcinoma, and 1 case of malignant melanoma) were observed during the OL extension phase in which all continuing patients received ocrelizumab.

o ORATORIO was an event-driven, Phase 3, double-blind, multicenter, placebo-controlled, RCT evaluating the efficacy and safety of ocrelizumab (600 mg administered by IV infusion every 6 months; given as 2-300 mg infusions 2 weeks apart for each dose) compared with placebo in 732 people with PPMS *(Montalban et al 2017, ClinicalTrials.gov Web site, Ocrevus Formulary Submission Dossier 2017)*. Double-blind treatment was administered for a minimum of 5 doses (120 weeks) until the occurrence of ~253 events of disability progression in the trial cohort that was confirmed for at least 12 weeks.

▪ The majority of patients (~88%) reported no previous use of DMTs within 2 years of trial entry. The proportion of patients with Gd-enhancing lesions was similar (27.5% in the ocrelizumab group vs 24.7% in the placebo group); however, there was an imbalance in the mean number of Gd-enhancing lesions at baseline, with nearly 50% fewer lesions in the placebo group (1.21 vs 0.6) (*Ocrevus FDA Medical and Summary Reviews 2017*).

▪ For the primary endpoint, the percentages of patients with 12-week confirmed disability progression were 32.9% with ocrelizumab vs 39.3% with placebo (HR = 0.76, 95% CI: 0.59 to 0.98; relative risk reduction of 24%; p = 0.03).

▪ The percentages of patients with 24-week CDP, a secondary endpoint, were 29.6% with ocrelizumab vs 35.7% with placebo (HR=0.75, 95% CI: 0.58 to 0.98; relative risk reduction of 25%; p = 0.04).

▪ Additional secondary endpoints included changes in the timed 25-foot walk, the total volume of hyperintense brain lesions on T2-weighted MRI, and brain volume loss.

- The proportion of patients with 20% worsening of the timed 25-foot walk confirmed at 12 weeks was 49% in ocrelizumab-treated patients compared to 59% in placebo-treated patients (25% risk reduction).
- From baseline to Week 120, the total volume of hyperintense brain lesions on T2-weighted MRI decreased by 3.37% in ocrelizumab-treated patients and increased by 7.43% in placebo-treated patients (p < 0.001).
- From Weeks 24 to 120, the percentage of brain volume loss was 0.90% with ocrelizumab vs 1.09% with placebo (p = 0.02).

▪ Infusion-related reactions, upper respiratory tract infections, and oral herpes infections occurred more frequently with ocrelizumab vs placebo.

▪ Neoplasms occurred in 2.3% (11/486) of patients treated with ocrelizumab vs 0.8% (2/239) of patients who received placebo. Among the ocrelizumab-treated patients that developed neoplasms, there were 4 cases of breast cancer, 3 cases of basal-cell carcinoma, and 1 case in each of the following: endometrial adenocarcinoma, anaplastic large-cell lymphoma (mainly T cells), malignant fibrous histiocytoma, and pancreatic carcinoma. In the placebo group, 1 patient developed cervical adenocarcinoma in situ and 1 patient developed basal-cell carcinoma.

- Between the clinical cutoff date (July 24, 2015) and June 30, 2016, 2 additional cases of neoplasm (1 case of basal-cell skin carcinoma and 1 case of squamous-cell carcinoma) were detected during the open-label extension phase in which all patients received ocrelizumab.

Mayzent (siponimod)

• The Phase 3 EXPAND trial was a double-blind, parallel-group, placebo-controlled, time-to-event RCT in patients with SPMS who had evidence of disability progression in the previous 2 years (*Kappos et al 2018*).

o A total of 1651 patients were randomized to treatment with either siponimod 2 mg (n = 1105) or placebo (n = 546).

o A total of 82% of the siponimod-treated patients and 78% of placebo-treated patients completed the study.

▪ The median age of patients was 49.0 years, 95% of patients were white, and 60% were female.

- For the primary endpoint, 288 (26%) of 1096 patients receiving siponimod and 173 (32%) of 545 patients receiving placebo had a 3-month CDP (HR 0.79; 95% CI: 0.65 to 0.95; RR reduction, 21%; p = 0.013).
- Key secondary endpoints included time to 3-month confirmed worsening of at least 20% from baseline in timed 25-foot walk (T25FW) and change from baseline in T2 lesion volume on MRI. Siponimod did not show a significant difference in T25FW.
- Patients treated with siponimod had a 55% relative reduction in ARR (0.071 vs 0.16), compared to placebo (nominal p < 0.01). The absolute reduction in the ARR was 0.089 with siponimod.

Mavenclad (cladribine)

- The 96-week Phase 3 trial, CLARITY, was a double-blind, 3-arm, placebo-controlled, multicenter RCT to evaluate the safety and efficacy of oral cladribine in 1326 patients with RRMS (*Giovannoni et al 2010*, *Giovannoni 2017*).
  - Patients were required to have at least 1 relapse in the previous 12 months. The median patient age was 39 years and the female-to-male ratio was 2:1. The mean duration of MS prior to study reenrollment was 8.7 years.
  - Patients were randomized to receive either placebo (n = 437), or a cumulative oral dose of cladribine 3.5 mg/kg (n = 433) or 5.25 mg/kg (n = 456) over the 96-week study period in 2 treatment courses.
  - The primary outcome was ARR:
    - ARRs at 96 weeks were reduced in both cladribine treatment groups vs placebo (0.14, 0.15, and 0.33 in the 3.5 mg/kg, 5.25 mg/kg and placebo groups, respectively; each p < 0.001).
  - A significantly higher percentage of patients remained relapse-free at 96 weeks in both cladribine treatment groups vs placebo; a total of 79.7% and 78.9% of patients in the 3.5 mg/kg and 5.25 mg/kg groups, respectively, were relapse free vs 60.9% in the placebo group (each p < 0.001 vs placebo).
  - Cladribine 3.5 mg/kg significantly lowered the ARR vs the 5.25 mg/kg treatment group.

Vumerity (diroximel fumarate)

- The efficacy of diroximel fumarate was established through bioavailability studies in patients with relapsing forms of MS and healthy subjects comparing oral dimethyl fumarate to diroximel fumarate (*Vumerity Prescribing Information 2020*).
- In a Phase 3, open-label, long-term safety study, 696 patients with RRMS (EVOLVE-MS-1) were administered diroximel fumarate 462 mg twice daily for up to 96 weeks (*Palte et al 2019*). Interim results revealed that GI treatment-emergent adverse events occurred in 215 (30.9%) of patients; the vast majority of these events (207 [96%]) were mild or moderate in severity. Gastrointestinal events occurred early in therapy, resolved (88.8%; 191/215), and were of short duration (median 7.5 days) in most patients. Discontinuation of treatment due to a GI treatment-emergent adverse event occurred in < 1% of patients.
- Topline results from the randomized, double-blind, 5-week, Phase 3, EVOLVE-MS-2 study also demonstrated significantly improved GI tolerability with diroximel fumarate vs dimethyl fumarate in 506 patients with RRMS (*Selmaj et al 2019*). Patients were randomized to diroximel fumarate 462 mg twice daily or dimethyl fumarate 240 mg twice daily. 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) rating scale. Results revealed that patients treated with diroximel fumarate self-reported significantly fewer days of key GI symptoms with intensity scores ≥ 2 as compared to dimethyl fumarate (p = 0.0003). The most commonly reported adverse events for both groups were flushing, diarrhea, and nausea.

Zeposia (ozanimod)

- The efficacy and safety of ozanimod were compared to Avonex (IFNβ-1a IM) in two multicenter, Phase 3, double-blind, double-dummy RCTs in patients with relapsing forms of MS– SUNBEAM and RADIANCE (*Comi et al 2019, Cohen et al 2019)*. In the studies, which were conducted over a minimum of 12 months, patients were randomized 1:1:1 to oral ozanimod 0.5 mg daily, oral ozanimod 1 mg daily, or Avonex (IFNβ-1a) 30 mcg IM once weekly. Patients randomized to ozanimod received a placebo IM injection once weekly, and those randomized to IFN received placebo capsules once daily.
  - All patients received an initial 7-day dose escalation of ozanimod or placebo prior to receiving their assigned dose on day 8. Prophylactic administration of acetaminophen or ibuprofen was recommended 1 hour before each IFN or placebo injection and every 6 hours for 24 hours after the injection.
  - Patients in both trials (n = 1346 for SUNBEAM and n = 1320 for RADIANCE) had an EDSS score of ≤ 5, and a history of at least 1 relapse within 12 months prior to screening or 1 relapse within 24 months in addition to at least 1 Gd-enhancing lesion within 12 months prior to screening. The primary endpoint in both trials was the ARR.

- In the SUNBEAM, the ARR was 0.18 (95% CI: 0.14 to 0.24) for ozanimod 1 mg, 0.24 (95% CI: 0.19 to 0.31) for ozanimod 0.5 mg, and 0.35 (95% CI: 0.28 to 0.44) for IFNβ-1a. Significant reductions in ARR were observed compared to IFNβ-1a with both ozanimod 1 mg (rate ratio, 0.52; 95% CI: 0.41 to 0.66; p < 0.0001) and ozanimod 0.5 mg (rate ratio, 0.69; 95% CI: 0.55 to 0.86; p = 0.0013).
- In the RADIANCE trial, adjusted ARRs were found to be 0.17 (95% CI: 0.14 to 0.21) for ozanimod 1 mg, 0.22 (95% CI: 0.18 to 0.26) for ozanimod 0.5 mg, and 0.28 (95% CI: 0.23 to 0.32) for IFNβ-1a. The rate ratios were significant when comparing ozanimod 1 mg (rate ratio, 0.62; 95% CI: 0.51 to 0.77; p < 0.0001) and ozanimod 0.5 mg (rate ratio, 0.79; 95% CI: 0.65 to 0.96; p = 0.0167) to IFNβ-1a.
- Clinically significant evidence of bradycardia, second-, or third-degree heart block was not noted after administration of the first dose in either trial.

Symptomatic MS

- Despite the demonstrated efficacy of DMTs, for many patients there is little evidence of their effect on quality of life (QOL) in general or symptom management in particular. Impaired mobility contributes to direct and indirect costs *(Miravelle et al 2011)*.
  - Ampyra (dalfampridine) is the only FDA-approved agent for the symptomatic treatment of impaired mobility in patients with MS. Improvement of walking ability with dalfampridine was demonstrated in two 14-week, double-blind, Phase 3, RCTs of 540 patients of all MS types. Compared to placebo, dalfampridine significantly improved the walking speed by about 25% in approximately one-third of MS patients as measured by the T25FW *(Goodman et al 2009, Jensen et al 2014, Ruck et al 2014)*.
  - However, questions have been raised regarding the cost-effectiveness of dalfampridine, and whether treatment leads to a long-term clinically meaningful therapeutic benefit. To address the benefit of long-term therapy with dalfampridine, an open-label, observational study of 52 MS patients with impaired mobility was conducted. Results demonstrated that about 60% of patients were still on treatment after 9 to 12 months. Two weeks after treatment initiation, significant ameliorations could be found for T25FW, maximum walking distance, as well as motoric and cognitive fatigue, which persisted after 9 to 12 months *(Ruck et al 2014)*.

Clinically Isolated Syndrome (CIS)

- IFNs, Copaxone (glatiramer acetate) and Aubagio (teriflunomide) have evidence supporting a significant delay in the time to development of a second exacerbation, compared to placebo, in patients with an isolated demyelinating event.
  - In the PRECISE trial, glatiramer acetate significantly reduced the risk of converting to a CDMS diagnosis by 45% compared to placebo in patients with CIS (p = 0.005). In addition, the time for 25% of patients to convert to CDMS was significantly prolonged with glatiramer acetate compared to placebo (722 vs 336 days; p = 0.0041) *(Comi et al 2009)*. In the 2 year, open-label extension phase of PRECISE, early initiation of glatiramer acetate demonstrated a 41% reduced risk of CDMS compared to delayed glatiramer acetate (HR: 0.59; 95% CI: 0.44 to 0.8; p = 0.0005). Over the 2-year extension, the baseline-adjusted proportions of patients who developed CDMS were 29.4% and 46.5% for the early and late initiation treatment groups (odds ratio [OR]: 0.48; 95% CI: 0.33 to 0.7; p = 0.0002) *(Comi et al 2012)*.
  - A meta-analysis of randomized, double-blind, placebo-controlled trials in patients with CIS found a significantly lower risk of CDMS with IFN therapy compared to placebo (p < 0.0001) *(Clerico et al 2008)*. A 10-year, multicenter, randomized clinical trial with IFNβ-1a IM demonstrated that immediate initiation of therapy in patients with CIS reduced the risk for relapses over 10 years, but it was not associated with improved disability outcomes compared to a control group that also initiated therapy relatively early in the disease *(Kinkel et al 2012)*. Over the 10-year study, the drop-out rate was significant. Similar results were observed with IFNβ-1b (BENEFIT study) over an 8-year observation period. Patients who received treatment early had a lower overall ARR compared to those patients who delayed treatment *(Kappos et al 2007, Edan et al 2014)*. In the first 3 years of BENEFIT, early treatment with IFNβ-1b reduced the risk for progression of disability by 40% compared to delayed treatment (16% vs 25%, respectively; HR = 0.6; 95% CI: 0.39 to 0.92; p = 0.022).
  - A 2018 systematic review and network meta-analysis of RCTs was conducted to assess the potential short- and long-term benefits of treatment with IFN-β or glatiramer acetate in patients with CIS (*Armoiry et al 2018)*. The review identified 5 primary RCTs that assessed the time to CDMS in patients with CIS treated with IFN-β or glatiramer acetate vs placebo. They found that all drugs reduced the time to CDMS when compared with placebo, with a pooled HR of 0.51 (95% CI: 0.44 to 0.61) and low heterogeneity, and there was no evidence that indicated that 1 active treatment was superior to another when compared indirectly. The authors noted that there was insufficient

information to rate the risk of selection bias, 4 of the 5 studies were at high risk of performance bias, and 1 study was rated to have a high risk for attrition bias. Four of the trials had open-label extension studies performed over 5 to 10 years, all of which indicated that early DMT therapy (regardless of agent) led to an increase in time to CDMS when compared with placebo (HR = 0.64, 95% CI: 0.55 to 0.74; low heterogeneity). These results should be taken with caution; however, as all of the open-label extension arms were at a high risk for attrition bias and had large losses to follow-up noted.

- The TOPIC study enrolled 618 patients with CIS and found teriflunomide 7 and 14 mg doses reduced the risk of relapse defining CDMS compared to placebo *(Miller et al 2014)*. Teriflunomide 14 mg reduced the risk of conversion to CDMS by 42.6% compared to placebo (HR, 0.574; 95% CI: 0.379 to 0.869; p = 0.0087) whereas teriflunomide 7 mg reduced the conversion to CDMS by 37.2% compared to placebo (HR, 0.628; 95% CI: 0.416 to 0.949; p = 0.0271).

Progressive MS

- Limited treatment options are available for patients with non-active SPMS and PPMS. Mitoxantrone is FDA-approved for treating SPMS, while ocrelizumab has been specifically approved for the treatment of PPMS (and relapsing forms of MS).
- Mitoxantrone was shown to reduce the clinical relapse rate and disease progression in aggressive RRMS, SPMS, and PRMS *(Hartung et al 2002, Krapf et al 2005)*. For MRI outcome measures, mitoxantrone was not statistically significantly different than placebo at month 12 or 24 for the total number of MRI scans with positive Gd-enhancement or at month 12 for the number of lesions on T2-weighted MRI. However, the baseline MRI lesion number and characteristics were different among the groups *(Krapf et al 2005)*. In 2010, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology evaluated all published data, including cohort data, for mitoxantrone. An evaluation of efficacy found that mitoxantrone is probably effective in modestly reducing clinical attack rate, MRI activity, and disease progression. A confirmatory trial is necessary before widespread adoption of mitoxantrone for DMT for MS can be made in light of the risks of cardiotoxicity and treatment-related leukemia *(Marriott et al 2010)*.
- The results of studies with the other agents for MS have failed to consistently demonstrate a benefit in progressive forms of MS. In the PROMISE trial, glatiramer acetate was no more effective than placebo in delaying the time to accumulated disability for patients with PPMS *(Wolinsky et al 2007)*. Results from the ASCEND trial, evaluating natalizumab in SPMS, found no significant difference in the rate of confirmed disability progression compared to placebo (*Kapoor et al 2018*).
- Several IFN trials in this population have yielded conflicting results *(Rizvi et al 2004)*. A systematic analysis evaluated 5 clinical trials (N = 3082) of IFNβ compared to placebo in the treatment of SPMS. In 4 trials with the primary outcome of sustained disability progression at 3 or 6 months, IFNβ demonstrated no benefit. The risk ratio for sustained progression with IFNβ was 0.98 (95% CI: 0.82 to 1.16; p = 0.79); however, between-study heterogeneity was high (I^2 = 57%) *(La Mantia et al 2013)*.

Timing of DMT initiation

- A 2017 systematic review by Merkel et al (2017) evaluated the effect of high-efficacy immunotherapies (ie, fingolimod, natalizumab, alemtuzumab) at different stages of MS. Twelve publications (9 RCTs + 3 observational studies) were identified as reporting information relevant to the outcomes of early vs delayed initiation of high-efficacy DMTs for RRMS. A number of these studies suggested that earlier commencement of high-efficacy DMTs resulted in more effective control of relapse activity than their later initiation. The evidence regarding the effect of the timing of high-efficacy therapies on disability outcomes was conflicting; additional data are required to answer this question.

Decisions to discontinue DMTs in MS

- Patients with RRMS eventually progress to SPMS. Patients experience worsening disability with or without relapses. Current therapies focus on relapsing forms of MS and are not indicated for non-active SPMS. The decision to discontinue DMTs has not been well studied. The Agency for Healthcare Research and Quality (AHRQ) published a comparative effectiveness review evaluating the decision dilemmas surrounding discontinuation of MS therapies in the setting of progressive disease and pregnancy *(Butler et al 2015)*. No studies directly assess continued therapy vs discontinued therapy for MS in comparable populations. Based on a low strength of evidence, long-term all-cause survival is higher for treatment-naïve MS patients who did not delay starting IFNβ-1b by 2 years and used DMT for a longer duration than those who delayed therapy. Very little evidence is available about the benefits and risks of discontinuation of therapy for MS in women who desire pregnancy (*Rae-Grant et al 2018*).

Meta-Analyses

- A 2017 systematic review conducted by the Institute for Clinical and Economic Review (ICER) included ocrelizumab in a comparative efficacy analysis with other DMTs used in the treatment of MS.
  - Network meta-analyses demonstrated that for the treatment of RRMS, alemtuzumab, natalizumab, and ocrelizumab (in that order) were the most effective DMTs for reducing ARRs (~70% reduction vs placebo).
  - Ocrelizumab and alemtuzumab had the greatest reductions in disability progression (53% to 58% reduction vs placebo, respectively), closely followed by natalizumab (44%).
- A systematic review that identified 28 RCTs found that the magnitude of ARR reduction varied between 15 to 36% for all IFNβ products, glatiramer acetate, and teriflunomide; and from 50 to 69% for alemtuzumab, dimethyl fumarate, fingolimod, and natalizumab. The risk of 3-month disability progression was reduced by 19 to 28% with IFNβ products, glatiramer acetate, fingolimod, and teriflunomide; by 38 to 45% for peginterferon IFNβ, dimethyl fumarate, and natalizumab; and by 68% with alemtuzumab *(Fogarty et al 2016)*.
- A total of 39 RCTs evaluating 1 of 15 treatments for MS were analyzed for benefits and acceptability in 25,113 patients with RRMS *(Tramacere et al 2015)*. Drugs included were IFNβ-1b, IFNβ-1a (IM and SC), glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, peginterferon IFNβ-1a, azathioprine, and immunoglobulins. Investigational agents, daclizumab and laquinimod, were also included. The studies had a median duration of 24 months with 60% of studies being placebo-controlled. The network meta-analysis evaluated the recurrence of relapses and disability progression.
  - Relapses: alemtuzumab, mitoxantrone, natalizumab, and fingolimod were reported to have greater treatment benefit compared to placebo. Over 12 months (29 studies; N = 17,897):
    - alemtuzumab: RR = 0.40, 95% CI: 0.31 to 0.51; moderate quality evidence
    - mitoxantrone: RR = 0.40, 95% CI: 0.20 to 0.76; low quality evidence
    - natalizumab: RR = 0.56, 95% CI: 0.43 to 0.73; high quality evidence
    - fingolimod: RR = 0.63, 95% CI: 0.53 to 0.74; low quality evidence
    - dimethyl fumarate: RR = 0.78, 95% CI: 0.65 to 0.93; moderate quality evidence
    - daclizumab (no longer on the market): RR = 0.79, 95% CI: 0.61 to 1.02; moderate quality evidence
    - glatiramer acetate: RR = 0.80, 95% CI: 0.68 to 0.93; moderate quality evidence
  - Relapses over 24 months vs placebo (26 studies; N = 16,800):
    - alemtuzumab: RR = 0.46, 95% CI: 0.38 to 0.55; moderate quality evidence
    - mitoxantrone: RR = 0.47, 95% CI: 0.27 to 0.81; very low quality evidence
    - natalizumab: RR = 0.56, 95% CI: 0.47 to 0.66; high quality evidence
    - fingolimod: RR = 0.72, 95% CI: 0.64 to 0.81; moderate quality evidence
  - Disability worsening over 24 months vs placebo (26 studies; N = 16,800):
    - mitoxantrone: RR = 0.20, 95% CI: 0.05 to 0.84; low quality evidence
    - alemtuzumab: RR = 0.35, 95% CI: 0.26 to 0.48; low quality evidence
    - natalizumab: RR = 0.64, 95% CI: 0.49 to 0.85; moderate quality evidence
  - Relapses and disability worsening over 36 months were only tested in 2 studies (CombiRx and CAMMS223). Both studies had a high risk of bias.
  - Acceptability: Higher rates of withdrawal due to adverse events compared to placebo over 12 months were reported for teriflunomide (RR = 2.24, 95% CI: 1.5 to 3.34); peginterferon beta-1a (RR = 2.8, 95% CI: 1.39 to 5.64); Avonex (RR = 4.36, 95% CI: 1.98 to 9.6); Rebif (RR = 4.83, 95% CI: 2.59 to 9); and fingolimod (RR = 8.26, 95% CI: 3.25 to 20.97).
  - Over 24 months, only fingolimod had a significantly higher proportion of participants who withdrew due to any adverse event (RR vs placebo = 1.69, 95% CI: 1.32 to 2.17).
    - mitoxantrone: RR = 9.82, 95% CI: 0.54 to 168.84
    - natalizumab: RR = 1.53, 95% CI: 0.93 to 2.53
    - alemtuzumab: RR = 0.72, 95% CI: 0.32 to 1.61
- Filippini et al (2013) conducted a Cochrane review of 44 RCTs on the relative effectiveness and acceptability of DMTs and immunosuppressants in patients with either RRMS or progressive MS (N = 17,401).
  - On the basis of high quality evidence, natalizumab and Rebif were superior to all other treatments for preventing clinical relapses in the short-term (24 months) in RRMS compared to placebo (OR = 0.32, 95% CI: 0.24 to 0.43; OR = 0.45, 95% CI: 0.28 to 0.71, respectively); they were also more effective than Avonex (OR = 0.28, 95% CI: 0.22 to 0.36; OR = 0.19, 95% CI: 0.06 to 0.6, respectively).

- Based on moderate quality evidence, natalizumab and Rebif decreased the odds of patients with RRMS having disability progression in the short-term, with an absolute reduction of 14% and 10%, respectively, vs placebo.
- Natalizumab and Betaseron were significantly more effective (OR = 0.62, 95% CI: 0.49 to 0.78; OR = 0.35, 95% CI: 0.17 to 0.7, respectively) than Avonex in reducing the number of patients with RRMS who had progression at 2 years of follow-up, and confidence in this result was graded as moderate.
- The lack of convincing efficacy data showed that Avonex, IV immunoglobulins (IVIG), cyclophosphamide, and long-term corticosteroids have an unfavorable benefit-risk balance in RRMS.

- The Canadian Agency for Drugs and Technologies in Health (CADTH) conducted a systematic review of 30 RCTs to assess the comparative clinical- and cost-effectiveness of drug therapies for the treatment of RRMS (N = 16,998) (*CADTH 2013).* Results suggested that all active treatments produce statistically significant reductions in ARR compared with no treatment, and that there were clear between-treatment differences.
  - Compared with no treatment, reductions in the ARR were approximately 70% for natalizumab and alemtuzumab, 50% for fingolimod or dimethyl fumarate, and 30% for SC IFNs, glatiramer acetate, or teriflunomide.
  - Among active comparisons, ARRs were lower for Betaseron (0.69, 95% CI: 0.54 to 0.87); Rebif (0.76, 95% CI: 0.59 to 0.98); and fingolimod (0.49, 95% CI: 0.38 to 0.63) compared with Avonex. In addition, ARRs were statistically lower for dimethyl fumarate (0.76, 95% CI: 0.62 to 0.93) compared with glatiramer acetate.
  - Compared with placebo, all active treatments exhibited a lower risk of sustained disability progression, but results were only statistically significant for Avonex, Rebif, natalizumab, fingolimod, teriflunomide, and dimethyl fumarate; RR (95% CI) for these agents ranged from 0.59 (95% CI: 0.46 to 0.75) for natalizumab to 0.74 (95% CI: 0.57 to 0.96) for teriflunomide. Between-treatment differences were less apparent.
  - Among active comparisons, the risk of sustained disability progression was statistically lower for alemtuzumab (0.59, 95% CI: 0.40 to 0.86) compared with Rebif, and for Betaseron (0.44, 95% CI: 0.2 to 0.80) compared with Avonex.
  - Among active comparisons, MRI findings were more favorable for alemtuzumab compared with Rebif, and more favorable for all 3 of fingolimod, Betaseron, and Rebif compared with Avonex. Compared with glatiramer acetate, Tecfidera resulted in a lower mean number of T2 lesions, but the mean number of Gd-enhancing lesions was not statistically different between these 2 treatments.
  - The incidence of serious adverse events and treatment discontinuations did not differ significantly between treatments in the majority of trials, except for a higher incidence of treatment discontinuation for Rebif compared to placebo and alemtuzumab.
- Hamidi et al (2018) conducted a systematic review and network meta-analysis of 37 studies including 26 RCTs from a health technology assessment (HTA) report and 11 supplemental RCTs published after the HTA. Eleven agents, including dimethyl fumarate, teriflunomide, IFNs, peginterferon, glatiramer acetate, natalizumab, fingolimod, and alemtuzumab were included and were compared to either placebo or any drug treatment in patients of varying treatment experience levels. Key findings from the network meta-analysis include:
  - Alemtuzumab 12 mg had the highest probability of preventing annual relapses (RR = 0.29, 95% CI: 0.23 to 0.35; high quality evidence).
  - Alemtuzumab 24 mg (RR = 0.36, 95% CI: 0.16 to 0.7; low quality evidence) and alemtuzumab 12 mg (RR = 0.40, 95% CI: 0.27 to 0.60; very low quality evidence) were the most effective against progression of disability.
  - Dimethyl fumarate 240 mg and fingolimod 0.5 mg and 1.25 mg were more effective treatments when considering annual relapse and disability progression:
    - Annual relapse:
      - Dimethyl fumarate 240 mg twice daily: RR = 0.5, 95% CI: 0.42 to 0.6; high quality evidence
      - Fingolimod 0.5 mg: RR = 0.46, 95% CI: 0.39 to 0.54; high quality evidence
      - Fingolimod 1.25 mg: RR = 0.45, 95% CI: 0.39 to 0.53; high quality evidence
    - Disability progression:
      - Dimethyl fumarate 240 mg twice daily: RR = 0.65, 95% CI: 0.49 to 0.85; high quality evidence
      - Fingolimod 0.5 mg: RR = 0.71, 95% CI: 0.55 to 0.90; high quality evidence
      - Fingolimod 1.25 mg: RR = 0.71, 95% CI: 0.56 to 0.90; high quality evidence
  - Withdrawal due to adverse events was difficult to assess due to the low quality of available evidence, however, the authors determined that:
    - Fingolimod 1.25 mg (RR = 2.21, 95% CI: 1.42 to 2.5; moderate quality evidence), and Rebif 44 mcg (RR = 2.21, 95% CI: 1.29 to 3.97; low quality evidence) were associated with higher withdrawals due to adverse events when compared with other treatment options.

- Alemtuzumab 24 mg (mean difference = -0.91; 95% CI: -1.48 to -0.40), and 12 mg (mean difference = -0.6; 95% CI: -1.02 to -0.24) were more effective than other therapies in lowering the EDSS.
- No treatments were found to significantly increase serious adverse events; peginterferon β-1a was associated with more adverse events overall when compared with other medications (RR = 1.66, 95% CI: 1.21 to 2.28).
- None of the 11 agents studied were associated with a statistically significantly higher risk of mortality when compared to placebo.

- A Bayesian network meta-analysis evaluating DMTs for RRMS ranked the most effective therapies based on SUCRA analysis (*Lucchetta et al 2018*). A total of 33 studies were included in the analysis. For the ARR, alemtuzumab (96% probability), natalizumab (96%), and ocrelizumab (85%) were determined to be the most effective therapies (high-quality evidence).
- A meta-analysis of randomized controlled trials was conducted to evaluate the efficacy and safety of teriflunomide in reducing the frequency of relapses and progression of physical disability in patients with relapsing multiple sclerosis (*Xu et al 2016*). The results showed that teriflunomide (7 and 14 mg) reduced the ARR and teriflunomide 14 mg decreased the disability progression in comparison to placebo (RR = 0.69, 95% CI: 0.55 to 0.87).

CLINICAL GUIDELINES

- The American Academy of Neurology (AAN) performed a systematic review that included 20 Cochrane reviews and 73 additional articles in order to assess the available evidence on initiation, switching, and stopping DMTs in patients with MS (*Rae Grant et al 2018[a]*). The results of the systematic review were used to assist in formulating updated AAN treatment guidelines (*Rae Grant et al 2018[b]*). The main recommendations were as follows:
  - Starting DMT
    - Clinicians should discuss the benefits and risks of DMTs for people with a single clinical demyelinating event with 2 or more brain lesions that have imaging characteristics consistent with MS (Level B). After discussing the risks and benefits, clinicians should prescribe DMTs to people with a single clinical demyelinating event and 2 or more brain lesions characteristic of MS who decide they want this therapy. (Level B)
    - Clinicians should offer DMTs to people with relapsing forms of MS with recent clinical relapses or MRI activity. (Level B)
    - Clinicians should monitor the reproductive plans of women with MS and counsel regarding reproductive risks and use of birth control during DMT in women of childbearing potential who have MS. (Level B)
    - Clinicians should counsel men with MS on their reproductive plans regarding treatment implications before initiating treatment with teriflunomide. (Level B)
    - Because of the high frequency of severe adverse events, clinicians should not prescribe mitoxantrone to people with MS unless the potential therapeutic benefits greatly outweigh the risks. (Level B)
    - Clinicians should prescribe alemtuzumab, fingolimod, or natalizumab for people with highly active MS. (Level B)
    - Clinicians may initiate natalizumab treatment in people with MS with positive anti-JCV antibody indices above 0.9 only when there is a reasonable chance of benefit compared with the low but serious risk of PML. (Level C)
    - Clinicians should offer ocrelizumab to people with PPMS who are likely to benefit from this therapy unless there are risks of treatment that outweigh the benefits. (Level B)
  - Switching DMTs
    - Clinicians should discuss switching from one DMT to another in people with MS who have been using a DMT long enough for the treatment to take full effect and are adherent to their therapy when they experience 1 or more relapses, 2 or more unequivocally new MRI-detected lesions, or increased disability on examination, over a 1-year period of using a DMT. (Level B)
    - Clinicians should evaluate the degree of disease activity, adherence, adverse event profiles, and mechanism of action of DMTs when switching DMTs in people with MS with breakthrough disease activity during DMT use. (Level B)
    - Clinicians should discuss a change to non-injectable or less frequently injected DMTs in people with MS who report intolerable discomfort with the injections or in those who report injection fatigue on injectable DMTs. (Level B)
    - Clinicians should inquire about medication adverse events with people with MS who are taking a DMT and attempt to manage these adverse events, as appropriate (Level B). Clinicians should discuss a medication switch with people with MS for whom these adverse events negatively influence adherence. (Level B)
    - Clinicians should monitor laboratory abnormalities found on requisite laboratory surveillance (as outlined in the medication's package insert) in people with MS who are using a DMT (Level B). Clinicians should discuss switching

DMTs or reducing dosage or frequency (where there are data on different doses [eg, interferons, teriflunomide]) when there are persistent laboratory abnormalities. (Level B)
- Clinicians should counsel people with MS considering natalizumab, fingolimod, ocrelizumab, and dimethyl fumarate about the PML risk associated with these agents (Level B). Clinicians should discuss switching to a DMT with a lower PML risk with people with MS taking natalizumab who are or who become JCV antibody–positive, especially with an index of above 0.9 while on therapy. (Level B)
- Clinicians should counsel that new DMTs without long-term safety data have an undefined risk of malignancy and infection for people with MS starting or using new DMTs (Level B). If a patient with MS develops a malignancy while using a DMT, clinicians should promptly discuss switching to an alternate DMT, especially for people with MS using fingolimod, teriflunomide, alemtuzumab, or dimethyl fumarate (Level B). People with MS with serious infections potentially linked to their DMTs should switch DMTs (does not pertain to PML management in people with MS using DMT). (Level B)
- Clinicians should check for natalizumab antibodies in people with MS who have infusion reactions before subsequent infusions, or in people with MS who experience breakthrough disease activity with natalizumab use (Level B). Clinicians should switch DMTs in people with MS who have persistent natalizumab antibodies. (Level B)
- Physicians must counsel people with MS considering natalizumab discontinuation that there is an increased risk of MS relapse or MRI-detected disease activity within 6 months of discontinuation (Level A). Physicians and people with MS choosing to switch from natalizumab to fingolimod should initiate treatment within 8 to 12 weeks after natalizumab discontinuation (for reasons other than pregnancy or pregnancy planning) to diminish the return of disease activity. (Level B)
- Clinicians should counsel women to stop their DMT before conception for planned pregnancies unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy (Level B). Clinicians should discontinue DMTs during pregnancy if accidental exposure occurs, unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy (Level B). Clinicians should not initiate DMTs during pregnancy unless the risk of MS activity during pregnancy outweighs the risk associated with the specific DMT during pregnancy. (Level B)

  - Stopping DMTs
    - In people with RRMS who are stable on DMT and want to discontinue therapy, clinicians should counsel people regarding the need for ongoing follow-up and periodic reevaluation of the decision to discontinue DMT (Level B). Clinicians should advocate that people with MS who are stable (that is, those with no relapses, no disability progression, and stable imaging) on DMT should continue their current DMT unless the patient and physician decide a trial off therapy is warranted. (Level B)
    - Clinicians should assess the likelihood of future relapse in individuals with SPMS by assessing patient age, disease duration, relapse history, and MRI-detected activity (eg, frequency, severity, time since most recent relapse or gadolinium-enhanced lesion) (Level B). Clinicians may advise discontinuation of DMT in people with SPMS who do not have ongoing relapses (or gadolinium enhanced lesions on MRI activity) and have not been ambulatory (EDSS 7 or greater) for at least 2 years. (Level C)
    - Clinicians should review the associated risks of continuing DMTs vs those of stopping DMTs in people with CIS using DMTs who have not been diagnosed with MS. (Level B)

- In September 2019, the MS Coalition published an update to its consensus paper on the principles and current evidence concerning the use of DMTs in MS *(MS Coalition 2019)*. Major recommendations included the following:
  - Initiation of treatment with an FDA-approved DMT is recommended as soon as possible following a diagnosis of relapsing MS, regardless of the person's age. Relapsing MS includes CIS, RRMS, and active SPMS with clinical relapses or inflammatory activity on MRI.
  - Clinicians should consider prescribing a high efficacy medication such as alemtuzumab, cladribine, fingolimod, ocrelizumab or natalizumab for newly diagnosed individuals with highly active MS.
  - Clinicians should also consider prescribing a high efficacy medication for patients who have breakthrough activity on another DMT, regardless of the number of previously used agents.
  - Treatment with a given DMT should be continued indefinitely unless any of the following occur (in which case an alternative DMT should be considered):
    - Suboptimal treatment response as determined by the individual and his or her treating clinician
    - Intolerable side effects
    - Inadequate adherence to the treatment regimen
    - Availability of a more appropriate treatment option

    - The healthcare provider and patient determine that the benefits no longer outweigh the risks.
  - Movement from one DMT to another should occur only for medically appropriate reasons as determined by the treating clinician and patient.
  - When evidence of additional clinical or MRI activity while on treatment suggests a sub-optimal response, an alternative regimen (eg, different mechanism of action) should be considered to optimize therapeutic benefit.
  - The factors affecting choice of therapy at any point in the disease course are complex and most appropriately analyzed and addressed through a shared decision-making process between the patient and his/her treating clinician. Neither an arbitrary restriction of choice nor a mandatory escalation therapy approach is supported by data.
  - Due to significant variability in the MS population, people with MS and their treating clinicians require access to the full range of treatment options for several reasons:
    - MS clinical phenotypes may respond differently to different DMTs.
    - Different mechanisms of action allow for treatment change in the event of a sub-optimal response.
    - Potential contraindications limit options for some individuals.
    - Risk tolerance varies among people with MS and their treating clinicians.
    - Route of delivery, frequency of dosing, and side effects may affect adherence and quality of life.
    - Individual differences related to tolerability and adherence may necessitate access to different medications within the same class.
    - Pregnancy and breastfeeding limit the available options.
  - Individuals' access to treatment should not be limited by their frequency of relapses, level of disability, or personal characteristics such as age, sex, or ethnicity.
  - Absence of relapses while on treatment is a characteristic of treatment effectiveness and should not be considered a justification for discontinuation of treatment.
- Treatment should not be withheld during determination of coverage by payors as this puts the patient at risk for recurrent disease activity. The European Committee for Research and Treatment of Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) published updated guidelines in 2018 (*Montalban et al 2018*). The main recommendations reported were the following:
  - The entire spectrum of DMTs should be prescribed only in centers with adequate infrastructure to provide proper monitoring of patients, comprehensive patient assessment, detection of adverse effects, and the capacity to address adverse effects properly if they occur. (Consensus statement)
  - Offer IFN or glatiramer acetate to patients with CIS and abnormal MRI findings with lesions suggesting MS who do not fulfill full criteria for MS. (Strong)
  - Offer early treatment with DMTs in patients with active RRMS, as defined by clinical relapses and/or MRI activity (active lesions: contrast-enhancing lesions; new or unequivocally enlarging T2 lesions assessed at least annually). (Strong)
  - For active RRMS, choosing among the wide range of available drugs from the modestly to highly effective will depend on patient characteristics and comorbidity, disease severity/activity, drug safety profile, and accessibility of the drug. (Consensus statement)
  - Consider treatment with IFN in patients with active SPMS, taking into account, in discussion with the patient, the dubious efficacy, as well as the safety and tolerability profile. (Weak)
  - Consider treatment with mitoxantrone in patients with active SPMS, taking into account the efficacy and specifically the safety and tolerability profile of this agent. (Weak)
  - Consider ocrelizumab for patients with active SPMS. (Weak)
  - Consider ocrelizumab for patients with PPMS. (Weak)
  - Always consult the summary of product characteristics for dosage, special warnings, precautions, contraindications, and monitoring of side effects and potential harms. (Consensus statement)
  - Consider combining MRI with clinical measures when evaluating disease evolution in treated patients. (Weak)
  - When monitoring treatment response in patients treated with DMTs, perform standardized reference brain MRI within 6 months of treatment onset and compare the results with those of further brain MRI, typically performed 12 months after starting treatment. Adjust the timing of both MRIs, taking into account the drug's mechanism and speed of action and disease activity, including clinical and MRI measures. (Consensus statement)
  - When monitoring treatment response in patients treated with DMTs, the measurement of new or unequivocally enlarging T2 lesions is the preferred MRI method, supplemented by Gd-enhancing lesions for monitoring treatment response. Evaluation of these parameters requires high-quality standardized MRI scans and interpretation by highly qualified readers with experience in MS. (Consensus statement)

- When monitoring treatment safety in patients treated with DMTs, perform a standard reference MRI every year in patients at low risk for PML, and more frequently (3 to 6 months) in patients at high risk for PML (JC virus positivity, natalizumab treatment duration over 18 months) and in patients at high risk for PML who switch drugs at the time the current treatment is discontinued and the new treatment is started. (Consensus statement)
- Offer a more efficacious drug to patients treated with IFN or glatiramer acetate who show evidence of disease activity, assessed as recommended above. (Strong)
- When deciding on which drug to switch to, in consultation with the patient, consider patient characteristics and comorbidities, drug safety profile, and disease severity/activity. (Consensus statement)
- When treatment with a highly efficacious drug is stopped, whether due to inefficacy or safety, consider starting another highly efficacious drug. When starting the new drug, take into account disease activity (clinical and MRI; the greater the disease activity, the greater the urgency to start new treatment), the half-life and biological activity of the previous drug, and the potential for resumed disease activity or even rebound (particularly with natalizumab). (Consensus statement)
- Consider continuing a DMT if the patient is stable (clinically and on MRI) and shows no safety or tolerability issues. (Weak)
- Advise all women of childbearing potential that DMTs are not licensed during pregnancy, except glatiramer acetate 20 mg/mL. (Consensus statement)
- For women planning a pregnancy, if there is a high risk for disease reactivation, consider using IFN or glatiramer acetate until pregnancy is confirmed. In some very specific (active) cases, continuing this treatment during pregnancy could also be considered. (Weak)
- For women with persistent high disease activity, it would generally be advised to delay pregnancy. For those who still decide to become pregnant or have an unplanned pregnancy, treatment with natalizumab throughout pregnancy may be considered after full discussion of potential implications; treatment with alemtuzumab could be an alternative for planned pregnancy in very active cases provided that a 4-month interval is strictly observed from the latest infusion until conception. (Weak)

- According to the 2013 Canadian recommendations for treatment of MS, treatment decisions should be based on the level of concern for the rate and severity of relapses, degree of functional impairment due to relapses, and disability progression. First-line treatment recommendations for RRMS include IFNβ products and glatiramer acetate. Second-line therapies for RRMS include fingolimod and natalizumab *(Freedman et al 2013)*.
- The 2015 Association of British Neurologists state that all available DMTs are effective in reducing relapse rate and MRI lesion accumulation *(Scolding et al 2015)*. Evidence is less clear on the impact of DMT on long-term disability. Drugs are separated into 2 categories based on relative efficacy. Category 1 – moderate efficacy includes IFNs (including peginterferon), glatiramer acetate, teriflunomide, dimethyl fumarate, and fingolimod. Category 2 – high efficacy includes alemtuzumab and natalizumab – these drugs should be reserved for patients with very active MS.

SAFETY SUMMARY

- Warnings for IFNβ include decreased peripheral blood cell counts including leukopenia, higher rates of depression, suicide and psychotic disorders, injection site reactions, anaphylaxis, congestive heart failure (CHF), potential development of autoimmune disorders (eg, lupus erythematosus), and risk of severe hepatic injury. IFNβ (Avonex, Rebif, Betaseron, Extavia, and Plegridy) are associated with influenza-like symptoms including musculoskeletal pain, fatigue, and headache. All IFNβ products carry a warning for thrombotic microangiopathy including thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. Adverse events related to IFNβ therapy appear to be dose-related and transient.
- Glatiramer acetate is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol. Patients treated with glatiramer acetate may experience a transient, self-limited, post-injection reaction of flushing, chest pain, palpitations, tachycardia, anxiety, dyspnea, constriction of the throat, or urticaria immediately following the injection. Injection site reactions including lipoatrophy and skin necrosis have been reported. Because glatiramer acetate can modify immune response, it may interfere with immune functions. In controlled studies of glatiramer acetate 20 mg/mL, the most common adverse reactions (≥ 10% and ≥ 1.5 times higher than placebo) were injection site reactions, vasodilatation, rash, dyspnea, and chest pain. In a controlled study of glatiramer acetate 40 mg/mL, the most common adverse reactions (≥ 10% and ≥ 1.5 times higher than placebo) were injection site reactions.
- Fingolimod is contraindicated in patients with a variety of cardiac issues and those with a hypersensitivity to the product. Because of a risk for bradyarrhythmia and atrioventricular (AV) blocks, patients should be monitored during Gilenya

treatment initiation. In controlled clinical trials, first-degree AV block after the first dose occurred in 4.7% of patients receiving Gilenya and 1.6% of patients on placebo.
  - Posterior Reversible Encephalopathy Syndrome (PRES) has been reported with fingolimod. Patients with pre-existing cardiac disease may poorly tolerate fingolimod and may require additional monitoring. In clinical trials, the most common adverse reactions (incidence ≥ 10% and > placebo) were headache, liver transaminase elevation, diarrhea, cough, influenza, sinusitis, back pain, abdominal pain, and pain in extremity. If a serious infection develops, consider suspending fingolimod and reassess risks and benefits prior to re-initiation. Elimination of the drug may take up to 2 months thus, monitoring for infections should continue during this time. Do not start fingolimod in patients with an active acute or chronic infection until the infection is resolved. Life-threatening and fatal infections have been reported in patients taking fingolimod. Establish immunity to varicella zoster virus prior to therapy initiation. Vaccination against human papilloma virus (HPV) should be considered before initiating treatment with fingolimod; HPV infections including papilloma, dysplasia, warts, and HPV-related cancer have been reported in post marketing reports. Recent safety labeling changes warn of an increased risk of cutaneous malignancies, including melanoma, and lymphoma in patients treated with fingolimod. Clinically significant hepatic injury has occurred in patients treated with fingolimod in the postmarketing setting; hepatic function should be monitored prior to, during, and until 2 months after medication discontinuation. Cases of PML have occurred in the postmarketing setting, primarily in patients who were treated with fingolimod for at least 2 years. At the first sign or symptom suggestive of PML, fingolimod should be withheld and an appropriate diagnostic evaluation performed. Monitoring for signs consistent with PML on MRI may be useful to allow for an early diagnosis. Additionally, severe increases in disability after discontinuation of fingolimod have been described in post marketing reports. Relapses of MS with tumefactive demyelinating lesions on imaging have been observed both during therapy with fingolimod and after discontinuation in post marketing reports. If a severe MS relapse occurs during or after discontinuation of treatment with fingolimod, tumefactive MS should be considered, and imaging evaluation and initiation of appropriate treatment may be necessary.
- Teriflunomide is contraindicated in patients with severe hepatic impairment; pregnancy, those with a history of hypersensitivity to the medication, women of childbearing potential who are not using reliable contraception; and with concurrent use of leflunomide. Labeling includes boxed warnings regarding hepatotoxicity and teratogenicity/embryolethality that occurred in animal reproduction studies at plasma teriflunomide exposures similar to or lower than in humans. Other warnings include bone marrow effects, immunosuppression leading to potential infections, malignancy risk, interstitial lung disease, peripheral neuropathy, severe skin reactions, and elevated blood pressure. Teriflunomide has a half-life of 4 to 5 months; therefore, use of activated charcoal or cholestyramine in an 11-day regimen upon discontinuation of teriflunomide is recommended to reduce serum levels more rapidly. The most common adverse reactions (≥ 10% and ≥ 2% greater than placebo) are headache, diarrhea, nausea, alopecia, and an increase in alanine aminotransferase (ALT).
- Dimethyl fumarate, diroximel fumarate, and monomethyl fumarate are contraindicated in patients with hypersensitivity to the products or any of their excipients. Warnings include anaphylaxis and angioedema, PML, lymphopenia, and clinically significant cases of liver injury. Serious cases of herpes zoster and other opportunistic viral (eg, herpes simplex virus, West Nile virus, cytomegalovirus), fungal (eg, Candida and Aspergillus), and bacterial (eg, Nocardia, Listeria monocytogenes, *Mycobacterium tuberculosis*) infections have been reported in patients treated with dimethyl fumarate, and may occur at any time during treatment with dimethyl fumarate, diroximel fumarate, or monomethyl fumarate. Patients with signs/symptoms of any of these infections should undergo diagnostic evaluation and receive appropriate treatment; treatment with dimethyl fumarate, diroximel fumarate, or monomethyl fumarate may need to be withheld until the infection has resolved. Consider therapy interruption if severe lymphopenia for more than 6 months occurs. Cases of PML have been reported following therapy. Monitoring for signs consistent with PML on MRI may be useful to allow for an early diagnosis. Common adverse events (incidence ≥ 10% and ≥ 2% more than placebo) were flushing, abdominal pain, diarrhea, and nausea. Administration of non-enteric aspirin up to 325 mg given 30 minutes prior to each dose or a temporary dose reduction may reduce flushing. Diroximel fumarate should not be coadministered with dimethyl fumarate.
- Natalizumab has a boxed warning regarding the risk of PML. PML is an opportunistic viral infection of the brain that usually leads to death or severe disability. Due to the risk of PML, natalizumab is only available through the TOUCH® Prescribing Program, which is a restricted distribution program. Natalizumab is contraindicated in patients who have or have had PML and in patients who have had a hypersensitivity reaction. The most common adverse reactions (incidence ≥ 10% in MS) were headache, fatigue, arthralgia, urinary tract infection, lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea, and rash. Monitoring for signs consistent with PML on MRI may be useful to allow for an early diagnosis. Other warnings with natalizumab include

hypersensitivity reactions, increased risk of herpes encephalitis and meningitis, increased risk of infections (including opportunistic infections), and hepatotoxicity.

- Mitoxantrone has boxed warnings for the risk of cardiotoxicity, risk of bone marrow suppression, and secondary leukemia. Congestive heart failure, potentially fatal, may occur either during therapy with mitoxantrone or months to years after termination of therapy. The maximum cumulative lifetime dose of mitoxantrone for MS patients should not exceed 140 mg/kg/m^2. Monitoring of cardiac function is required prior to all mitoxantrone doses.
- Alemtuzumab is contraindicated in patients with human immunodeficiency virus (HIV). The boxed warning for alemtuzumab includes autoimmunity conditions (immune thrombocytopenia, autoimmune hepatitis, and anti-glomerular basement membrane disease), serious and life-threatening infusion reactions, serious and life-threatening stroke within 3 days of administration, and the possibility of an increased risk of malignancies (ie, thyroid cancer, melanoma, and lymphoproliferative disorders/lymphoma). Alemtuzumab is only available through a restricted distribution and REMS program, which requires the member, provider, pharmacy, and infusion facility to be certified. Approximately one-third of patients who received alemtuzumab in clinical trials developed thyroid disorders. The most commonly reported adverse events reported in at least 10% of alemtuzumab-treated patients and more frequently than with IFNβ-1a were rash, headache, pyrexia, nasopharyngitis, nausea, urinary tract infection, fatigue, insomnia, upper respiratory tract infection, herpes viral infection, urticaria, pruritus, thyroid disorders, fungal infection, arthralgia, pain in extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, paresthesia, dizziness, abdominal pain, flushing, and vomiting. Nearly all patients (99.9%) in clinical trials had lymphopenia following a treatment course of alemtuzumab. Alemtuzumab may also increase the risk of acute acalculous cholecystitis; in controlled clinical studies, 0.2% of alemtuzumab-treated MS patients developed acute acalculous cholecystitis, compared to 0% of patients treated with IFNβ-1a. During postmarketing use, additional cases of acute acalculous cholecystitis have been reported in alemtuzumab-treated patients. Other safety concerns within the product labeling include a warning that patients administered alemtuzumab are at risk for serious infections, including those caused by *Listeria monocytogenes,* the potential development of pneumonitis, and PML. Patients that are prescribed alemtuzumab should be counseled to avoid or appropriately heat any foods that may be a source of *Listeria*, such as deli meats and unpasteurized cheeses. Patients should also undergo tuberculosis screening according to local guidelines. With regard to PML, alemtuzumab should be withheld, and appropriate diagnostic evaluations performed, at the initial occurrence of suggestive signs or symptoms.
- The labeling of ocrelizumab does not contain any boxed warnings; however, ocrelizumab is contraindicated in patients with active hepatitis B virus (HBV) infection and in those with a history of life-threatening infusion reactions to ocrelizumab. Additional warnings for ocrelizumab concern infusion reactions, infections, and an increased risk of malignancies.
  - As of June 30, 2016, the overall incidence rate of first neoplasm among ocrelizumab-treated patients across all 3 pivotal studies and a Phase 2, dose-finding study *(Kappos et al [2011])* was 0.40 per 100 patient-years of exposure to ocrelizumab (6467 patient-years of exposure) vs 0.20 per 100 patient-years of exposure in the pooled comparator groups (2053 patient-years of exposure in groups receiving Rebif or placebo) *(Hauser et al 2017, Ocrevus Formulary Submission Dossier 2017)*.
    - Since breast cancer occurred in 6 out of 781 females treated with ocrelizumab (vs in none of 668 females treated with Rebif or placebo), the labeling of ocrelizumab additionally recommends that patients follow standard breast cancer screening guidelines.
    - In related postmarketing requirements, the FDA has asked the manufacturer to conduct a prospective, longitudinal, observational study in adult patients with relapsing MS and PPMS exposed to ocrelizumab to determine the incidence and mortality rates of breast cancer and all malignancies. All patients enrolled in the study need to be followed for a minimum of 5 years or until death following their first exposure to ocrelizumab and the protocol must specify 2 appropriate populations to which the observed incidence and mortality rates will be compared *(FDA approval letter 2017)*.
  - No cases of PML have been reported to date in any studies of ocrelizumab (*Hauser et al 2017, McGinley et al 2017, Montalban et al 2017, Ocrevus Formulary Submission Dossier 2017*).
  - In patients with relapsing MS, the most common adverse reactions with ocrelizumab (incidence ≥ 10% and greater than Rebif) were upper respiratory tract infections and infusion reactions. In patients with PPMS, the most common adverse reactions (incidence ≥ 10% and greater than placebo) were upper respiratory tract infections, infusion reactions, skin infections, and lower respiratory tract infections.
  - Live or live-attenuated vaccines should not be administered until B-cell count recovery is confirmed (as measured by CD19+ B-cells) in infants born from mothers who were exposed to ocrelizumab during pregnancy.

- Dalfampridine is contraindicated in patients with a history of seizure, moderate or severe renal impairment (CrCl ≤ 50 mL/min), and a history of hypersensitivity to dalfampridine or 4-aminopyridine. Dalfampridine may cause seizures; permanently discontinue this medication in patients who have a seizure while on treatment. Dalfampridine can also cause anaphylaxis; signs and symptoms of anaphylaxis have included respiratory compromise, urticaria, and angioedema of the throat and or tongue. Urinary tract infections (UTIs) were reported more frequently as an adverse reaction in controlled studies in patients receiving dalfampridine 10 mg twice daily (12%) as compared to placebo (8%). The most common adverse events (incidence ≥ 2% and at a rate greater than the placebo rate) for dalfampridine were UTI, insomnia, dizziness, headache, nausea, asthenia, back pain, balance disorder, MS relapse, paresthesia, nasopharyngitis, constipation, dyspepsia, and pharyngolaryngeal pain.
- Siponimod is contraindicated in patients with a cytochrome P4502C9*3/*3 genotype, presence of Mobitz type II second-degree, third degree AV block or sinus syndrome. It is also contraindicated in patients that have experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, Class III/IV heart failure, or decompensated heart failure requiring hospitalization in the past 6 months. Warnings and precautions of siponimod include an increased infection risk, macular edema, increased blood pressure, bradyarrhythmia and AV conduction delays, decline in pulmonary function, and liver injury. Mayzent may result in a transient decrease in heart rate; titration is required for treatment initiation. Consider resting heart rate with concomitant beta-blocker use; obtain cardiologist consultation before concomitant use with other drugs that decrease heart rate. Women of childbearing potential should use effective contraception during and for 10 days after stopping siponimod due to fetal risk. The most common adverse events (incidence > 10%) are headache, hypertension, and transaminase increases.
- Ozanimod is contraindicated in patients that have experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, Class III/IV heart failure, or decompensated heart failure requiring hospitalization in the past 6 months. It is also contraindicated in patients with Mobitz type II second- or third-degree atrioventricular block, sick sinus syndrome, or sinoatrial attack unless the patient has a functioning pacemaker. Use is also contraindicated in patients with severe, untreated sleep apnea and those taking a monoamine oxidase inhibitor. Warnings and precautions for ozanimod include an increased infection risk, macular edema, increased blood pressure, bradyarrhythmia and AV conduction delays, decline in pulmonary function, and liver injury. Women of childbearing potential should use effective contraception during and for 3 months after stopping ozanimod due to fetal risk. The most common adverse events (incidence > 10%) are upper respiratory tract infections and hepatic transaminase elevations. Zeposia (ozanimod) does not have a recommendation for first-dose cardiac observation like fingolimod and siponimod.
- Cladribine is contraindicated in patients with current malignancy, HIV infection, active chronic infection such as hepatitis or tuberculosis, hypersensitivity to cladribine, and in pregnant women. There is a boxed warning for potential malignancy and risk of teratogenicity. The warnings and precautions are lymphopenia, active infection, hematologic toxicity, liver injury, and graft vs host disease with blood transfusion. The most common adverse events (incidence > 20%) are upper respiratory tract infection, headache, and lymphopenia.

Table 3. Dosing and Administration*

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ampyra (dalfampridine)	Tablets	Oral	Twice daily	May be taken with or without food. Tablets should only be taken whole; do not divide, crush, chew, or dissolve. In patients with mild renal impairment (CrCl 51 to 80 mL/min), dalfampridine may reach plasma levels associated with a greater risk of seizures, and the potential benefits of dalfampridine should be carefully considered against the risk of seizures in these patients. Dalfampridine is contraindicated in patients with moderate or

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				severe renal impairment (CrCl ≤ 50 mL/min). There are no adequate and well-controlled studies of dalfampridine in pregnant women; use during pregnancy only if the benefit justifies the potential fetal risk.
Aubagio (teriflunomide)	Tablets	Oral	Once daily	May be taken with or without food. No dosage adjustment is necessary for patients with mild and moderate hepatic impairment; contraindicated in patients with severe hepatic impairment. Teriflunomide is contraindicated for use in pregnant women and in women of reproductive potential who are not using effective contraception because of the potential for fetal harm. Exclude pregnancy before the start of treatment with teriflunomide in females of reproductive potential and advise females of reproductive potential to use effective contraception during teriflunomide treatment and during an accelerated drug elimination procedure after teriflunomide treatment. Teriflunomide should be stopped and an accelerated drug elimination procedure used if the patient becomes pregnant. Teriflunomide is detected in human semen; to minimize any possible risk, men not wishing to father a child and their female partners should use effective contraception. Men wishing to father a child should discontinue use of teriflunomide and either undergo an accelerated elimination procedure or wait

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				until verification that the plasma teriflunomide concentration is less than 0.02 mg/L.
Avonex (interferon β-1a)	Injection; pen, prefilled syringe	IM	Once weekly Titration: To reduce the incidence and severity of flu-like symptoms that may occur during initiation, Avonex may be started at a dose of 7.5 mcg and the dose may be increased by 7.5 mcg each week for the next 3 weeks until the recommended dose of 30 mcg is achieved.	Following initial administration by a trained healthcare provider, Avonex may be self-administered. Rotate injection sites to minimize the likelihood of injection site reactions. Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with Avonex use. Use caution in patients with hepatic dysfunction.
Bafiertam (monomethyl fumarate)	Capsules (delayed-release)	Oral	Twice daily Titration: 95 mg twice daily for 7 days (initiation), then 190 mg twice daily (maintenance) Temporary dose reductions to 95 mg twice a day may be considered for individuals who do not tolerate the maintenance dose.	May be taken with or without food; must be swallowed whole. Do not crush, chew, or sprinkle capsule contents on food. The incidence or severity of flushing may be reduced by administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to monomethyl fumarate; studies did not show that the presence of food had an impact on the incidence of flushing with monomethyl fumarate. Obtain a complete blood cell count including lymphocyte count before initiation of therapy. Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to treatment.
Betaseron (interferon β-1b)	Injection	SC	Every other day Titration: Generally, start at 0.0625 mg (0.25 mL) every other day, and increase over a 6-week period to 0.25 mg (1 mL) every other day.	Following initial administration by a trained healthcare provider, IFNβ-1b may be self-administered. Rotate injection sites to minimize the likelihood of injection site reactions.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with IFNβ-1b use.
Copaxone (glatiramer acetate) [and Glatopa]	Injection	SC	20 mg once daily **OR** 40 mg 3 times per week at least 48 hours apart Note: The 2 strengths are not interchangeable.	Following initial administration by a trained healthcare provider, glatiramer acetate may be self-administered. Areas for SC self-injection include arms, abdomen, hips, and thighs.
Extavia (interferon β-1b)	Injection	SC	Every other day Titration: Generally, start at 0.0625 mg (0.25 mL) every other day, and increase over a 6-week period to 0.25 mg (1 mL) every other day.	Following initial administration by a trained healthcare provider, IFNβ-1b may be self-administered. Rotate injection sites to minimize the likelihood of injection site reactions. Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with IFNβ-1b use.
Gilenya (fingolimod)	Capsules	Oral	Once daily Note: Patients who initiate fingolimod and those who re-initiate treatment after discontinuation for longer than 14 days require first dose monitoring (see right).	May be taken with or without food. Approved for adults and pediatric patients 10 years of age or older. For pediatric patients ≤40 kg, a lower dose is recommended. First dose monitoring: Observe all patients for bradycardia for at least 6 hours; monitor pulse and blood pressure hourly. Electrocardiograms (ECGs) prior to dosing and at end of the observation period are required. Monitor until resolution if HR < 45 bpm in adults, < 55 bpm in pediatric patients ≥ 12 years of age, or < 60 bpm in pediatric patients 10 or 11 years of age, new onset second degree or

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				higher AV block, or if the lowest post-dose heart rate is at the end of the observation period. Monitor symptomatic bradycardia with continuous ECG until resolved. Continue overnight if intervention is required; repeat first dose monitoring for second dose. Observe patients overnight if at higher risk of symptomatic bradycardia, heart block, prolonged QTc interval, or if taking drugs with a known risk of torsades de pointes or drugs that slow heart rate or AV conduction. Fingolimod exposure is doubled in patients with severe hepatic impairment; patients with severe hepatic impairment should be closely monitored. No dose adjustment is necessary in mild-to-moderate hepatic impairment. The blood level of some fingolimod metabolites is increased (up to 13-fold) in patients with severe renal impairment; blood levels were not assessed in patients with mild or moderate renal impairment. Fingolimod may cause fetal harm when administered to a pregnant woman. Before initiation of treatment with fingolimod, females of reproductive potential should be counseled on the potential for serious risk to the fetus and the need for effective contraception during treatment and for 2 months after treatment to allow the compound to be eliminated from the body. In females planning to become pregnant, fingolimod should be stopped 2

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				months before planned conception.
Lemtrada (alemtuzumab)†	Injection	IV	**2 treatment courses** First course: 12 mg/day on 5 consecutive days Second course: 12 mg/day on 3 consecutive days 12 months after the first treatment course Subsequent course: 12 mg/day for 3 consecutive days may be administered, as needed, at least 12 months after the last dose of any prior treatment courses. Important monitoring: Complete blood count with differential (prior to treatment initiation and at monthly intervals thereafter); serum creatinine levels (prior to treatment initiation and at monthly intervals thereafter); urinalysis with urine cell counts (prior to treatment initiation and at monthly intervals thereafter); a test of thyroid function, such as thyroid stimulating hormone level (prior to treatment initiation and every 3 months thereafter); serum transaminases and total bilirubin (prior to treatment initiation and periodically thereafter) Measure the urine protein to creatinine ratio prior to treatment initiation Conduct baseline and yearly skin exams to monitor for melanoma.	Infused over 4 hours for both treatment courses; patients should be observed for infusion reactions during and for at least 2 hours after each Lemtrada infusion. Vital signs should be monitored before the infusion and periodically during the infusion. Pre-medicate with high-dose corticosteroids prior to Lemtrada infusion for the first 3 days of each treatment course. Administer antiviral agents for herpetic prophylaxis starting on the first day of alemtuzumab dosing and continuing for a minimum of 2 months after completion of Lemtrada dosing or until CD4+ lymphocyte count is more than 200 cells/microliter, whichever occurs later. Patients should complete any necessary immunizations at least 6 weeks prior to treatment with alemtuzumab.
Mavenclad (cladribine)	Tablet	Oral	Cumulative dosage of 3.5 mg/kg divided into 2 yearly treatment courses of 1.75 mg/kg per treatment course. Each treatment course is	The use of Mavenclad in patients weighing less than 40 kg has not been investigated. Mavenclad is contraindicated in pregnant women and in

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			divided into 2 treatment cycles: • First course/first cycle: start anytime • First course/second cycle: administer 23 to 27 days after the last dose of first course/first cycle. • Second course/first cycle: administer at least 43 weeks after the last dose of first course/second cycle. • Second course/second cycle: administer 23 to 27 days after the last dose of second course/first cycle.	female/males of reproductive potential that do not plan to use effective contraception. Follow standard cancer screening guidelines because of the risk of malignancies. Administer all immunizations according to guidelines prior to treatment initiation. Obtain a complete blood count with differential including lymphocyte count. Lymphocytes must be within normal limits before treatment initiation and at least 800 cells/microliter before starting the second treatment course.
Mayzent (siponimod)	Tablets	Oral	Once daily Initiate treatment with a 5-day titration; a starter pack should be used for patients who will be titrated to the maintenance dosage starting on Day 6 (refer to prescribing information for titration regimen).	Mayzent can cause fetal harm when administered to pregnant women. Dosage should be titrated based on patient's CYP2C9 genotype. Patients with sinus bradycardia (HR < 55 bpm), first- or second-degree AV block, or a history of myocardial infarction or heart failure should undergo first dose monitoring for bradycardia.
mitoxantrone	Injection	IV	Every 3 months Note: Left ventricular ejection fraction (LVEF) should be evaluated prior to administration of the initial dose of mitoxantrone injection (concentrate) and all subsequent doses. In addition, LVEF evaluations are recommended if signs or symptoms of CHF develop at any time during treatment with mitoxantrone. Complete blood counts, including platelets, should be monitored prior to each	For MS-related indications: 12 mg/m^2 given as a short IV infusion over 5 to 15 minutes Mitoxantrone injection (concentrate) should not be administered to MS patients with an LVEF < 50%, with a clinically significant reduction in LVEF, or to those who have received a cumulative lifetime dose of ≥ 140 mg/m^2. Mitoxantrone generally should not be administered to MS patients with neutrophil counts less than 1500 cells/mm^3.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			course of mitoxantrone and in the event that signs or symptoms of infection develop. Liver function tests should be monitored prior to each course of therapy.	Mitoxantrone therapy in MS patients with abnormal liver function tests is not recommended because mitoxantrone clearance is reduced by hepatic impairment and no laboratory measurement can predict drug clearance and dose adjustments. Mitoxantrone may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant.
Ocrevus (ocrelizumab)	Injection	IV	Every 6 months (24 weeks) Titration: Initial dose: 300 mg IV, followed 2 weeks later by a second 300 mg IV infusion. Subsequent doses: 600 mg IV infusion every 6 months Hepatitis B virus screening is required before the first dose.	Observe patients for at least 1 hour after the completion of the infusion. Dose modifications in response to infusion reactions depend on the severity. See package insert for more details. Pre-medicate with methylprednisolone (or an equivalent corticosteroid) and an antihistamine (eg, diphenhydramine) prior to each infusion. An antipyretic (eg, acetaminophen) may also be considered. Administer all necessary immunizations according to immunization guidelines at least 2 (non-live vaccines) to 4 (live or live-attenuated vaccines) weeks prior to initiation of ocrelizumab. Women of childbearing potential should use contraception while receiving ocrelizumab and for 6 months after the last infusion of ocrelizumab.
Plegridy (peginterferon β-1a)	Injection; pen, prefilled syringe	SC	Every 14 days Titration: Start with 63 mcg on day 1, 94 mcg on day 15, and 125 mcg (full dose) on day 29	Following initial administration by a trained healthcare provider, Plegridy may be self-administered. Patients should be advised to rotate injection sites; the usual

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				sites are the abdomen, back of the upper arm, and thigh. Analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms. Monitor for adverse reactions due to increased drug exposure in patients with severe renal impairment.
Rebif (interferon β-1a); Rebif Rebidose	Injection	SC	Three times per week at least 48 hours apart Titration: Generally, the starting dose should be 20% of the prescribed dose 3 times per week, and increased over a 4-week period to the targeted recommended dose of either 22 mcg or 44 mcg injected SC 3 times per week	Following initial administration by a trained healthcare provider, Rebif may be self-administered. Patients should be advised to rotate the site of injection with each dose to minimize the likelihood of severe injection site reactions or necrosis. Decreased peripheral blood counts or elevated liver function tests may necessitate dose reduction or discontinuation of Rebif administration until toxicity is resolved. Concurrent use of analgesics and/or antipyretics may help ameliorate flu-like symptoms associated with Rebif use on treatment days.
Tecfidera (dimethyl fumarate)	Capsules (delayed-release)	Oral	Twice daily Titration: 120 mg twice daily for 7 days (initiation), then 240 mg twice daily (maintenance) Temporary dose reductions to 120 mg twice a day may be considered for individuals who do not tolerate the maintenance dose.	May be taken with or without food; must be swallowed whole. Do not crush, chew, or sprinkle capsule contents on food. The incidence of flushing may be reduced by administration of dimethyl fumarate with food. Alternatively, administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to dimethyl fumarate dosing may reduce the incidence or severity of flushing. Obtain a complete blood cell count including lymphocyte count before initiation of therapy.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to treatment with dimethyl fumarate.
Tysabri (natalizumab)†	Injection	IV	Once a month (every 4 weeks)	Both MS and Crohn's disease indications are dosed the same: 300 mg infused over 1 hour and given every 4 weeks. Tysabri should not be administered as an IV push or bolus injection. Patients should be observed during the infusion and for 1 hour after the infusion is complete.
Vumerity (diroximel fumarate)	Capsules (delayed-release)	Oral	Twice daily Titration: 231 mg twice daily for 7 days (initiation), then 462 mg twice daily (maintenance) Temporary dose reductions to 231 mg twice a day may be considered for individuals who do not tolerate the maintenance dose.	Must be swallowed whole. Do not crush, chew, or sprinkle capsule contents on food. Avoid administration with a high-fat, high-calorie meal/snack. Avoid co-administration with alcohol. The incidence or severity of flushing may be reduced by administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to diroximel fumarate. Obtain a complete blood cell count including lymphocyte count before initiation of therapy. Obtain serum aminotransferase, alkaline phosphatase, and total bilirubin levels prior to treatment with diroximel fumarate.
Zeposia (ozanimod)	Capsules	Oral	Once daily Titration: 0.23 mg once daily on days 1 to 4, then 0.46 mg once daily on days 5 to 7, then 0.92 mg once daily on day 8 and thereafter.	May be taken with or without food. Capsules should be swallowed whole. Obtain a complete blood count (including lymphocyte count), transaminase and bilirubin levels, electrocardiogram, and ophthalmic assessment before initiation of therapy.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				If a dose is missed during the first 2 weeks of treatment, treatment should be restarted using the titration regimen; if a dose is missed after 2 weeks of treatment, continue treatment as planned. Use in patients with hepatic impairment is not recommended.

*See the current prescribing information for full details
†Currently available through a restricted distribution program as part of a REMS requirement.

CONCLUSION

- DMTs for MS have shown benefits in patients with relapsing MS such as a decreased relapse rate and a slower accumulation of brain lesions on MRI. Therefore, it is recommended that all patients with a diagnosis of definite relapsing MS begin DMTs *(MS Coalition 2019)*.
- IFNβ products have been shown to decrease MRI lesion activity, prevent relapses, and delay disease progression. In general, patients treated with IFNβ or glatiramer acetate can expect a 30% reduction in ARR during a 2-year period *(MS Coalition 2019)*. Head-to-head clinical trials have found IFNβ and glatiramer acetate to be comparable in terms of efficacy on relapse rate. Several studies have demonstrated an improved tolerability at the cost of a decreased therapeutic response with low dose IM IFNβ-1a compared to higher dose SC IFNβ-1a *(Panitch et al 2002, Panitch et al 2005, Schwid et al 2005, Schwid et al 2007, Traboulsee et al 2008)*. Influenza-type symptoms, injection site reactions, headache, nausea, and musculoskeletal pain are the most frequently reported adverse events with IFNβ products. With IFNβ, use caution in patients with depression or other mood disorders. The adverse effect profile is similar among the IFNs.
- The most frequently reported adverse events with glatiramer acetate include a transient, self-limiting, post-injection systemic reaction immediately following drug administration consisting of flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and urticaria. Glatiramer acetate does not have any known drug interactions and is not associated with an increased risk of hepatotoxicity or depression. Glatiramer acetate is generically available.
- Despite advancements in treatment, many patients fail initial DMTs with glatiramer acetate or IFNβ, primarily due to intolerable adverse effects or inadequate efficacy *(Coyle 2008, Portaccio et al 2008)*. Clinical trials have shown that patients switching from IFNβ to glatiramer acetate therapy and vice versa, due to poor response, may achieve a significant reduction in relapse rates and a delay in disease and disability progression *(Coyle 2008, Caon et al 2006, Zwibel 2006)*. The guidelines suggest that all first-line MS DMTs should be made accessible, and the choice of initial treatment should be based on patient-specific factors *(MS Coalition 2017, Scolding et al 2015, Montalban et al 2018)*. The premature discontinuation rate is high among patients with MS; therefore, factors that will maximize adherence should be considered when initiating therapy. Failure with 1 agent does not necessarily predict failure with another. Therefore, patients experiencing an inadequate response or drug-induced adverse event should be switched to a different DMT *(Coyle 2008, Portaccio et al 2008)*.
- There are now 8 available oral agents: Gilenya (fingolimod), which was approved in 2010, Aubagio (teriflunomide), which was approved in 2012, and Tecfidera (dimethyl fumarate), which was approved in 2013. Mavenclad (cladribine), Mayzent (siponimod), and Vumerity (diroximel fumarate) were all approved in 2019; Zeposia (ozanimod) and Bafiertam (monomethyl fumarate) were approved in 2020. Among other potential benefits, it is expected that the availability of oral agents may increase convenience and improve patient adherence *(Sanvito et al 2011)*. The available oral drugs each have different mechanisms of action and/or tolerability profiles. The efficacy of the oral products has not been directly compared in any head-to-head trials. Cases of PML have been reported in patients taking fingolimod and dimethyl fumarate.
  - Gilenya (fingolimod) is a sphingosine 1-phosphate receptor modulator. In a trial comparing fingolimod to placebo, fingolimod-treated patients had a decreased ARR, improved MRI outcomes, and a lower likelihood of disability

progression *(Kappos et al 2010)*. In a trial comparing fingolimod to IFNβ-1a IM (Avonex), fingolimod-treated patients had a decreased ARR and improved MRI outcomes, but disability progression was similar in the 2 groups *(Cohen et al, 2010)*. The adverse event profile for fingolimod includes cardiovascular risks including bradycardia. First dose administration of fingolimod requires at least 6 hours of observation with hourly monitoring of heart rate and blood pressure, and patients should have an ECG before dosing and at the end of the observation period.
    - Fingolimod is also FDA-approved for MS in the pediatric population. In a trial evaluating patients between 10 and 17 years of age, fingolimod significantly reduced ARR and the rate of new or newly enlarged lesions compared to IFNβ-1a (*Chitnis et al 2018*).
- Mayzent (siponimod) is a sphingosine 1-phosphate receptor modulator, similar to fingolimod. In a trial comparing Mayzent to placebo, Mayzent significantly reduced the risk of 3-month CDP, delayed the risk of 6-month CDP, and reduced the ARR (*Kappos et al 2018*). First dose cardiac monitoring is recommended for patients with a heart rate < 55 bpm or a history of cardiac disease. Siponimod shares many of the same warnings as fingolimod.
- Zeposia (ozanimod) is another sphingosine 1-phosphate receptor modulator that was approved by the FDA in March 2020. Clinical trials have shown ozanimod to significantly decrease ARR compared to IFNβ-1a; however, unlike other drugs in this class it does not require first dose cardiac monitoring (*Comi 2019, Cohen 2019*).
- Tecfidera (dimethyl fumarate) has efficacy similar to that of fingolimod; its benefit-risk profile makes it a reasonable initial or later stage DMT option for most patients with RRMS *(CADTH 2013, Wingerchuk et al 2014)*. Gastrointestinal intolerance and flushing are common side effects that may wane with time; slow titration to maintenance doses, taking the medication with food, and premedication with aspirin may reduce their severity.
- Vumerity (diroximel fumarate) is a recently approved oral agent for MS and is rapidly converted to monomethyl fumarate, which is also the active metabolite of Tecfidera (dimethyl fumarate). Diroximel fumarate may offer improved GI tolerability as compared to dimethyl fumarate (*Naismith et al 2019, Selmaj et al 2019).*
- Bafiertam (monomethyl fumarate) was approved by the FDA in April 2020 and is considered to be a “bioequivalent alternative” to dimethyl fumarate (*Drugs@FDA 2020*).
- Aubagio (teriflunomide) inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme involved in de novo pyrimidine synthesis. Although its exact mechanism of action is unknown, it may involve a reduction in the number of activated lymphocytes in the CNS. Patients treated with teriflunomide in a clinical trial experienced a reduction in the ARR and improved MRI outcomes compared to placebo. Patients in the higher dose group (14 mg) also had a lower likelihood of disability progression, but this difference was not statistically significant in the lower dose group (7 mg) as compared to placebo *(O’Connor et al, 2011)*. Teriflunomide has boxed warnings for the possibility of severe liver injury and teratogenicity. The most common adverse reactions include increases in ALT, alopecia, diarrhea, influenza, nausea, and paresthesia.
- Mavenclad (cladribine) is a purine antimetabolite indicated for the treatment of relapsing forms of MS, to include relapsing-remitting disease and active secondary progressive disease. In a trial comparing Mavenclad to placebo, both Mavenclad 3.5 mg/kg and 5.25 mg/kg treatment groups had reduced ARRs and disability progression vs placebo (*Giovannoni et al 2010*). Mavenclad carries a boxed warning for risk of malignancies and teratogenicity. Lymphopenia is the most common adverse effect.

- Tysabri (natalizumab) is a recombinant monoclonal antibody indicated for the treatment of relapsing forms of MS and is also approved for use in the treatment of moderately to severely active CD in patients with an inadequate response to or who are unable to tolerate conventional CD therapies and TNF inhibitors.
    - In a 2011 systematic review of trials evaluating natalizumab for RRMS, pooled efficacy data from 2 RCTs (AFFIRM and SENTINEL) showed that natalizumab significantly reduced the risk for having a relapse during 2 years of treatment. In addition, natalizumab significantly reduced the risk for experiencing 12-week CDP at 2 years (RR, 0.74, 95% CI: 0.62 to 0.89) *(Pucci et al 2011)*. Natalizumab has been associated with an increased risk of PML; however, the overall incidence of PML has remained low (0.4%). Natalizumab can only be obtained through a restricted distribution program.
- Lemtrada (alemtuzumab) is a highly efficacious DMT that has demonstrated superiority in reducing relapses when compared to Rebif in both treatment-naïve and treatment-experienced patients. The dosing schedule of 2 annual treatment courses is counterbalanced by the need for regular monitoring of the increased risk for autoimmunity. Lemtrada is best reserved for patients who have failed at least 2 other DMTs and are not candidates for natalizumab (*Garnock-Jones 2014*).
- Ocrevus (ocrelizumab) is a recombinant monoclonal antibody designed to selectively target CD20-positive B cells. As a humanized form of Rituxan (rituximab), ocrelizumab is expected to be less immunogenic with repeated infusions and may have a more favorable benefit-to-risk profile than Rituxan *(Sorensen et al 2016)*.

  - Ocrevus provides another DMT option to the growing armamentarium of highly effective agents indicated for the treatment of relapsing MS. Ocrelizumab is also indicated for the treatment of PPMS, making it the first DMT with substantial evidence supporting its use in this form of MS. Although the pivotal studies of ocrelizumab were of sufficient length to assess efficacy, more long-term safety data are needed to evaluate the effects of ocrelizumab on emergent neoplasms and the risk of PML.
- Mitoxantrone is a synthetic intercalating chemotherapeutic agent. While it is approved for the treatment of RRMS, SPMS, and PRMS, cumulative dose-related cardiac toxicity and the risk for secondary leukemia markedly limit its use. Mitoxantrone is reserved for use in patients with aggressive disease.
- While DMTs do not sufficiently address QOL in RRMS, symptomatic agents such as Ampyra (dalfampridine) can be used to complement treatment with DMTs. Although a 25% improvement in T25FW may appear marginal, it has been established that improvements in T25FW speed of ≥ 20% are meaningful to people with MS. Dalfampridine can complement DMTs, which do not address the specific symptom of walking speed. Improved walking could potentially contain some of the direct and indirect costs (eg, reduced productivity, disability, unemployment, costs of assistive devices and caregivers) associated with MS.
- With an increasing number of DMTs currently on the market and no specific MS algorithm in place to guide treatment decisions, the selection of an agent is generally based on considerations of the risks and benefits of each therapy, physician experience, patient comorbidities, and patient preferences.
  - Clinicians should consider prescribing a high efficacy medication such as alemtuzumab, cladribine, fingolimod, ocrelizumab or natalizumab for newly-diagnosed individuals with highly active MS (*MS Coalition 2019*).
  - Clinicians should also consider prescribing a high efficacy medication for patients who have breakthrough activity on another DMT, regardless of the number of previously used agents (*MS Coalition 2019*).

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Publication Date: June 22, 2020

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 (AHA) Heart Disease and Stroke Statistics 2020 update. The age-adjusted prevalence of all types of heart disease was 10.6% in 2017. Deaths related to cardiovascular disease were most often caused by coronary heart disease (42.6%), followed by stroke (17.0%), high blood pressure (10.5%), heart failure (9.4%) and other causes (17.6%) *(Virani et al 2020)*.
- 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 2020, 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 2020, 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 2020, 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 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 2020*). Non-dihydropyridines dilate the arteries somewhat less than dihydropyridines, but they also reduce heart rate and contractility (*Micromedex 2.0 2020, 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 2020*).
  - 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 2019, 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)	✔
Consensi (amlodipine/celecoxib)	-
Conjupri (levamlodipine)	-
Felodipine extended-release	✔
Isradipine	✔
Katerzia (amlodipine suspension)	-
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.
†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 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. FDA-Approved Indications – Dihydropyridines

Indication	Amlodipine	Consensi (amlodipine/ Celecoxib)	Felodipine	Isradipine	Levamlodipine	Nicardipine	Nifedipine	Nimodipine	Nisoldipine
	Angina Pectoris								
Treatment of chronic stable angina	✔ *					✔ †			
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.
†Alone or in combination with beta blockers.
‡Confirmed or suspected vasospastic angina. May be used alone or 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, Conjupri 2019, Consensi 2020, felodipine ER 2018, isradipine 2017, Katerzia 2019, nicardipine capsule 2017, nimodipine 2017, nisoldipine extended-release tablet 2017, Norvasc 2019, Nymalize 2020, 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		
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 2019, Cardizem 2016, Cardizem CD 2020, Cardizem LA 2019, DILT-XR 2012, Tiazac 2016, Verelan 2019, Verelan PM 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

Dihydropyridines

- Clinical trials have demonstrated the efficacy of these agents for their respective indications.
- Amlodipine oral suspension has a pharmacokinetic profile comparable to the tablet formulations, and received FDA approval based on these pharmacokinetic parameters and the efficacy of amlodipine tablet (*Katerzia prescribing information 2019)*.
- 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*).
- Levamlodipine, the pharmacologically active isomer of amlodipine, was recently approved for the treatment of hypertension (*Conjupri prescribing information 2019*). Approval of this agent is based on historical clinical trials demonstrating the efficacy and safety of amlodipine in adult and pediatric patients.

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)/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, Knuuti et al 2019, 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 2020, Micromedex 2.0 2020)

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration - Dihydropyridine

Drug	Available Formulations	Usual Recommended Frequency	Comments
Amlodipine	Oral tablets Oral suspension	Angina pectoris (chronic stable and vasospastic): Tablet, suspension: maintenance, 5 to 10 mg once daily; maximum, 10 mg once daily CAD: Tablet, suspension: maintenance, 5 to 10 mg once daily; maximum, 10 mg once daily Hypertension: Tablet, suspension: 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, suspension: initial, 2.5 mg once daily; maintenance, 2.5 to 5 mg once daily; maximum, 5 mg once daily	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.
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.
Levamlodipine	Oral tablets	Hypertension: Tablets: initial, 2.5 mg once daily; maximum, 5 mg once daily	Small, fragile, or elderly patients, or patients with hepatic insufficiency may be started on 1.25 mg once daily.

Drug	Available Formulations	Usual Recommended Frequency	Comments
			Pediatric starting dose is 1.25 mg to 2.5 mg once daily; doses above 2.5 mg daily have not been studied in pediatric patients.
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 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	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.
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

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

Drug	Available Formulations	Usual Recommended Frequency	Comments
		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	
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 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	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 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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Publication Date: June 30, 2020

Therapeutic Class Overview
Acne Agents

INTRODUCTION

- Acne vulgaris is a chronic inflammatory dermatosis characterized by open and/or closed comedones (blackheads and whiteheads) and inflammatory lesions including papules, pustules, or nodules (*Zaenglein et al 2016*). Four primary pathogenic factors interact in a complex manner to produce the different acne lesions. The four factors include sebum production by the sebaceous gland, Propionibacterium acnes (*P. acnes*) follicular colonization, alteration in the keratinization process, and the release of inflammatory mediators to the skin (*Thiboutot et al 2009*).
- Several options exist for the treatment of acne vulgaris including topical agents, systemic antibacterial agents, hormonal agents, isotretinoin, laser and light therapies, miscellaneous therapies, complementary and alternative therapies, and dietary restrictions. Topical therapy of acne vulgaris includes agents that are available over the counter or by prescription, and choice of therapy can be influenced by various factors including patient age, site of involvement, extent and severity of disease, and patient preference. Topical agents include antibiotics, benzoyl peroxide, retinoids, azelaic acid, dapsone, and salicylic acid (*Gollnick et al 2016, Zaenglein et al 2016*).
- Traditionally, the treatment of acne vulgaris has been directed toward controlling *P. acnes* and centered on the use of antibiotics. Current treatment modalities are directed toward as many pathogenic factors as possible. Combination treatment has the ability to target multiple pathogenic factors, including inflammatory and noninflammatory lesions (*Eichenfield et al 2013, Thiboutot et al 2009*). Data have shown that combination therapy results in faster and more complete clearing of acne vulgaris lesions compared with monotherapy (*Eichenfield et al 2013, Nast et al 2016, Thiboutot et al 2009*). Combination therapy should be used in the majority of patients with acne (*Gollnick et al 2016, Zaenglein et al 2016*). Additionally, antibiotics and benzoyl peroxide both target *P. acnes*; however, unlike antibiotics, benzoyl peroxide has not been associated with the development of bacterial resistance (*Zaenglein et al 2016*).
- Topical retinoids are recommended as monotherapy in primarily mild, comedonal acne, or in combination with topical or oral antibiotics in patients with mixed or primarily inflammatory moderate acne vulgaris (*Gollnick et al 2016, Zaenglein et al 2016*). The comedolytic and anti-comedogenic properties associated with topical retinoids result in a reduction in the formation of microcomedones and comedones (*Zaenglein et al 2016*). For severe acne, oral antibiotics with topical therapy or oral isotretinoin is recommended for first-line treatment (*Zaenglein et al 2016*, *Zaenglein et al 2018*). Oral isotretinoin is one of several alternatives for treatment-resistant moderate acne.
- The focus of this review will be the use of the topical agents and oral isotretinoin for the treatment of acne. Agents prescribed solely for rosacea and products combining hyaluronate, niacinamide, or resorcinol will not be included in this review. The following table may not be all inclusive as products enter and leave the market frequently in this class.
- Medispan Class: Acne Products

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Antibiotics	
Aczone (dapsone) gel 5%	✔
Aczone (dapsone) gel 7.5%	-
Clindagel (clindamycin) gel 1%	✔
Cleocin T (clindamycin) gel, lotion, solution 1%	✔
Clindacin-P, Clindacin ETZ (clindamycin) swab 1%	✔
Clindacin Pac, Clindacin ETZ (clindamycin and cleanser kit) swab 1%	✔
NuCaraClinPAK (clindamycin and moisturizer kit) gel 1%	✔
Evoclin (clindamycin) foam 1%	✔
Erygel (erythromycin) gel 2%	✔
Ery (erythromycin) pads, solution 2%	✔
Amzeeq (minocycline) topical foam 4%	-

Drug	Generic Availability
Benzoyl Peroxide and Combinations	
benzoyl peroxide bar 10%; cream 2.5%, 10%; cleanser 3.5%; cleanser ER 4.4%; external liquid 2.5%, 4%, 5%, 5.5%, 6%, 6.9%, 7%, 10%; foam 5.3%, 9.8%, 10%; gel 2.5%, 2.75%, 4%, 5%, 5.25%, 8%, 10%; foaming cloths 6%; lotion 5%, 8%, 10%; wash/lotion kits 2.5/3.7%, 2.5/10%	✔ †
Enzoclear (benzoyl peroxide) foam 9.8%	-
Riax (benzoyl peroxide) foam 5.5%, 9.5%	-
BenzePrO, BPO (benzoyl peroxide) foam 5.2%, 9.7%; external liquid 6.8%; foaming cloths 5.8%	-
Zaclir (benzoyl peroxide) lotion 8%	-
Benziq LS (benzoyl peroxide) external liquid 5.25%	-
Vanoxide-HC (benzoyl peroxide/hydrocortisone) lotion 5/0.5%, 7.5/1%	✔
Benzoyl Peroxide – Antibiotic Combinations	
Acanya (benzoyl peroxide/clindamycin) gel 2.5/1.2%	✔
Benzaclin (benzoyl peroxide/clindamycin) gel 5/1%	✔
Duac, Neuac (benzoyl peroxide/clindamycin) gel, kit 5/1.2%	✔
Neuac, NuCaraRxPAK (benzoyl peroxide/clindamycin) gel, kit 2.5/1%	✔
Onexton (benzoyl peroxide/clindamycin) gel 3.75/1.2%	-
Benzamycin (benzoyl peroxide/erythromycin) gel 5/3%	✔
Topical Retinoids – Single Entity	
adapalene external solution 0.1%	✔
adapalene pad 0.1%	✔
Differin (adapalene) cream 0.1%	✔
Differin (adapalene) gel 0.1%†, 0.3%	✔
Differin (adapalene) lotion 0.1%	-
Arazlo (tazarotene) lotion 0.045%	-
Fabior (tazarotene) foam 0.1%	-
Tazorac (tazarotene) gel and cream 0.05%, gel 0.1%	-
Tazorac (tazarotene) cream 0.1%	✔
Altreno (tretinoin) lotion 0.05%	-
Atralin (tretinoin) gel 0.05%	✔
Avita (tretinoin) cream and gel 0.025%	✔
Retin-A (tretinoin) cream 0.025%, 0.05%, 0.1%; gel 0.01%, 0.025%	✔
Retin-A Micro (tretinoin microsphere) gel 0.04%, 0.1%	✔
Retin-A Micro (tretinoin microsphere) gel 0.06%, 0.08%	-
Aklief (trifarotene) cream 0.005%	-
Topical Retinoids – Combination	
Epiduo (adapalene/benzoyl peroxide) gel 0.1/2.5%	✔
Epiduo Forte (adapalene/benzoyl peroxide) gel 0.3/2.5%	-
adapalene/benzoyl peroxide/clindamycin gel 0.3/2.5/1%	✔
Veltin, Ziana (clindamycin phosphate/tretinoin) gel 1.2/0.025%	✔
Miscellaneous Topical Therapies	
Azelex (azelaic acid) cream 20%	-
Sulfacetamide/Sulfur and Combinations	

Drug	Generic Availability
sodium sulfacetamide cream 10% (Ovace Plus); lotion 9.8% (Ovace Plus), 10% (Klaron); shampoo 10% (Ovace Plus); wash external liquid 10% (Ovace, Ovace Plus); wash external gel 10% (Ovace Plus); foam 9.8% (Ovace Plus)	✔
sulfacetamide with sulfur wash 9/4% (Sumaxin), 9/4.5% (Sumadan); with sulfur cleanser 9.8/4.8% (Plexion), 10/2% (Avar LS); with sulfur emulsion 10/1% (BP 10-1, Sulfamez), 10/5% (Avar); with sulfur in urea emulsion 10/4% (BP Cleansing Wash), 10/5%; with sulfur suspension 8/4% (SulfaCleanse 8/4), 10/5%; with sulfur cream 9.8/4.8% (Plexion), 10/2% (Avar-e LS), 10/5% (Avar-e Emollient, Avar-e Green, SSS 10-5); with sulfur foam 10/5% (SSS 10-5); with sulfur lotion 9.8/4.8% (Plexion), 10/5%; with sulfur pad 10/4% (Sumaxin); with sulfur cloths 9.8/4.8% (Plexion)	✔
Sumadan kit wash 9/4.5%, Sumaxin CP kit pad 10/4%, (sulfacetamide sodium/sulfur/skin cleanser)	✔
Sumadan XLT kit wash 9/4.5% (sulfacetamide sodium/sulfur/sunscreen)	✔
sulfur external bar 3%, 10%; lotion 5%	✔ *
SAStid (sulfur/salicylic acid) external bar 3/5%	✔ *
Oral Retinoids	
Absorica (isotretinoin) oral capsule 10 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg	- ‡
Absorica LD (isotretinoin) oral capsule 8 mg, 16 mg, 24 mg, 32 mg	-
Amnesteem, Claravis, Myorisan, Zenatane (isotretinoin) oral capsule 10 mg, 20 mg, 30 mg, 40 mg	✔ δ

Abbreviation: ER = extended-release
*Over-the-counter (OTC) only product(s)
†Prescription and/or OTC product(s)
‡Absorica 10, 20, 30, and 40 mg products are BX rated according to the Orange Book, considered to be not therapeutically equivalent to other pharmaceutically equivalent products.
δClaravis is the reference standard and other products are branded generics considered bioequivalent to Claravis

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications*

Drug	Acne vulgaris	Inflammatory acne vulgaris	Adjunctive therapy for acne vulgaris, acne rosacea, and seborrheic dermatitis	Treatment and prevention of mild to moderate acne vulgaris	Treatment of severe recalcitrant nodular acne
Antibiotics					
Aczone (dapsone)	✔	-	-	-	-
Clindamycin	✔	-	-	-	-
Erythromycin	✔	-	-	-	-
Amzeeq (minocycline)	✔	-	-	-	-
Benzoyl Peroxide – Single Entity					
Benzoyl peroxide	✔	-	-	✔	
Benzoyl Peroxide – Antibiotic Combinations					
Benzoyl peroxide/clindamycin	✔ (Acanya, Benzaclin, Onexton)	✔ (Duac, Neuac)	-	-	-
Benzoyl peroxide/ erythromycin	✔ (Benzamycin)	-	-	-	-
Benzoyl Peroxide – Other Combinations					

Drug	Acne vulgaris	Inflammatory acne vulgaris	Adjunctive therapy for acne vulgaris, acne rosacea, and seborrheic dermatitis	Treatment and prevention of mild to moderate acne vulgaris	Treatment of severe recalcitrant nodular acne
Vanoxide-HC (benzoyl peroxide/hydrocortisone)	✔	-	-	-	-
Topical Retinoids – Single Entity					
Differin (adapalene)	✔	-	-	-	-
Arazlo, Fabior, Tazorac (tazarotene)†	✔ (0.1% Tazorac strengths only)	-	-	-	-
Tretinoin	✔	-	-	-	-
Aklief (trifarotene)	✔	-	-	-	-
Topical Retinoids – Combination					
Epiduo, Epiduo Forte (adapalene/benzoyl peroxide)	✔	-	-	-	-
Veltin, Ziana (clindamycin/tretinoin)	✔	-	-	-	-
Miscellaneous Topical Therapies					
Azelex (azelaic acid)	-	✔	-	-	-
Sulfacetamide	✔ (gel, lotion)	-	-	-	-
Sulfacetamide/sulfur	-	-	✔	-	-
Oral Retinoids					
Absorica, Absorica LD, Amnesteem, Claravis, Myorisan, Zenatane (isotretinoin)	-	-	-	-	✔

*Approved ages vary by product.
†Tazorac is also approved for the treatment of psoriasis.

(*Prescribing information: Absorica/Absorica LD 2019, Acanya 2016, Aczone 7.5% 2019, Aczone 5% 2018, adapalene topical solution 2019, adalapene swab 2019, adapalene/benzoyl peroxide/clindamycin gel 2019, Aklief 2019, Altreno 2018, Amnesteem 2018, Amzeeq 2019, Arazlo 2019, Atralin 2016, Azelex 2019, Benzaclin 2017, Benzamycin 2019, BPO 4% gel 2018, Claravis 2018, Cleocin T 2019, Clindagel 2017, Differin cream 2011, Differin lotion 2018, Duac 2015, Epiduo 2018, Epiduo Forte 2015, Fabior 2018, Myorisan 2018, Onexton 2018, Retin-A 2019, Retin-A MICRO 2017, Tazorac gel 2018, Tazorac cream 2017,Vanoxide-HC 2018, Veltin 2019, Zenatane 2019, Ziana 2017, Clinical Pharmacology 2020, Lexi-comp 2020, Micromedex 2020*)

- 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

- All agents included in this review are FDA-approved for the treatment of acne vulgaris, and clinical trials have demonstrated their effectiveness compared to a placebo vehicle. In addition, there have been some trials evaluating the comparative efficacy of the agents in the class. This clinical efficacy summary will focus on comparative trials.

Dapsone

- Dapsone was shown to be effective in the management of acne. In a clinical trial comparing dapsone 5% gel to the combination of dapsone plus adapalene, dapsone plus benzoyl peroxide, or dapsone plus moisturizer, all treatment arms showed similar efficacy in reducing inflammatory lesions over 12 weeks (*Fleischer et al 2010*).
- The approval of dapsone 7.5% gel was based on 2 randomized, double-blind (DB), vehicle-controlled, multicenter (MC) studies. A total of 4,340 patients were randomized to receive dapsone 7.5% gel or vehicle once daily for 12 weeks. The primary endpoint was the percentage of patients with none (score of 0) or minimal (score of 1) on the 5-point Global

Acne Assessment Score (GAAS) scale at week 12. The key secondary endpoints were mean absolute change from baseline in both inflammatory and non-inflammatory lesion counts (*Eichenfield et al 2016, Stein et al 2016*).
  - The majority of the subjects had moderate acne vulgaris, ie, 20 to 50 inflammatory and 30 to 100 non-inflammatory lesions at baseline.
  - In both studies, the GAAS success rate was approximately 30% in the dapsone arm and 21% in the vehicle arm.
  - In Study 1, the mean percent reduction in inflammatory lesions was 55.5% in the dapsone group and 49% in the vehicle group. In Study 2, it was 53.8% and 47.3%, respectively.
  - For the mean percent reduction in non-inflammatory lesions, 44.4% was reported in the dapsone group and 38.4% in the vehicle group in Study 1. In Study 2, it was 45.9% in the dapsone group and 40.4% in the vehicle group.

Benzoyl Peroxide

- There is limited evidence that differentiates the various formulations (gels, lotions, solutions, etc.) and strengths of the benzoyl peroxide and antibiotic combination agents. Clinical studies evaluating combination therapy with benzoyl peroxide and either clindamycin or erythromycin have consistently demonstrated that these agents are more effective compared to their respective monotherapies (*Chalker et al 1983, Cunliffe et al 2002, Leyden et al 2001, Lookingbill et al 1997, Thiboutot et al 2008b, Webster et al 2009, Xu et al 2016*).
- In a study by Leyden et al (N = 492), patients with moderate to severe acne vulgaris were randomized to receive benzoyl peroxide/clindamycin, benzoyl peroxide/erythromycin, or benzoyl peroxide alone for 10 weeks. The decrease in the number of inflammatory lesions from baseline, the primary endpoint, was significantly greater for those treated with benzoyl peroxide/clindamycin compared to benzoyl peroxide alone (P = 0.04). The average decrease in the number of inflammatory lesions was similar in patients treated with benzoyl peroxide/clindamycin and benzoyl peroxide/erythromycin (P = 0.4) (*Leyden et al 2001*).
- In a meta-analysis by *Seidler et al,* there was a significantly greater percent reduction in noninflammatory acne lesion count with benzoyl peroxide/clindamycin 2.5%/1.2% (-43.4%; 95% confidence interval [CI] depicted but not reported) compared to benzoyl peroxide/clindamycin 5%/1% (-38.2%; 95% CI depicted but not reported), benzoyl peroxide alone (-34.2%; 95% CI depicted but not reported), clindamycin alone (-27.9%; 95% CI depicted but not reported) and placebo (-14.9%; 95% CI depicted but not reported) over 10 to 12 weeks of treatment (*Seidler et al 2011*).
- Three clinical trials comparing benzoyl peroxide/clindamycin to adapalene monotherapy have reported consistently that the combination of benzoyl peroxide/clindamycin significantly reduces total lesion count over 12 weeks compared to adapalene (*Langner et al 2008, Ko et al 2009*). The combination of benzoyl peroxide/clindamycin in two trials also significantly reduced inflammatory lesion counts compared to baseline at week 12 to a greater extent than adapalene (*Langner et al 2008, Ko et al 2009*). For non-inflammatory lesion count, there were conflicting results among the studies (*Guerra-Tapia et al 2012, Ko et al 2009, Langner et al 2008*).

Topical Retinoids

- Topical retinoids can be used alone or in combination with antibiotics to treat both inflamed and noninflamed acne lesions, or for maintenance treatment of acne (*Medical Letter 2016*). All topical retinoids normalize keratinization and appear to have anti-inflammatory effects.
- Several comparative studies have been conducted evaluating the topical retinoids. Efficacy results are mixed, with trials demonstrating:
  - Equivalent efficacy between tretinoin 0.04% microgel and tretinoin 0.1% microgel (*Berger et al 2007*)
  - Equivalent efficacy between adapalene 0.1% gel and tretinoin 0.025% gel (*Cunliffe et al 1997, Ellis et al 1998, Grosshans et al 1998*)
  - Equivalent efficacy between adapalene 0.1% gel and tretinoin 0.1% microgel (*Nyirady et al 2001*)
  - Equivalent efficacy between adapalene 0.1% gel and tazarotene 0.1% cream (*Pariser et al 2008*)
  - Equivalent efficacy between adapalene 0.3% gel and tazarotene 0.1% gel (*Thiboutot et al 2008a*)
  - Greater efficacy with tazarotene 0.1% plus clindamycin 1% gel over adapalene 0.1% plus clindamycin 1% gel (*Maiti et al 2017*).
  - Greater efficacy with tazarotene 0.1% cream over adapalene 0.3% gel (*Tanghetti et al 2010*)
  - Greater efficacy with tazarotene 0.1% cream over adapalene 0.1% cream (*Shalita et al 2005*)
  - Greater efficacy with tretinoin 0.05% gel over adapalene 0.1% gel (*Pierard-Franchimont et al 1999*)
  - Greater efficacy with adapalene 0.1% gel over tretinoin 0.025% gel (*Cunliffe et al 1997, Shalita et al 1996*)

- Two studies (n = 820 for each study) demonstrated that tretinoin 0.05% lotion was more effective than a vehicle in improving Evaluator's Global Severity Score (EGSS) and reducing the number of inflammatory and non-inflammatory facial lesions at week 12 in patients aged ≥ 9 years (all P < 0.001). Success rates were 9.6% higher in Study 1 and 7.3% higher in Study 2 compared to the vehicle (*Tyring et al 2018*).
- Two studies (n = 1614 total) found that tazarotene 0.045% lotion significantly improved EGSS and the number of inflammatory and non-inflammatory lesions compared to vehicle in patients aged ≥ 9 years with moderate to severe acne. Success rates were 12.3% to 12.5% higher compared to vehicle in Study 1 and 2, respectively (*Arazlo prescribing information 2019*).
- Two randomized studies (n = 2420 total) found that patients aged ≥ 9 years with moderate acne experienced greater improvement in Investigator's Global Assessment (IGA) of the face and the number of inflammatory and non-inflammatory lesions (all P < 0.001) with trifarotene 0.005% cream compared to vehicle (*Tan et al 2019*).
- A meta-analysis of 5 MC, investigator-blinded, randomized controlled trials (RCTs) compared the efficacy of adapalene 0.1% gel to tretinoin 0.025% gel in the treatment of patients with acne vulgaris (N = 900) (*Cunliffe et al 1998*). Overall, adapalene demonstrated equivalent efficacy to tretinoin in terms of reducing inflammatory lesions (P = 0.51), non-inflammatory lesions (P = 0.38), and total lesion count (P = 0.48) at week 12, but demonstrated more rapid efficacy in reducing inflammatory and total lesions at week 1 compared to tretinoin (P < 0.05).
- A systematic review of 54 clinical trials compared the efficacy and safety/tolerability of the topical retinoids for the treatment of acne vulgaris:
  - Of 5 studies that compared use of adapalene to tazarotene, 4 found no difference in the percent change of the total lesion count between the two treatments. One study, which combined both adapalene and tazarotene with clindamycin, found a significant change in lesion count with tazarotene plus clindamycin (17.54 vs 11.03; P = 0.007).
  - In 1 study comparing adapalene 0.3%, 0.1% to tretinoin 0.05%, a significantly greater reduction in total lesion count was found with tretinoin at week 12 (76.7% tretinoin vs 66.4% adapalene 0.3% vs 57.8% adapalene 0.1%; P < 0.001).
  - In a 12-week study of 40 patients, no difference in efficacy was found between tretinoin and tazarotene in the change in IGA, absolute change in inflammatory and noninflammatory lesion count, and total lesion count from baseline to week 12.
  - When comparing safety, 62% of patients receiving tretinoin 0.05% reported adverse effects (AE), compared to 19% and 40% with adapalene 0.1% and 0.3%, respectively. Treatment with tazarotene was associated with significantly more AE than treatment with adapalene (55.4 vs 24.4%; P < 0.0012) (*Kolli et al 2019*).
- A retrospective, investigator-blinded, vehicle-controlled, photographic assessment study was conducted to assess the efficacy of topical retinoids as monotherapy for the treatment of inflammatory acne (*Leyden et al 2005*). Five investigators rated pre- and post-treatment photographs of patients (N = 577) who had participated in 12- or 15-week, DB, RCTs of tazarotene 0.1% gel, adapalene 0.1% gel, tretinoin 0.1% microgel, tretinoin 0.025% gel, and tazarotene 0.1% cream.
  - Tazarotene, adapalene, and tretinoin were all superior to vehicle. Between-retinoid comparisons showed greater incidences of clinically significant improvements in overall acne severity in the tazarotene group compared with the groups receiving adapalene (P ≤ 0.001) or tretinoin (P ≤ 0.01).
- There are several limitations to these studies, including relatively small sample sizes (Range: N = 25 to 323), short duration (typically 12 weeks), enrollment of patients with varying degrees of acne severity, and comparisons between different strengths and formulations of topical retinoids. In addition, most studies that showed greater efficacy data with adapalene were sponsored by Galderma, greater efficacy data with tretinoin were sponsored by Johnson and Johnson (Ortho Dermatologics), and greater efficacy data with tazarotene were sponsored by Allergan. Based on the varying efficacy results and study limitations, it is not clear whether one topical retinoid is more effective than another.
- Tazarotene foam led to greater decreases from baseline for all types of acne lesions compared to vehicle foam; direct comparisons to other forms of tazarotene and other therapies have not been completed (*Fabior prescribing information, 2018, Feldman et al 2013*).
- For the combination products, several studies evaluated the effectiveness of the combination products compared to their individual components. The adapalene/benzoyl peroxide combination showed a statistically superior success rate compared to monotherapy with adapalene or benzoyl peroxide (*Gold et al 2009, Gollnick et al 2009, Pariser et al 2007, Thiboutot et al 2007*). In addition, the clindamycin/tretinoin combination had statistically significant superiority for all comparisons vs monotherapy with clindamycin or tretinoin (*Jarratt et al 2012, Leyden et al 2006, Schlessinger et al 2007*).

Oral retinoids

- A 2018 Cochrane review evaluated 31 RCTs of oral isotretinoin to assess its efficacy and safety for acne vulgaris. Included trials were comparisons to placebo, systemic antibiotics plus topical agents (combination therapy), or isotretinoin in various formulations or dose regimens (*Costa et al 2018*). For the primary outcome of total inflammatory lesion count, oral isotretinoin did not produce a greater reduction in acne lesions compared to combination therapy after 20 to 24 weeks of therapy in patients with moderate to severe acne (risk ratio [RR] 1.01; 95% CI 0.96 to 1.06; n=3 studies; 400 patients). Another primary outcome of serious adverse effect frequency detected 1 serious event of Stevens-Johnson syndrome in the isotretinoin group. The risk of serious adverse effects was higher with oral isotretinoin compared to combination therapy but was not considered statistically significant (RR 3.0; 95% CI 0.12 to 72.98). Less serious adverse effects were significantly higher with isotretinoin compared to combination therapy (RR 1.67; 95% CI 1.42 to 1.98; n=2 studies; 351 patients). Oral isotretinoin compared to oral isotretinoin plus topical agents did not demonstrate a significant difference in outcomes. For dose regimens, continuous low dose and conventional isotretinoin dose demonstrated a greater decrease in inflammatory lesion count compared to intermittent dosing (1 week each month). Due to study design limitations, the authors of the review rated the level of this evidence as low to very low.

Other products

- No pertinent clinical studies were recently identified for the treatment of acne vulgaris with sulfacetamide or azelaic acid as monotherapy. Both are FDA-approved for the treatment of acne vulgaris.

CLINICAL GUIDELINES

- The American Academy of Dermatology (AAD) 2016 guidelines, the 2016 European evidence-based recommendations, and a 2018 consensus from the Global Alliance to Improve Outcomes in Acne generally suggest the use of combinations to treat acne (*Nast et al 2016, Thiboutot et al 2018, Zaenglein et al 2016*). The 2016 AAD Guidelines recommend retinoids as monotherapy in primarily comedonal acne, or in combination with topical or oral antibiotics in patients with mixed or primarily inflammatory acne lesions. Topical antibiotics are noted as effective therapies for acne; however, they are not recommended as monotherapy due to the risk of resistance. Benzoyl peroxide or combinations with antibiotics (erythromycin or clindamycin) are effective treatments as well and are recommended as monotherapy for mild acne, or with a topical retinoid or systemic antibiotic therapy for moderate to severe acne. Oral isotretinoin is one of the recommended treatment options for severe nodular acne and moderate acne that is treatment resistant or that causes scarring or psychosocial distress. Azelaic acid (Azelex) is a useful adjunctive therapy per the AAD and topical dapsone 5% gel can be recommended for inflammatory acne, particularly in adult females (*Zaenglein et al 2016, Thiboutot et al 2018*).
- A 2016 consensus-based guideline for the treatment of acne recommends that patients with predominant comedonal acne should initially be treated with a topical retinoid (preferred), azelaic acid or salicylic acid. For patients with predominant papulopustular acne, fixed combination topicals are recommended, and should be used along with oral antibiotics, oral isotretinoin, oral zinc, or oral anti-androgenic hormonal therapy (women only) for patients with moderate to severe disease. For nodular/conglobate acne, treatment should include monotherapy with oral isotretinoin, or fixed combination topicals plus oral antibiotics for men; for women, these options may be supplemented with oral anti-androgenic hormonal therapy. To prevent the disease from recurring, maintenance therapy with a topical retinoid (preferred) or azelaic acid is recommended once a patient is clear or almost clear of their acne (*Gollnick et al 2016*).
- The 2013 recommendations from the American Academy of Pediatrics (AAP) state that acne management of pediatric patients is similar to acne treatment in older adolescents and adults. For mild acne, AAP recommends benzoyl peroxide, a topical retinoid, or a combination of benzoyl peroxide with an antibiotic or retinoid. For moderate and severe acne, combination topical therapy with the possible addition of oral antibiotics may be considered. Oral isotretinoin may be considered for some patients with severe, refractory, and scarring acne (*Eichenfield et al 2013*).

SAFETY SUMMARY

- Oral isotretinoin carries a black box warning regarding its teratogenicity risk; therefore, its use is contraindicated in female patients who are or may become pregnant. If pregnancy does occur during treatment, the drug should be discontinued and the patient should be referred to a specialist in reproductive toxicity. The drug is available only through a restricted program call the iPLEDGE program which requires enrollment by prescribers, patients, pharmacies, and

distributors. The restricted program has very specific requirements regarding use of contraception if the drug is used in females with reproductive potential.

- Contraindications for the acne agents are primarily hypersensitivity to any component of the product. For clindamycin-containing products, clindamycin is contraindicated in patients with a history of regional enteritis, ulcerative colitis or antibiotic-associated colitis. Tazarotene (Arazlo, Fabior, Tazorac) is contraindicated in pregnant women.
- Warnings for antibiotics include the risk for superinfection and pseudomembranous colitis. Gels contain alcohol and may be flammable; use caution. Benzoyl peroxide-containing products may cause bleaching of fabric or hair; use care when applying. Retinoids and benzoyl peroxide-containing products may cause ultraviolet (UV) sensitivity; avoid exposure or limit exposure with sunscreen. Retinoids may cause local application site reactions such as erythema, scaling, and dryness especially for the first few weeks of use. Azelaic acid products may cause hypopigmentation, and can irritate the eyes and mucous membranes. Dapsone gel can cause methemoglobinemia resulting in hospitalization, particularly in patients with glucose-6 phosphate dehydrogenase deficiency or idiopathic methemoglobinemia.
- Warnings for oral isotretinoin include avoidance of micro-dosed progesterone preparations as contraception, risk of psychiatric disorders (depression, psychosis, suicidal behavior/thoughts), pseudotumor cerebri, Stevens-Johnson syndrome, acute pancreatitis, lipid abnormalities, hearing impairment, hepatotoxicity, inflammatory bowel disease, skeletal abnormalities, ocular abnormalities, and glucose and creatine phosphokinase abnormalities.
- Adverse events for topical acne agents are generally limited to local application site reactions including burning/stinging, erythema, scaling, and dryness.
- Common adverse reactions of oral isotretinoin include dryness in skin, lips, and eyes; arthralgia; headache; dermatitis; musculoskeletal discomfort; reduced visual acuity; and upper respiratory symptoms/infection.
- Avoid concurrent use of clindamycin with erythromycin due to possible antagonistic therapeutic effects based on in vitro data.
- In June 2014, the FDA warned that certain OTC topical acne products can cause rare but serious and potentially life-threatening allergic reactions or severe irritation. The hypersensitivity reactions may occur within minutes to a day or longer after product use.
  - The OTC topical acne products of concern are marketed under various brand names such as Proactiv, Neutrogena, MaxClarity, Oxy, Ambi, Aveeno, Clean & Clear, and as store brands. They are available as gels, lotions, face washes, solutions, cleansing pads, toners, face scrubs, and other products.
  - Based on the information reported to the FDA, it cannot be determined if the serious hypersensitivity reactions were triggered by the acne products' active ingredients, benzoyl peroxide or salicylic acid, the inactive ingredients, or by a combination of both. The FDA is continuing to monitor and evaluate this safety issue, and will work with manufacturers regarding any future label changes that would address the risk of severe hypersensitivity reactions.
  - The hypersensitivity reactions may occur within minutes to a day or longer after product use. These serious hypersensitivity reactions differ from the local skin irritation that may occur at the product application site, such as redness, burning, dryness, itching, peeling, or slight swelling, that are already included in the Drug Facts labels.

(*Clinical Pharmacology 2020, FDA Drug Safety Communication 2014, Micromedex 2020*)

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Antibiotics				
Aczone (dapsone)	Gel	Topical	Apply once (7.5% dose) to twice daily (5% dose).	If no improvement in 12 weeks, treatment should be reassessed. The 7.5% gel is indicated in age ≥ 9 years. The 5% gel is indicated in age ≥ 12 years.
Clindagel, Cleocin T, Clindacin-P, Clindacin ETZ, Clindacin Pac,	Foam, gel, lotion, solution, swab, swab + cleanser kit, gel kit	Topical	Foam and gel (Clindagel): Apply once daily.	If topical antibiotic therapy is longer than a few weeks, the

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Evoclin, NuCaraClinPAK (clindamycin)			Gel (Cleocin T), lotion, solution, or swab: Apply twice daily.	addition of topical benzoyl peroxide is recommended. Indicated in age ≥ 12 years.
Erygel, Emgel, Ery (erythromycin)	Gel, pads, solution	Topical	Apply once to twice daily.	If no improvement after 6 to 8 weeks, or if the condition worsens, discontinue treatment. If topical antibiotic therapy is longer than a few weeks, the addition of topical benzoyl peroxide is recommended.
Amzeeq (minocycline)	Foam	Topical	Apply once daily.	Indicated in age ≥ 9 years.
Benzoyl Peroxide and Combinations				
BenzePrO, BPO, Benziq LS, Enzoclear, Riax, Zaclir (benzoyl peroxide)	Rx and/or OTC products: bar, cream, cleanser, cleanser ER, external liquid, foam, gel, lotion, wash + lotion kits, wash Rx products: Cleansing lotion, external liquid, foam, foaming cloths, gel, lotion, wash	Topical	Cream, foam, gel, solution, lotion: Apply once daily. Foaming cloths, lotion, cleanser, bar, wash, liquid: Apply 1 to 3 times daily.	Improvement is usually noted in 3 to 4 weeks.
Vanoxide-HC (benzoyl peroxide/ hydrocortisone)	Lotion	Topical	Apply 1 to 3 times daily.	Product expires 3 months after dispensed.
Benzoyl Peroxide – Antibiotic Combinations				
Acanya, Benzaclin, Duac, Neuac, NuCaraClinPAK, Onexton (benzoyl peroxide/clindamycin)	Gel, gel kit	Topical	Benzaclin: Apply twice daily. All other products: Apply once daily in the evening.	Indicated in age ≥ 12 years.
Benzamycin (benzoyl peroxide/erythromycin)	Gel	Topical	Apply twice daily.	Indicated in age ≥ 12 years.
Topical Retinoids – Single Entity				
Differin (adapalene)	Rx only: cream, lotion, solution, pad Rx/OTC: gel	Topical	Apply once daily in the evening.	Indicated in age ≥ 12 years.
Arazlo, Fabior, Tazorac (tazarotene)	Foam, gel, cream, lotion	Topical	Apply once daily in the evening.	Efficacy has not been established past 12 weeks. Indicated in age ≥ 12 years. Arazlo is indicated in age ≥ 9 years.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Altreno, Atralin, Avita, Retin-A, Retin-A Micro (tretinoin)	Lotion, gel, cream, microsphere gel	Topical	Apply once daily.	Altreno is indicated in age ≥ 9 years, Atralin is indicated in age ≥ 10 years, and all other products in age ≥ 12 years.
Aklief (trifarotene)	Cream	Topical	Apply once daily in the evening.	Indicated in age ≥ 9 years.
Topical Retinoids - Combination				
Epiduo, Epiduo Forte (adapalene/benzoyl peroxide)	Gel	Topical	Apply once daily.	Epiduo is indicated in age ≥ 9 years and Epiduo Forte in age ≥ 12 years.
adapalene/benzoyl peroxide/clindamycin	Gel	Topical	Apply once daily.	
Veltin, Ziana (clindamycin/tretinoin)	Gel	Topical	Apply once daily in the evening.	Indicated in age ≥ 12 years.
Miscellaneous Topical Therapies				
Azelex (azelaic acid)	Cream	Topical	Apply twice daily.	Indicated in age ≥ 12 years.
Sulfacetamide/Sulfur and Combinations				
Klaron, Ovace, Ovace Plus (sulfacetamide) Avar, Avar LS, Avar-e LS, Avar-e Emollient, Avar-e Green, BP 10-1, BP Cleansing Wash, Plexion, SSS 10-5, SulfaCleanse 8/4, Sulfamez, Sumadan, Sumadan XLT, Sumaxin, Sumaxin CP (sulfacetamide/sulfur)	Monotherapy: Cream, foam, gel, lotion, shampoo, wash external liquid With sulfur: cleanser, cloths, cream, emulsion, foam, gel, lotion, pad, suspension, wash Kits with sulfur: wash + cleanser, pad + cleanser, wash + sunscreen	Topical	Foam, cleanser cream, lotion, gel, bar, wash, kits: Apply 1 to 3 times daily.	Indicated in age ≥ 12 years.
Sulfur SAStid (sulfur/salicylic acid)	OTC only: Bar	Topical	Apply 1 to 3 times daily.	
Oral Retinoids				
Absorica, Absorica LD, Amnesteem, Claravis, Myorisan, Zenatane (isotretinoin)	Capsule	Oral	Amnesteem, Claravis, Myorisan, Zenatane: Twice daily with food. Absorica, Absorica LD: Twice daily with or without food.	Once daily dosing is not recommended. Duration of treatment: 15 to 20 weeks Pregnancy tests should be performed before prescribing, each month during therapy, and 1 month after discontinuation.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Baseline lipids and liver function tests should be performed. Absorica and Absorica LD are indicated in age ≥ 12 years. The other oral isotretinoin products have not been studied in children < 12 years of age.

Abbreviation: ER = extended release, OTC = over-the-counter, Rx = prescription
See the current prescribing information for full details
(*Clinical Pharmacology 2020, Lexi-comp 2020*)

CONCLUSION

- Current treatment of acne vulgaris is primarily topical agents. Guidelines suggest the use of combinations to treat acne (*Eichenfield et al 2013, Gollnick et al 2016, Nast et al 2016, Thiboutot et al 2018, Zaenglein et al 2016*).
- Dapsone (Aczone), clindamycin, erythromycin, and minocycline (Amzeeq) are topical antibiotics for the treatment of acne vulgaris. Most agents have formulations available as generics (Aczone 7.5% remains brand only, while the 5% formulation is available as a generic; minocycline is brand-only). Antibiotics have a slow onset of action and are at increased risk for bacterial resistance. Antibiotics should be used in combination therapy if used for more than a few weeks (*Eichenfield et al 2013, Thiboutot et al 2009*).
- Many benzoyl peroxide products are OTC agents. Various dosage formulations and strengths are available. Benzoyl peroxide is used in combination with other topical agents for acne. Excessive drying may occur with benzoyl peroxide use and may be observed as marked peeling, erythema, possible edema, and allergic contact sensitization. Additionally, benzoyl peroxide may bleach hair and/or fabric so care must be used to limit accidental exposure (*Lexi-comp 2020*). In 2014, the FDA warned that certain OTC topical acne products can cause rare but serious and potentially life-threatening allergic reactions or severe irritation. The hypersensitivity reactions may occur within minutes to a day or longer after product use. Based on the information reported to the FDA, it cannot be determined if the serious hypersensitivity reactions were triggered by the acne products' active ingredients, benzoyl peroxide or salicylic acid, the inactive ingredients, or by a combination of both (*FDA Drug Safety Communication 2014*).
- Topical retinoids, including adapalene (Differin), tazarotene (Arazlo, Fabior, Tazorac), tretinoin (Retin-A, Altreno, Atralin, Avita), and Aklief (trifarotene) are effective in the treatment of acne vulgaris. Combinations of topical retinoids include adapalene/benzoyl peroxide (Epiduo, Epiduo Forte) and clindamycin/tretinoin (Veltin, Ziana). In studies comparing the agents, no one agent was consistently more efficacious than another, and combination agents demonstrated greater efficacy when compared to monotherapy with their components. Guidelines do not recommend one retinoid over another (*Eichenfield et al 2013, Gollnick et al 2016, Thiboutot et al 2009, Zaenglein et al 2016*). Most of the adverse reactions associated with retinoids are dermatological and may lessen with continued use. Retinoids cause increased sun sensitivity, and their use should be avoided with other agents that cause excessive drying. Differin gel is now available as an OTC product.
- The topical benzoyl peroxide and antibiotic combination products include benzoyl peroxide/clindamycin (Acanya, Benzaclin, Duac, Neuac, and Onexton) and benzoyl peroxide/erythromycin (Benzamycin). The benzoyl peroxide/clindamycin products primarily differ in their respective strengths. Acanya contains 2.5% benzoyl peroxide and 1.2% clindamycin, Benzaclin contains 5% benzoyl peroxide and 1% clindamycin, Duac and Neuac contain 5% benzoyl peroxide and 1.2% clindamycin, and Onexton contains 3.75% benzoyl peroxide and 1.2% clindamycin. The benzoyl peroxide and antibiotic combination agents are effective for the treatment of acne vulgaris. Combination treatment with benzoyl peroxide and either clindamycin or erythromycin has been shown to be more effective than treatment with each individual agent alone (*Lookingbill et al 1997, Webster et al 2009, Thiboutot et al 2008, Chalker et al 1983, Cunliffe et al 2002, Leyden et al 2001, Xu et al 2016*). Current clinical guidelines support the use of combination treatment in order to limit the development of bacterial resistance (*Eichenfield et al 2013, Gollnick et al 2016, Thiboutot et al 2009, Zaenglein et al 2016*).

- Oral isotretinoin is a recommended treatment option for severe nodular acne and treatment-resistant moderate acne. (*Eichenfield et al 2013, Gollnick et al 2016, Thiboutot et al 2018, Zaenglein et al 2016*). Its efficacy was not found to be better than the combination of a systemic antibiotic with a topical agent (*Costa et al 2018*). It is available only through a restricted distribution program due to its teratogenic effects. If used in female patients, appropriate contraception is required (*Absorica/Absorica LD 2019*). Additionally, the agent is associated with several other adverse events that require monitoring.
- Two other treatment options are sulfacetamide and azelaic acid (Azelex). Sulfacetamide is available in a variety of dosage forms and strengths and in combination with sulfur. Azelaic acid, a branded agent, is another topical treatment option for acne and is recommended by the guidelines for both mild acne as monotherapy and for moderate acne in combination with another class of topical acne agents (*Nast et al 2016, Gollnick et al 2016, Zaenglein et al 2016*).

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Publication Date: April 3, 2020

Therapeutic Class Overview
Irritable Bowel Syndrome and Constipation Agents

INTRODUCTION

Irritable bowel syndrome (IBS)

- IBS is a gastrointestinal disorder that most commonly manifests as chronic abdominal pain and altered bowel habits in the absence of any organic disorder (*Wald 2019a, Wald 2019b*).
- IBS may consist of diarrhea-predominant (IBS-D; abnormal BMs are usually diarrhea), constipation-predominant (IBS-C; abnormal BMs are usually constipation), IBS with a mixed symptomatology (IBS-M), or unclassified IBS (IBS-U). Switching between the subtypes of IBS is also possible (*Ford et al 2018, Wald 2019a, Wald 2019b*).
- IBS is a functional disorder of the gastrointestinal tract characterized by symptoms of abdominal pain, discomfort and bloating, and abnormal bowel habits with bouts of diarrhea and/or constipation. The exact pathogenesis of the disorder is unknown; however, it is believed that altered gastrointestinal tract motility, visceral hypersensitivity, autonomic dysfunction, and psychological factors indicate disturbances within the enteric nervous system, which controls the gastrointestinal system (*Andresen et al 2008, Ford et al 2009, Quigley et al 2012, World Gastroenterology Organization [WGO] 2015*).
- Prevalence estimates of IBS range from 10 to 12%, and it typically occurs in young adulthood (*Ford et al 2018*). IBS-D is more common in men, and IBS-C is more common in women (*WGO 2015*).
- Symptoms of IBS often interfere with daily life and social functioning (*WGO 2015*).
- The general goals of therapy in IBS are to alleviate the patient's symptoms and to target any specific exacerbating factors (eg, medications, dietary changes), concerns about serious illness, stressors, or potential psychiatric comorbidities that may exist (*Ford et al 2018*).
- Non-pharmacological interventions to combat IBS symptoms include dietary modifications such as exclusion of gas-producing foods (eg, beans, prunes, Brussel sprouts, bagels, etc.), and consumption of probiotics, as well as psychosocial therapies (eg, hypnosis, biofeedback, etc.) (*Ford et al 2018*).
- Depending upon the clinical presentation of an individual's IBS condition, a number of therapies exist to help alleviate the constellation of disease symptoms. Commonly used agents that are often initiated for disease control include selective chloride channel activators (eg, Amitiza [lubiprostone]); guanylate cyclase-C agonists (eg, Linzess [linaclotide], Trulance [plecanatide]); mu-opioid receptor agonists (eg, Viberzi [eluxadoline]); poorly absorbable antibiotics (eg, Xifaxan [rifaximin]); serotonin-3 receptor antagonists (eg, Lotronex [alosetron]); antidepressants such as tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs); antispasmodics (eg, dicyclomine, hyoscine, etc.); select probiotics; and peppermint oil (*Ford et al 2018*).
- Amitiza (lubiprostone), Ibsrela (tenapanor), Linzess (linaclotide), Trulance (plecanatide), and Zelnorm (tegaserod) are Food and Drug Administration (FDA)-approved for the treatment of IBS-C in adults. Lubiprostone is indicated in women ≥ 18 years of age; tegaserod is indicated for the treatment of IBS-C in adult women < 65 years of age.
  - Tegaserod is a serotonin type 4 (5-HT_4) agonist FDA-approved in July 2002 for the short-term treatment of IBS-C in women and in August 2004 for the treatment of chronic idiopathic constipation (CIC) in men and women < 65 years of age. In 2007, tegaserod was removed from the United States (U.S) market due to safety concerns based on a postmarketing pooled safety analysis of 29 clinical trials which demonstrated a higher rate of serious cardiovascular events (including angina, myocardial infarction and stroke) in patients treated with tegaserod vs placebo (*FDA Gastrointestinal Drugs Advisory Committee [Zelnorm] 2018, FDA Multi-disciplinary review [Zelnorm] 2019*).
  - In 2018, the FDA Gastrointestinal Drugs Advisory Committee evaluated the safety and efficacy of tegaserod and recommended approval of tegaserod for the treatment of female patients < 65 years of age with IBS-C at a low cardiovascular risk; tegaserod was re-introduced in March 2019 (*Drugs@FDA 2020; FDA Gastrointestinal Drugs Advisory Committee [Zelnorm] 2018, FDA Multi-disciplinary review [Zelnorm] 2019*).
- Viberzi (eluxadoline) and Xifaxan (rifaximin) are FDA-approved for the treatment of IBS-D. Viberzi is a schedule IV controlled substance. Lotronex (alosetron) is FDA-approved with restrictions for the treatment of women who exhibit severe IBS-D and have failed conventional therapy.

Chronic idiopathic constipation (CIC)

- Amitiza (lubiprostone), Linzess (linaclotide), Motegrity (prucalopride), and Trulance (plecanatide) are indicated for the treatment of CIC. Symptoms of constipation are common with a prevalence of approximately 16% in adults overall and 33% in adults >60 years of age. Constipation is defined as < 3 bowel movements (BMs) per week with symptoms that may include hard stools, a feeling of incomplete evacuation, abdominal discomfort, bloating, and distention. Initial treatment typically includes osmotic laxatives, stimulant laxatives, and increased fiber intake (*American Gastroenterological Association [AGA] Medical Position Statement 2013, Bharucha et al 2013*).
  - Prucalopride, a selective 5-HT_4 receptor agonist, is a gastrointestinal prokinetic agent that stimulates colonic peristalsis (high-amplitude propagating contractions [HAPCs]), which increases bowel motility (*Shin et al 2014*).
  - The intestinal secretagogues, ie, lubiprostone, linaclotide, and plecanatide, exert their effects by increasing intestinal and colonic secretion of chloride-rich fluid into the intestinal lumen. There is no reported evidence indicating that these agents induce HAPCs.

Opioid-induced constipation (OIC)

- OIC is a frequent adverse event of opioid therapy. Opioids exert their action on the enteric nervous system causing dysmotility, decreased fluid secretion and sphincter dysfunction. Laxatives are typically prescribed but often are inadequate to completely relieve constipation (*Brock et al 2012*). There are 4 products approved for use in OIC:
  - Amitiza (lubiprostone) is FDA-approved for the treatment of OIC in adults with chronic, non-cancer related pain.
  - Relistor (methylnaltrexone) injection is an opioid receptor antagonist indicated for treatment of OIC in adults with chronic non-cancer pain and in patients with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care. Relistor has also been FDA-approved in a tablet formulation, which is indicated for the treatment of OIC in adults with chronic non-cancer pain.
  - Movantik (naloxegol) and Symproic (naldemedine) are once-daily oral peripherally acting mu-opioid receptor antagonists (PAMORAs) indicated for the treatment of OIC in adult patients with chronic non-cancer pain.
- For management of OIC, the AGA recommends laxatives as a first-line treatment (*Crockett et al 2019*). For patients with laxative-refractory OIC, naldemedine or naloxegol are recommended over no treatment, methylnaltrexone is suggested over no treatment, and there are no recommendations for the use of lubiprostone or prucalopride.

Traveler's diarrhea (TD)

- TD is a type of acute diarrhea that develops after the consumption of contaminated food or water during periods of travel. The disease is characterized by symptoms of loose stools and abdominal cramps. Although generally not serious, TD may result in inconveniences during travel, including changes to an itinerary, overseas medical encounters, and hospitalization (*Riddle et al 2017*).
  - For the prevention of TD, a 2017 guideline recommends prophylaxis with rifaximin in high-risk groups (eg, underlying health conditions); bismuth subsalicylate may be considered second-line in these situations. If rifaximin is used as prophylaxis, azithromycin should also be provided to patients in case of need for break-through therapy. For the treatment of TD, antimicrobials such as azithromycin, rifaximin, or a fluoroquinolone are recommended, with the travel destination guiding the drug(s) of choice (*Riddle et al 2017*).

Hepatic encephalopathy (HE)

- HE is a common complication of severe liver disease. Neuropsychiatric abnormalities, ranging from shortened attention span to lethargy, confusion, and coma, are all possible manifestations depending on disease severity. At this time, pharmacological treatment is only recommended for patients with overt HE, which is diagnosed based on a clinical examination and use of the West Haven Criteria and the Glasgow Coma Score. Secondary prophylaxis of HE after an overt HE episode is also recommended, as is primary prophylaxis in high-risk patients with cirrhosis (*Vilstrup et al 2014*).
  - Rifaximin is FDA-approved for the reduction in risk of overt HE recurrence in adults. A joint guideline from the American Association for the Study of Liver Diseases and the European Association for the Study of the Liver (AASLD/EASL) also recommend this agent as an adjunct therapy to lactulose for the prevention of overt HE recurrence and overt HE recurrence after the second episode (*Vilstrup et al 2014*).
- The scope of this review will focus upon Amitiza (lubiprostone), Ibsrela (tenapanor), Linzess (linaclotide), Lotronex (alosetron), Motegrity (prucalopride), Movantik (naloxegol), Relistor (methylnaltrexone bromide), Symproic (naldemedine), Trulance (plecanatide), Viberzi (eluxadoline), Xifaxan (rifaximin), and Zelnorm (tegaserod) for their respective FDA-approved indications, which are outlined in Table 2.
- Medispan Classes: Agents for CIC (Motegrity, Trulance); Gastrointestinal Chloride Channel Activators (Amitiza); IBS Agents (Ibsrela, Lotronex, Linzess, Viberzi, Zelnorm); Peripheral Opioid Receptor Antagonists (Movantik, Relistor, Symproic); Anti-infective Agents – Misc (Xifaxan)

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Amitiza (lubiprostone)	-
Ibsrela (tenapanor)	-
Linzess (linaclotide)	-
Lotronex (alosetron)	✔
Motegrity (prucalopride)	-
Movantik (naloxegol)	-
Relistor (methylnaltrexone bromide)	-
Symproic (naldemedine)	-
Trulance (plecanatide)	-
Viberzi (eluxadoline)	-
Xifaxan (rifaximin)	-
Zelnorm (tegaserod)	-

(*Clinical Pharmacology Web site 2020, Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. FDA Approved Indications

Indication	Amitiza (lubiprostone)	Ibsrela (tenapanor)	Linzess (linaclotide)	Lotronex (alosetron)	Motegrity (prucalopride)	Movantik (naloxegol)	Relistor (methylnaltrexone bromide)	Symproic (naldemedine)	Trulance (plecanatide)	Viberzi (eluxadoline)	Xifaxan (rifaximin)	Zelnorm (tegaserod)
Treatment of CIC in adults	✔		✔		✔				✔			
Treatment of OIC in adults with chronic, non-cancer pain	✔ *					✔	✔	✔				
Treatment of OIC in patients with chronic pain related to prior cancer or its treatment who do not require frequent (eg, weekly) opioid dosage escalation.	✔ *					✔	✔	✔				
Treatment of OIC in patients with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care							✔ †					
Treatment of IBS-C in women ≥ 18 years of age	✔											
Treatment of IBS-C in adult women < 65 years of age												✔ ‡
Treatment of IBS-C in adults		✔	✔						✔			
Treatment of IBS-D in adults										✔	✔	
Women with severe IBS-D who have: • chronic IBS symptoms (generally lasting 6 months or longer) • had anatomic or biochemical abnormalities of the gastrointestinal tract excluded, and not responded adequately to conventional therapy§				✔								

Indication	Amitiza (lubiprostone)	Ibsrela (tenapanor)	Linzess (linaclotide)	Lotronex (alosetron)	Motegrity (prucalopride)	Movantik (naloxegol)	Relistor (methylnaltrexone bromide)	Symproic (naldemedine)	Trulance (plecanatide)	Viberzi (eluxadoline)	Xifaxan (rifaximin)	Zelnorm (tegaserod)
Reduction in risk of overt HE recurrence in adults											✔	
Treatment of TD caused by noninvasive strains of *Escherichia coli* in patients ≥ 12 years of age											✔ ‖	

*Effectiveness of Amitiza in the treatment of opioid-induced constipation in patients taking diphenylheptane opioids such as methadone has not been established.
† Injection formulation only. Use of Relistor beyond 4 months in the treatment of OIC in patients with advanced illness has not been studied.
‡The safety and efficacy of Zelnorm have not been established in men with IBS-C.
§ IBS-D is severe if it includes diarrhea and ≥ 1 of the following: frequent and severe abdominal pain/discomfort, frequent bowel urgency or fecal incontinence, disability or restriction of daily activities due to IBS.
‖ Xifaxan should not be used in patients with TD complicated by fever or blood in the stool or diarrhea due to pathogens other than *E. coli*.

(*Prescribing information: Amitiza 2018, Ibsrela 2019, Linzess 2018, Lotronex 2019, Motegrity 2018, Movantik 2019, Relistor 2018, Symproic 2019, Trulance 2019, Viberzi 2018, Xifaxan 2019, Zelnorm 2019*)

- Lotronex was approved by the FDA in February of 2000 and was later withdrawn from the market due to numerous reports of serious and fatal gastrointestinal adverse events. Approval of a supplemental New Drug Application (sNDA) was accepted in July 2002 by the FDA to allow restricted marketing of Lotronex to treat only women with severe IBS-D. Physicians are required to complete training before prescribing Lotronex to ensure that the benefits and risks of the agent are considered before administering it to patients (*Lotronex FDA press release 2016*).

- 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

- There are currently no head-to-head trials comparing the available agents used in the treatment of CIC, OIC, IBS-C, and IBS-D.

IBS

- In 2 meta-analyses, linaclotide demonstrated significant improvements in the FDA-defined composite endpoint of improvement in both daily worst abdominal pain scores and complete spontaneous bowel movement (CSBM) frequency from baseline compared to placebo after 12 weeks and demonstrated a similar result when compared over 26 weeks (*Atluri et al 2014, Videlock et al 2013*). More patients in the placebo treatment arm failed to achieve the FDA endpoint compared with patients treated with linaclotide (82.6% vs 66%; relative risk [RR] of failure to respond, 0.80; 95% CI, 0.76 to 0.85).
- A 2018 network meta-analysis compared the relative efficacy of the secretagogues linaclotide, lubiprostone, plecanatide, and tenapanor (not available in the U.S.) for the treatment of IBS-C in 15 randomized controlled trials (N = 8462). Linaclotide 290 mg once daily was ranked first in efficacy based on the FDA-recommended endpoint for IBS-C trials, abdominal pain, and CSBMs; plecanatide 6 mg once daily was ranked highest for safety (*Black et al 2018*).
  - The network meta-analysis was updated in 2019 to include 3 12-week Phase 3 randomized controlled trials evaluating the efficacy of tegaserod in 2472 female patients with IBS-C. For the FDA-recommended endpoint, all agents, including tegaserod, were significantly more effective than placebo, but linaclotide 290 mcg daily was ranked as the most effective for achieving at least a 30% improvement in abdominal pain along with an increase of at least 1 CSBM/week from baseline for at least 50% of treatment-weeks; tegaserod 6 mg twice a day was ranked third. Indirect comparison of active treatments showed no significant differences between individual drugs and dosages (*Black et al 2019*).
- A network meta-analysis published in 2020 included 18 randomized controlled trials (N = 9844) and compared the efficacy of alosetron, eluxadoline, ramosetron, and rifaximin in patients with IBS-D or IBS-M. All agents were found to be more effective than placebo. In an analysis that ranked agents based on their efficacy in improving both abdominal pain

and stool consistency, effect on global symptoms of IBS, and effect on stool consistency, alosetron 1 mg twice daily was ranked highest (ie, most effective). Ramosetron 2.5 mcg once daily was ranked highest for relief from abdominal pain (*Black et al 2020*). For the treatment of IBS-C, placebo-controlled trials demonstrated that lubiprostone had a significantly higher percentage of overall responders. In multiple 12-week studies, lubiprostone-treated patients reported significant improvements in abdominal pain/discomfort, stool consistency, straining, constipation severity, and quality of life (*Drossman et al 2007, Drossman et al 2009, Johanson et al 2004, Johanson et al 2005, Johanson et al 2007, Johanson et al 2008a, Johanson et al 2008b*).

- In 2 randomized, double-blind, placebo-controlled, 12-week studies, there were significantly more overall responders (based on improved abdominal pain and weekly CSBM from baseline) with plecanatide 3 mg and 6 mg vs placebo in patients with IBS-C (Study 1: 30.2% vs 29.5% vs 17.8%, respectively; Study 2: 21.5% vs 24.0% vs 14.2%) (*Brenner et al 2018*).
- Three Phase 3 double-blind, placebo-controlled, multicenter, randomized controlled trials (301, 358, and 307) of similar design in 2470 adults patients evaluated the efficacy and safety of tegaserod vs placebo. In trial 301, treatment with tegaserod resulted in a statistically significant improvement in response rate vs placebo with a difference of 11.4% (95% CI, 3 to 30; p < 0.005). Trials 358 and 307 demonstrated treatment differences vs placebo of 4.7% and 5.3%, respectively, but results were not statistically significant. (*FDA Medical review(s) [Zelnorm] 2002, FDA Multi-disciplinary review [Zelnorm] 2019, Müller-Lissner et al 2001, Novick et al 2002*).
- A systematic review of various therapies for the treatment of IBS included 11 RCTs (n = 9242) evaluating tegaserod vs placebo for the treatment of IBS-C. The outcome of proportion of patients with persistent IBS-C symptoms with tegaserod was 55% (3301/6041) vs 64% (2032/3201) with placebo. Treatment with tegaserod was shown to be superior vs placebo with an RR of 0.85 (95% CI, 0.80 to 0.90) with a number needed to treat (NNT) of 10 (95% CI, 8 to 14) (*Ford et al 2009, Ford and Vandvik 2012*).
- A 2004 systematic review and meta-analysis included 4 double-blind controlled trials (n = 3564) evaluating tegaserod in the treatment of IBS-C. In each trial, a statistically significant effect on constipation, abdominal pain/discomfort, bloating and global relief with tegaserod treatment was demonstrated in women, with the difference between placebo and tegaserod of 10 to 15%, primarily due to a high placebo response (*Lesbros-Pantoflickova et al 2004*).
- Treatment with alosetron is associated with a significantly greater proportion of patients reporting adequate relief of IBS pain and discomfort, and improvements in bowel function compared to placebo (*Camilleri et al 2000, Camilleri et al 2001, Chey et al 2004, Lembo et al 2001, Lembo et al 2004, Rahimi et al 2008, Watson et al 2001*).
- A meta-analysis concluded that the 5-hydroxytryptamine type 3 (5-HT3) antagonists as a class significantly improve symptoms of non-constipating or IBS-D in both men and women compared to placebo; however, these agents were also associated with a greater increase in the risk of causing constipation compared to placebo (*Andresen et al 2008*).
- Alosetron treatment has been shown to positively impact global symptoms, as well as pain and discomfort in non-constipated females with IBS. This analysis further supports the increased chance of developing constipation with alosetron compared to placebo (*Cremonini et al 2003*).
- The safety and efficacy of eluxadoline for treatment of IBS-D were established in 2 randomized, multicenter, multinational, double-blind, placebo-controlled, Phase 3 clinical trials in which 2427 patients with IBS-D (meeting Rome III criteria) had average abdominal pain scores greater than 3 on a 0 to 10 scale during the week prior to randomization, and a Bristol Stool Scale (BSS) of 5.5 or greater with at least 5 days of BSS of 5 or more during the week prior to randomization. Patients were randomly assigned to receive eluxadoline 75 mg, 100 mg, or placebo twice daily. The primary endpoint was defined by the simultaneous improvement in the daily worst abdominal pain score by 30% or more compared to the baseline weekly average and a reduction in the BSS to 5 or less on at least 50% of the days within a 12-week or 26-week time interval. From weeks 1 through 12, the primary endpoint was achieved by 23.9% of patients in the 75 mg group (p = 0.01) and 25.1% of patients in the 100 mg group (p = 0.004) versus 17.1% of patients in the placebo group. From weeks 1 through 26, 23.4% in the 75 mg group (p = 0.11) and 29.3% in the 100 mg group (p < 0.001) achieved the primary endpoint compared to 19% in the placebo group (*Lembo et al 2016a*).
- The safety and efficacy of eluxadoline for the treatment of IBS-D were also studied in patients with an inadequate response to loperamide in a randomized, multicenter, multinational, double-blind, placebo-controlled, Phase 4 trial (n = 346). Patients with IBS-D (meeting Rome III criteria), average abdominal pain scores > 3 on a 0 to 10 scale during the week prior to randomization, a BSS of ≥ 5.5 with at least 5 days of BSS ≥ 5 during the week prior to randomization, and a self-reported inadequate response to loperamide within the previous year were randomized to eluxadoline 100 mg or placebo twice daily. The primary endpoint was the proportion of composite responders, defined as improvement in the daily worst abdominal pain score by 40% and < 5 BSS score for at least 50% of treatment days. Over the 12-week treatment period, significantly more eluxadoline- vs placebo-treated patients achieved the primary composite endpoint

(22.7% vs 10.3%; p = 0.002) as well as the individual components of the endpoint (improvement in stool consistency [27.9% vs 16.7%; p = 0.01] and improvement in the daily worst abdominal pain score by 40% [43.6% vs 31.0%; p = 0.02]) (*Brenner et al 2019*).

- The safety and effectiveness of rifaximin for treatment of IBS-D were established in 3 double-blind, placebo-controlled trials.
  - In the first 2 trials, 1,258 patients with IBS-D (Rome II criteria) were randomly assigned to receive rifaximin 550 mg 3 times daily (n = 624) or placebo (n = 634) for 14 days, and then followed for a 10-week treatment-free period. The primary endpoint for both trials was the proportion of patients who achieved adequate relief of IBS signs and symptoms for at least 2 of 4 weeks during the month following 14 days of treatment. More rifaximin-treated patients reported improvements in abdominal pain and stool consistency than those on placebo (Trial 1: 47% vs 39%; p < 0.05; Trial 2: 47% vs 36%; p < 0.01 in rifaximin and placebo groups, respectively).
  - TARGET3 was the third trial, which evaluated repeat courses of rifaximin in adult patients with IBS-D (Rome III criteria) for up to 46 weeks. During a 14-day open-label phase, 1,074 patients responded to rifaximin and were evaluated over 22 weeks for continued response or recurrence of IBS symptoms. A total of 636 patients who developed recurrent signs and symptoms after a single treatment course of rifaximin were randomized to receive either rifaximin 550 mg 3 times daily (n = 328) or placebo (n = 308) for 2 additional 14-day courses separated by 10 weeks. More patients treated with rifaximin than placebo were responders in abdominal pain and stool consistency in this phase of the study (38% vs 31% in rifaximin and placebo groups, respectively; p < 0.05) (*Lembo et al 2016b*).
- The safety and effectiveness of tenapanor for treatment of IBS-C were established in 2 double-blind, placebo-controlled, randomized, multicenter trials.
  - In the T3MPO-1 trial, 606 patients with IBS-C received tenapanor 50 mg 2 times daily (n = 307) or placebo (n = 299) for 12 weeks, followed by a 4-week withdrawal period. The primary endpoint was the proportion of patients achieving a reduction in weekly worst abdominal pain ≥ 30% and an increase of ≥ 1 CSBM, both in the same week, for ≥ 6 weeks. After 12 weeks, 27.0% of patients treated with tenapanor met the primary endpoint compared to 18.7% of patients treated with placebo (p = 0.02). More patients in the tenapanor group had reduced abdominal pain compared with placebo (44.0% vs 33.1%, respectively; p = 0.008) (*Chey et al 2020*).
  - In the the T3MPO-2 trial, 620 patients with IBS-C received tenapanor 50 mg 2 times daily or placebo for 26 weeks. The primary endpoint was the proportion of patients achieving a reduction in weekly abdominal pain ≥ 30% and an increase of ≥ 1 CSBM, both in the same week, for ≥ 6 weeks during the first 12 weeks of treatment. After 12 weeks, 37.0% of patients treated with tenapanor met the primary endpoint vs 24% of patients treated with placebo (treatment difference, 13%; 95% CI, 6% to 20%) (*ClinicalTrials.gov Web site, Ibsrela prescribing information 2019*).

IBS and CIC

- A 2018 systematic review and meta-analysis compared the efficacy of intestinal secretagogues (ie, linaclotide, lubiprostone, plecanatide, and tenapanor [currently under investigation for IBS-C]) for the treatment of chronic constipation or IBS-C (*Lasa et al 2018*). For patients with chronic constipation, intestinal secretagogues were superior to placebo for increasing the number of CSBMs per week (RR, 1.87; 95% CI, 1.24 to 2.83 [analysis included linaclotide, lubiprostone, and plecanatide]) and for achieving ≥ 3 SBMs per week (RR, 1.56; 95% CI, 1.31 to 1.85 [analysis included linaclotide and lubiprostone]). For those with IBS-C, intestinal secretagogues were superior to placebo for increase in CSBMs per week (RR, 2.44; 95% CI, 1.51 to 3.93 [analysis included linaclotide and tenapanor]) and for achieving ≥ 3 SBMs per week (RR, 1.97; 95% CI, 1.74 to 2.24 [analysis included linaclotide only).
- In a systematic review and meta-analysis, both linaclotide and plecanatide were efficacious for IBS-C and CIC compared to placebo. Diarrhea was more frequent with both drugs compared to placebo. In an indirect comparison, there were no differences between the 2 agents for efficacy in CIC, efficacy in IBS-C, frequency of diarrhea, or study withdrawal due to diarrhea (*Shah et al 2018*).
- A network meta-analysis of 13 RCTs evaluated the efficacy and tolerability of tegaserod for the treatment of IBS and chronic constipation in patients, predominantly women, ≥ 12 years of age (*Evans et al 2007*).
  - In patients with IBS-C, for the Subject Global Assessment (SGA) of relief in patients, tegaserod resulted in a statistically significant benefit in 2 trials, compared with a nonsignificant trend for benefit in the remaining 2 studies. For abdominal pain and discomfort, the RR for being a responder with tegaserod vs placebo was non-significant; for bowel habits (as measured by responder rate), 1 trial did not suggest a benefit with tegaserod, and 2 trials showed a nonsignificant trend in favor of tegaserod.
  - For patients with chronic constipation, the RR of being a responder in terms of CSBMs/week with tegaserod 12 mg vs placebo was 1.54 (95% CI, 1.35 to 1.75), with a weighted mean difference (WMD) of 0.6 (95% CI, 0.42 to 0.78). Differences between tegaserod and placebo in increases in BM frequency were small (< 1/week).

CIC

- A network meta-analysis demonstrated linaclotide and lubiprostone to be superior to placebo for the treatment of CIC. Treatment with linaclotide resulted in a significant increase in the proportion of patients with ≥ 3 CSBMs/week compared with placebo with an RR of 1.96 (95% confidence interval [CI], 1.12 to 3.44), and was superior vs placebo with an increase over baseline by ≥ 1 CSBM/week (RR, 1.72; 95% CI, 1.18 to 2.52). For change from baseline in the number of SBMs/week, the weighted mean difference (WMD) with lubiprostone was 1.91 (95% CI, 1.41 to 2.41) and WMD with linaclotide was 2.11 (95% CI, 1.68 to 2.54) (*Nelson et al 2017*).
- A meta-analysis demonstrated the total pooled treatment effect of spontaneous bowel movements (SBMs)/week in patients with CIC or IBS-C was greater in lubiprostone-treated patients compared with placebo (combined standardized difference in means, 0.419; 95% CI, 0.088 to 0.750; p < 0.001) (*Li et al 2016*).
- A meta-analysis of 16 randomized controlled trials evaluated the safety and efficacy of prucalopride in the management of CIC (*Sajid et al 2016*). The primary outcome measure was the incidence of SBMs per week, and the secondary outcome measure was adverse events.
  - Based on data from 9 trials, prucalopride 2 mg significantly increased the frequency of SBMs per week compared with placebo (standardized mean difference [SMD] 0.34; 95% CI, 0.11 to 0.56; I^2 = 78%; p = 0.003).
  - The risk of developing adverse events (eg, headache, abdominal cramps, excessive flatulence, dizziness, diarrhea, rash) was higher in the prucalopride 2 mg group (odds ratio [OR], 1.76; 95% CI, 1.33 to 2.34; I^2 = 53%; p < 0.0001). The majority of adverse events were reported within the first 24 hours of initiation of therapy and were transient.
- A systematic review and meta-analysis evaluated the efficacy of serotonin type 4 (5-HT_4) agonists, including prucalopride, velusetrag, and naronapride (not approved in the U.S.) for the treatment of CIC. 5-HT_4 agonists were superior to control for all measured outcomes (*Shin et al 2014*).
  - The proportion of patients randomized to a 5-HT_4 agonist who achieved a mean of ≥ 3 CSBMs per week was 27.5% vs 17.2% of patients randomized to control (RR, 1.85; 95% CI, 1.23 to 2.79; I^2 = 89%; p < 0.001).
  - Overall, 46.7% of patients randomized to a 5-HT_4 agonist achieved a mean increase of ≥ 1 CSBM per week over baseline vs 30.8% of control patients (RR, 1.57; 95% CI, 1.19 to 2.06; I^2 = 89%; p < 0.001).
  - 5-HT_4 agonists also showed significant improvement over control for patient-reported quality of life (QOL) measures.
  - Adverse events were more common with 5-HT_4 agonists than with control (RR, 1.25; 95% CI, 1.14 to 1.38) and included headache, diarrhea, nausea, and abdominal pain.
- In another meta-analysis, treatment with linaclotide 145 mcg demonstrated significant improvements in the weekly frequency of CSBMs from baseline compared with placebo in patients with CIC (RR, 3.80; 95% CI, 2.20 to 6.55). Results were similar for abdominal discomfort or bloating responders for linaclotide 145 mg vs placebo, with pooled RRs of 1.57 (95% CI, 1.26 to 1.97) and 1.97 (95% CI, 1.44 to 2.69), respectively (*Videlock et al 2013*).
- A network meta-analysis of 33 randomized controlled trials involving 17,214 adult patients with CIC ranked prucalopride 2 mg once daily first for efficacy among other agents used for CIC (RR, 0.82; 95% CI, 0.78 to 0.86), when the endpoint was defined as failure for achieving ≥ 3 CSBMs/week at 12 weeks (*Luthra et al 2019*).
- A double-blind, placebo-controlled, multicenter, randomized controlled trial demonstrated that treatment with linaclotide 72 mcg improved the CSBM frequency over 12-weeks compared with placebo, with 13.4% of linaclotide-treated patients meeting responder requirements compared with 4.7% in the placebo group (OR 3.0; 95% CI, 1.8% to 5.2%) (*Schoenfeld et al 2018*).
- Results from a long-term safety study illustrated that overall lubiprostone was well tolerated. The most commonly reported events were diarrhea, nausea, urinary tract infection, sinusitis, abdominal distension, and headache. Significant changes from baseline in hematology, laboratory values, vital signs, weight, body mass index and physical examination were not seen over the study duration (*Chey et al 2012*).
- Two double-blind, placebo-controlled, multicenter, randomized controlled trials demonstrated that treatment with plecanatide 3 mg significantly increased weekly CSBM frequency as measured by the overall CSBM responder rate vs placebo (Study 1: 21.0% vs 10.2%; p < 0.001; Study 2: 20.1% vs 12.8%; p = 0.004) (*DeMicco et al 2017, Miner et al 2017*).
- Six double-blind, placebo-controlled, multicenter, randomized controlled trials of similar design in adults (N = 2484) evaluated the safety and efficacy of prucalopride for the treatment of CIC in an integrated analysis of the results (*Camilleri et al 2016, FDA briefing document [Prucalopride] 2018).*
  - The percentage of patients with a mean frequency of ≥ 3 CSBMs/week over a 12-week treatment period was significantly higher with prucalopride 2 mg/day (27.8%) vs placebo (13.2%) (OR, 2.68; 95% CI, 2.16 to 3.33; p < 0.001); the NNT with prucalopride was 8.8 (95% CI, 7.1 to 11.6). Efficacy and safety outcomes were not significantly different between men and women.

- The proportion of patients with a mean increase of ≥ 1 CSBM/week was 47.0% with prucalopride vs 29.9% with placebo ($p < 0.001$).
- Out of the 6 trials, the 24-week trial failed to demonstrate statistical significance for the primary endpoint after both 12 and 24 weeks, causing moderate heterogeneity. The reasons for the smaller treatment effect in this study remain unclear.
- Due to its differing mode of action, prucalopride may be beneficial for patients with CIC who have an insufficient quantity of high-amplitude propagating contractions (HAPCs) or in those who do not respond to other medications (*Camilleri et al 2016*).

OIC

- Two randomized, double-blind, placebo-controlled trials, COMPOSE-1 and COMPOSE-2, were conducted in adult patients with chronic non-cancer pain and OIC to assess the efficacy and safety of naldemedine. The primary endpoint was the proportion of responders, where response was defined as at ≥ 3 SBMs per week. Patients in COMPOSE-1 and COMPOSE-2 were randomized to receive naldemedine 0.2 mg (n = 274; n = 277) or placebo (n = 273; n = 276) once daily for 12 weeks. Results from both COMPOSE-1 and COMPOSE-2 showed that participants receiving naldemedine 0.2 mg experienced a significantly higher response compared to patients receiving placebo in both studies (COMPOSE-1 responders: 47.6% vs 34.6%; $p = 0.002$ and COMPOSE-2 responders: 52.5% vs 33.6%; $p<0.0001$, respectively). Treatment-related adverse events due to gastrointestinal disorders were more common with naldemedine than with placebo in both studies (15% vs 7% and 16% and 7%, respectively) (*Hale et al 2017*).
- COMPOSE-4 was a 2-week randomized, double-blind, placebo-controlled trial of naldemedine 0.2 mg in patients with OIC and cancer, and COMPOSE-5 was a 12-week, open-label extension study. In COMPOSE-4, there were significantly more SBM responders in the naldemedine group compared to placebo (71.1% vs 34.4%; $p < 0.0001$). Treatment-emergent adverse events were also higher with naldemedine vs placebo (44.3% vs 26.0%; $p = 0.01$). In the extension study, 80.2% of patients experienced a treatment-emergent adverse event, most commonly gastrointestinal adverse events (*Katakami et al 2017*).
- In a 2019 meta-analysis of 6 randomized controlled trials (N = 2762), naldemedine was superior to placebo in SBM response rate (OR, 3.00; 95% CI, 1.93 to 4.65), change in SBM frequency (OR, 6.46; 95% CI, 4.73 to 8.20), and change in complete SBM frequency (OR, 5.93; 95% CI, 4.90 to 6.96) (*Esmadi et al 2019*).
- A total of 1,300 patients were enrolled in 3, double-blind, randomized controlled trials evaluating lubiprostone compared to placebo in patients with chronic, non-cancer related pain on stable opioid therapy and constipation. In Study 1, overall responder rate, the primary outcome, was defined as ≥ 1 SBM improvement over baseline for all treatment weeks and ≥ 3 SBMs per week for at least 9 weeks of the 12-week study period. Lubiprostone (27.1%) had a significantly higher "overall responder rate" than placebo (18.9%; $p = 0.03$) (*Jamal et al 2015*). The primary outcome parameter for Study 2 and 3 was the mean change from baseline in SBM frequency at week 8. In Study 2, lubiprostone significantly increased the mean change from baseline in SBM frequency compared to placebo ($p = 0.004$). In Study 3, the difference was not statistically significant; however, Study 3 was the only study that enrolled patients who received diphenylheptane opioids such as methadone (*Amitiza prescribing information 2018*). Studies 2 and 3 have not been published in a peer-reviewed journal at this time.
- A prospective, randomized, double-blind, placebo-controlled trial was conducted to evaluate the efficacy and safety of lubiprostone for relieving symptoms of OIC in adult patients with chronic non-cancer pain. OIC was defined as < 3 SBMs per week. Patients were randomized to receive lubiprostone 24 mcg (n = 210) or placebo (n = 218) twice daily for 12 weeks. The primary endpoint was change from baseline in SBM frequency at week 8. Changes from baseline in SBM frequency rates were significantly higher at week 8 ($p = 0.005$) and overall ($p = 0.004$) in patients treated with lubiprostone compared with placebo. The most common treatment-related adverse events with lubiprostone and placebo were nausea (16.8% vs 5.8%, respectively), diarrhea (9.6% vs 2.9%, respectively), and abdominal distention (8.2% vs 2.4%, respectively). No lubiprostone-related serious adverse events occurred (*Cryer et al 2014*).
- A 2013 systematic review evaluated pharmacological therapies for the treatment of OIC. A total of 14 randomized clinical trials of mu-opioid receptor antagonists were included. All treatments, including methylnaltrexone, naloxone, and alvimopan, were superior to placebo for the treatment of OIC. Lubiprostone was included in the review; however, the reporting of data precluded meta-analysis (*Ford et al 2013*).
- In 2014, another systematic review of 21 randomized clinical trials evaluated 7 pharmacological treatments for OIC. Efficacy assessment was based on objective outcome measures (OOMs): BM frequency, BM within 4 hours, and time to first BM. Methylnaltrexone showed improvements in all 3 OOMs. Randomized controlled trials with naloxone and alvimopan tended to be effective for BM frequency measures. Naloxegol (≥12.5 mg) improved all OOMs. Though effectiveness of lubiprostone was demonstrated for all OOMs, group differences were small to moderate. CB-5945 (not

FDA-approved) and prucalopride (not FDA-approved for OIC) tended to increase BM frequency, especially with doses of 0.1 mg twice daily and 4 mg daily, respectively. Besides nausea and diarrhea, abdominal pain was the most frequent adverse event for all drugs except for alvimopan. Treatment-related serious adverse events were slightly higher for alvimopan (cardiac events) and prucalopride (severe abdominal pain, headache) (*Siemens et al 2015*).

- The efficacy of naloxegol has been established in K4 and K5, 2 replicate Phase 3 clinical trials with a total of 1,352 participants with OIC who had taken opioids for at least 4 weeks for non-cancer related pain. Participants were randomly assigned to receive oral naloxegol 12.5 mg or 25 mg or placebo once daily for 12 weeks. The trials were designed to measure a response rate, defined as ≥ 3 SBMs per week and an increase of ≥ 1 SBM from baseline.
  - Results from K4 showed that participants receiving naloxegol 25 mg or naloxegol 12.5 mg both experienced a significantly higher response rate compared to participants receiving placebo ($p = 0.001$ and $p = 0.02$, respectively). Results from K5 also showed significantly higher response rates in participants receiving naloxegol 25 mg vs placebo ($p = 0.02$) but did not show a significant difference in response rate in patients receiving naloxegol 12.5 mg vs placebo ($p = 0.2$) (*Chey et al 2014*).
  - In K4, patients with an inadequate response to laxatives achieved a significantly higher response with naloxegol 25 mg vs placebo ($p = 0.002$) and with naloxegol 12.5 mg vs placebo ($p = 0.03$). In K5, patients receiving naloxegol 25 mg achieved a significantly higher response rate vs placebo ($p = 0.01$); however, patients receiving naloxegol 12.5 mg did not have a significantly higher response rate.
  - Median time to first SBM was significantly shorter with both naloxegol 12.5 mg and 25 mg compared to placebo in K4 and was significantly shorter with naloxegol 25 mg in K5 ($p < 0.001$ for all comparisons).
  - Average pain scores and opioid use remained relatively stable in both studies for patients receiving naloxegol; thus, centrally mediated analgesia was preserved.
- Clinical trials of methylnaltrexone injection in patients with advanced illness have shown response over several months with most patients reporting laxative effects similar to SBMs and predictable timing (*Bull et al 2015, Thomas et al 2008*). Similar findings have been reported in patients with OIC with chronic non-cancer pain (*Michna et al 2011, Webster et al 2017*).
- The efficacy of methylnaltrexone tablets was demonstrated in a randomized, double-blind, placebo-controlled study in patients using opioids for chronic non-cancer pain. Patients were randomized to methylnaltrexone (150 mg, 300 mg, or 450 mg) or placebo once daily for a period of 4 weeks followed by as-needed dosing for 8 weeks. A responder to methylnaltrexone treatment was defined as a patient with ≥ 3 SBMs per week, with an increase of ≥ 1 SBMs per week over baseline, for at least 3 weeks in the 4-week treatment period. The percentage of patients classified as responders was 42.8%, 49.3% ($p = 0.03$ vs placebo), 51.5% ($p = 0.005$ vs placebo), and 38.3% in the methylnaltrexone 150 mg, 300 mg, 450 mg and placebo groups, respectively (*Rauck et al 2017*).
- A systematic review and network analysis compared the efficacy and safety of agents for the treatment of OIC, including lubiprostone, naldemedine, naloxegol, subcutaneous (SC) and oral methylnaltrexone, and prucalopride (not FDA-approved for OIC) and alvimopan (not FDA-approved for OIC) (*Sridharan and Sivaramakrishan 2018*). Observations from 16 randomized controlled trials with 4048 patients demonstrated that lubiprostone, naldemedine, naloxegol, and SC and oral methylnaltrexone performed better vs placebo in terms of rescue-free bowel movements (RFBM). Based on the odds ratios from direct and indirect pooled estimates, treatment with SC methylnaltrexone resulted in significantly improved RFBMs vs lubiprostone, naloxegol, and oral methylnaltrexone. Lubiprostone and naldemedine were associated with increased risks of adverse events, while SC methylnaltrexone did not significantly affect the analgesia due to background opioid use. Of note, the quality of evidence for the comparisons was either low or very low.
- Another systematic review and network analysis of 27 studies found methylnaltrexone, naloxone, naloxegol, naldemedine, alvimopan, and lubiprostone significantly more efficacious than placebo for OIC (*Nee et al 2018*).
- A systematic review and network meta-analysis of 27 studies compared the efficacy and safety of methylnaltrexone, naloxone, naldemedine, naloxegol, lubiprostone, linaclotide, plecanatide, and several agents that are not currently approved in the U.S. in OIC. The authors found that when non-response was defined as a failure to achieve an average of ≥ 3 BMs per week with an increase of ≥ 1 BM per week from baseline or an average of ≥ 3 BMs per week, naloxone was the most efficacious treatment for OIC (RR, 0.65; 95% CI, 0.52 to 0.80) and the safest when ranked against other agents. When non-response was defined as only failure to achieve an average of ≥ 3 BMs per week with an increase of ≥ 1 BM per week from baseline, naldemedine was found to be the most efficacious (RR, 0.66; 95% CI, 0.56 to 0.77), followed by alvimopan (RR, 0.74; 95% CI; 0.57 to 0.94) (*Luthra et al 2018*).

TD

- Both a 2012 and 2017 meta-analysis including 4 and 5 randomized, placebo-controlled trials, respectively, demonstrated the superiority of rifaximin in preventing TD. In the 2012 analysis by *Alajbegovic et al*, rifaximin reduced the risk of

disease by 67% (RR, 0.33; 95% CI, 0.24 to 0.45), while the 2017 analysis by *Ng et al* showed a 52.2% RR reduction (RR, 0.478; 95% CI, 0.375 to 0.610). Neither analysis reported any new safety signals (*Alajbegovic et al 2012, Ng et al 2017*).

HE

- Interventions for the treatment of overt HE were compared in a 2014 network meta-analysis of 20 randomized controlled trials (N = 10,007). Results showed no significant difference between neomycin and rifaximin when considering the outcomes of clinical improvement, blood ammonia concentration, and mental status. However, neomycin demonstrated an increased risk of adverse events when compared to rifaximin (OR, 14.03; 95% CI, 0.06 to 3035.53) (*Zhu et al 2015*).
- A 2019 meta-analysis evaluated whether the addition of rifaximin to lactulose improved outcomes in patients with overt HE. A total of 2276 patients were included across 5 randomized controlled trials and 5 observational studies. In a pooled analysis of data from all 10 studies, combination therapy improved efficacy (risk difference [RD], 0.26; 95% CI, 0.19 to 0.32) and reduced the risk of death (RD, -0.11; 95% CI, -0.19 to -0.03). Similar trends were seen in separate analyses that included only data from the randomized controlled trials. The risk of adverse events was similar between combination therapy and lactulose alone (RD, −0.06; 95% CI, −0.24 to 0.13) (*Wang et al 2019*).
- A meta-analysis of 25 randomized controlled trials involving 1564 patients with cirrhosis and minimal HE revealed that rifaximin (OR, 7.53; 95% predictive interval [PrI], 4.45 to 12.73) and lactulose (OR, 5.39; 95% PrI, 3.60 to 8.0) are more effective agents to reverse minimal HE compared with placebo or no treatment (*Dhiman et al 2019*).

CLINICAL GUIDELINES

IBS

- The 2018 American College of Gastroenterology (ACG) monograph on the management of IBS makes the following statements (reported with the strength of recommendation and quality of evidence, respectively) (*Ford et al 2018*):
  - Recommends linaclotide, plecanatide, and lubiprostone for overall symptom improvement in patients with IBS-C (strong; high, moderate, and moderate quality of evidence rating, respectively).
  - Suggests rifaximin for reduction in global IBS symptoms, as well as bloating in non-constipated patients (weak; moderate)
  - Suggests alosetron for overall symptom improvement in female patients with IBS-D (weak; low quality).
  - Suggests eluxadoline for overall symptom improvement in patients with IBS-D (weak; moderate).
  - Recommends fiber for overall symptom improvement (strong; moderate).
  - Antidepressants: Recommends TCAs for overall symptom improvement (strong; high quality); suggests SSRIs for overall symptom improvement (weak; low quality).
  - Suggests against polyethylene glycol (PEG) and loperamide for overall symptom improvement.
- The AGA guideline on management of IBS makes the following statements (reported with the strength of recommendation and quality of evidence, respectively) (*Weinberg et al 2014*):
  - Recommends using linaclotide (over no drug treatment) in patients with IBS-C (strong; high)
  - Suggests using lubiprostone (over no drug treatment) in patients with IBS-C (conditional; moderate)
  - Suggests using rifaximin (over no drug treatment) in patients with IBS-D (conditional; moderate)
  - Suggests using alosetron (over no drug treatment) in patients with IBS-D to improve global symptoms (conditional; moderate)
- The 2015 WGO guideline on IBS lists rifaximin and alosetron as second-line therapies for IBS-D, although it notes a risk of ischemic colitis and constipation with alosetron. Lubiprostone and linaclotide are noted to be safe and effective for the treatment of IBS-C (*WGO 2015*).

CIC

- The 2014 ACG monograph on the management of IBS and CIC makes the following statements (reported with the strength of recommendation and quality of evidence, respectively) (*Ford et al 2014*). Of note, only statements pertaining to CIC are included as the monograph on IBS management was updated in 2018:
  - Linaclotide is effective in CIC (strong; high)
  - Lubiprostone is effective in the treatment of CIC (strong; high)
  - Prucalopride is more effective than placebo in improving symptoms of CIC (strong; moderate)
  - Although supported by varying levels of evidence, fiber supplements, osmotic laxatives (PEG, lactulose), and stimulant laxatives (sodium picosulfate [not available in the U.S. as a single agent], bisacodyl) are recommended for the treatment of CIC (all strong recommendations).

- Additional guidelines on the management of constipation suggest increased fiber intake and osmotic laxatives. Stimulant laxatives are to be used as needed or as “rescue agents”. Lubiprostone and linaclotide can be considered when symptoms of constipation do not respond to laxatives (*AGA 2013, Bharucha et al 2013, Lindberg et al 2010*).

OIC

- For the management of OIC, the AGA recommends laxatives as a first-line treatment (*Crockett et al 2019*). For patients with laxative-refractory OIC, naldemedine or naloxegol are recommended over no treatment. Methylnaltrexone is suggested over no treatment, but authors note that evidence supporting the use of this agent for OIC is low and costs may be prohibitive. The AGA does not make any recommendations for the use of lubiprostone or prucalopride for OIC due to lack of evidence.

TD

- Guidelines for TD were published in 2017 and recommend rifaximin for moderate-to-severe cases of the disease. If rifaximin is used as prophylaxis, azithromycin should also be provided to patients in case of need for breakthrough therapy. For the treatment of TD, antimicrobials such as azithromycin, rifaximin, or a fluoroquinolone are recommended, with the travel destination guiding the drug(s) of choice (*Riddle et al 2017*).

HE

- A joint guideline from AASLD and EASL recommends rifaximin as an adjunct therapy to lactulose for the prevention of overt HE and recurrent episodes of HE after the second episode (*Vilstrup et al 2014*).

SAFETY SUMMARY

- Contraindications:
  - Amitiza is contraindicated with known or suspected mechanical gastrointestinal obstruction.
  - Lotronex has several contraindications, including a history of chronic or severe constipation or sequelae from constipation; intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation, and/or adhesions; ischemic colitis; impaired intestinal circulation, thrombophlebitis, or hypercoagulable state; Crohn’s disease or ulcerative colitis; diverticulitis; severe hepatic impairment.
  - Ibsrela, Linzess, and Trulance are contraindicated in patients 6 years of age or younger and in patients with known or suspected mechanical gastrointestinal obstruction.
  - Motegrity is contraindicated in patients with intestinal perforation or obstruction due to a structural or functional disorder of the gut wall, obstructive ileus, and severe inflammatory conditions of the intestinal tract such as Crohn’s disease, ulcerative colitis, and toxic megacolon/megarectum; and when there is a known serious or severe hypersensitivity reaction to the drug or any of its excipients.
  - Movantik is contraindicated in patients with known or suspected gastrointestinal obstruction and at increased risk of recurrent obstruction, in patients with concomitant use of strong cytochrome (CYP) 3A4 inhibitors (eg, clarithromycin, ketoconazole), and when there is a known serious or severe hypersensitivity reaction to the drug or any of its excipients.
  - Relistor is contraindicated in patients with known or suspected mechanical gastrointestinal obstruction and at increased risk of recurrent obstruction.
  - Symproic is contraindicated in patients with a known or suspected gastrointestinal obstruction or at increased risk of recurrent obstruction, and when there is a known serious or severe hypersensitivity reaction to the drug or any of its excipients.
  - Viberzi has several contraindications, including use in patients with the following conditions: known or suspected biliary duct obstruction or sphincter of Oddi disease or dysfunction; alcoholism, alcohol abuse, alcohol addiction, or more than 3 alcoholic beverages daily; history of pancreatitis or structural diseases of the pancreas including known or suspected pancreatic duct obstruction; severe hepatic impairment; history of severe constipation or sequelae from constipation; known or suspected mechanical gastrointestinal obstruction; use in patients without a gallbladder; or known hypersensitivity to the drug.
    - On March 15, 2017, the FDA warned that Viberzi should not be used in patients who do not have a gallbladder. The safety announcement was based on an FDA review that found these patients have an increased risk of developing serious pancreatitis that could result in hospitalization or death (*FDA Drug Safety Communication 2017*). A contraindication was added to the prescribing label for patients without a gallbladder due to an increased risk of developing serious pancreatitis. Pancreatitis was reported in patients taking either the 75 mg or 100 mg dose with most of the cases of serious pancreatitis occurring within a week of starting treatment.
  - Xifaxan is contraindicated in patients with a hypersensitivity to rifaximin, any of the rifamycin antimicrobial agents, or any of the components in Xifaxan.

- Zelnorm is contraindicated in patients with a history of myocardial infarction, stroke, transient ischemic attack, or angina; a history of ischemic colitis or other forms of intestinal ischemia; severe renal impairment or end-stage renal disease; moderate or severe hepatic impairment; a history of bowel obstruction, symptomatic gallbladder disease, suspected sphincter of Oddi dysfunction, or abdominal adhesions; and hypersensitivity to tegaserod.

- Boxed Warnings:
  - Ibsrela, Linzess, and Trulance are contraindicated in pediatric patients 6 years of age and younger due to the risk of serious dehydration; use should be avoided in children 6 to 17 years of age for Linzess and Trulance and in children 6 to 12 years of age for Ibsrela.
  - Lotronex has a Boxed Warning regarding serious gastrointestinal adverse reactions such as ischemic colitis and serious complications of constipation that may lead to hospitalization, blood transfusion, surgery, and/or death. If patients develop constipation or ischemic colitis, Lotronex should be discontinued. Lotronex should be used only in female patients with severe IBS-D who have not benefited from usual therapies.
- Warnings/precautions:
  - Amitiza: nausea (29% incidence in CIC), diarrhea (12% in CIC), syncope and hypotension, dyspnea, and bowel obstruction
  - Motegrity and Zelnorm: Worsening of depression and emergence of suicidal thoughts and behavior may occur during therapy. Patients should discontinue the drug and contact their provider if these situations occur.
  - Movantik, Relistor, Trulance, and Zelnorm: Discontinue in the event of severe, persistent, or worsening abdominal pain or diarrhea.
  - Ibsrela: Dosing should be suspended if severe diarrhea occurs.
  - Relistor and Symproic: Use with caution in patients with known or suspected lesions of the gastrointestinal tract; discontinue in the event of severe, persistent, or worsening abdominal pain.
  - Viberzi: Constipation, sometimes requiring hospitalization, has been reported following administration of Viberzi. Patients who develop severe constipation should discontinue treatment and contact their health care provider immediately.
  - Xifaxan: Use in travelers' diarrhea complicated by fever and/or blood in the stool should be avoided due to pathogens other than *E.coli*. The agent may contribute to *Clostridium difficile*-associated diarrhea.
  - Zelnorm: Avoid use in patients with severe diarrhea. Patients should contact their healthcare provider if severe diarrhea, hypotension or syncope occur. Zelnorm may increase the risk for stroke, myocardial infarction, and cardiovascular death; patients should be assessed for cardiovascular risk factors prior to therapy initiation. Patients may develop ischemic colitis, which may require hospitalization. Patients should be monitored for worsening of depression and any signs of suicide attempt and/or ideation.
- Drug Interactions
  - Amitiza: Diphenylheptane opioids such as methadone may interfere with the efficacy of Amitiza.
  - Ibsrela: Co-administration with itraconazole decreases levels of Ibsrela.
  - Lotronex: Clinically significant drug interactions associated with Lotronex include CYP1A2 moderate inhibitors, CYP3A4 inhibitors, drugs that decrease gastrointestinal motility, and fluvoxamine. Concomitant use of Lotronex and fluvoxamine is contraindicated.
  - Motegrity: Concomitant administration of Motegrity and erythromycin may increase erythromycin concentrations via an unknown mechanism. Concomitant administration of Motegrity and ketoconazole may increase the Motegrity concentrations.
  - Movantik: Concomitant use of Movantik should be avoided with the following drug classes: moderate CYP3A4 inhibitors (eg, diltiazem, erythromycin, verapamil) due to increased naloxegol concentrations, strong CYP3A4 inducers (eg, rifampin) due to decreased naloxegol concentrations, and other opioid antagonists due to potentially additive effects that may increase risk of opioid withdrawal. In the event concomitant use with moderate CYP3A4 inhibitors is unavoidable, a dose reduction of Movantik is warranted.
  - Relistor: Concomitant use of Relistor with other opioid antagonists should be avoided due to potentially additive effects that may increase the risk of opioid withdrawal.
  - Symproic: Concomitant use of Symproic should be avoided with strong CYP3A inducers (eg, rifampin, carbamazepine, phenytoin, St. John's Wort) due to a significant decrease in naldemedine concentrations, and other opioid antagonists due to potentially additive effect of opioid receptor antagonism that may increase the risk of opioid withdrawal. Moderate CYP3A inhibitors (eg, fluconazole, atazanavir, aprepitant, diltiazem, erythromycin), strong CYP3A inhibitors (eg, itraconazole, ketoconazole, clarithromycin, ritonavir, saquinavir), and P-glycoprotein inhibitors (eg, amiodarone, captopril, cyclosporine, quinidine, verapamil) can increase Symproic concentrations.

- Viberzi: Drug interactions with Viberzi which potentially may result in clinically relevant effects include the following drug classes: organic anion transporting polypeptide (OATP) 1B1 inhibitors (eg, cyclosporine, gemfibrozil, antiretrovirals, rifampin, eltrombopag, etc.), strong CYP inhibitors (eg, ciprofloxacin, fluconazole, clarithromycin, paroxetine, bupropion), constipation-inducing drugs (eg, alosetron, anticholinergics, opioids), OATP1B1 and breast cancer resistance protein (BCRP) substrates (eg, rosuvastatin), and CYP3A substrates (eg, alfentanil, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus).
- Xifaxan: Concomitant administration of drugs that are P-glycoprotein inhibitors with Xifaxan can substantially increase systemic exposure to Xifaxan. Caution should be exercised when concomitant use of Xifaxan and a P-glycoprotein inhibitor such as cyclosporine is needed. Concomitant use with warfarin may cause changes in international normalized ratio (INR).
- Zelnorm: Co-administration with P-glycoprotein (P-gp) inhibitors (eg, ritonavir, clarithromycin, itraconazole) and quinidine may increase exposure to Zelnorm.

- Risk Evaluation and Mitigation Strategy (REMS):
  - Lotronex has REMS that distributes education to providers about the risks for ischemic colitis and serious complications of constipation (*FDA REMS 2020*).
- Adverse events:
  - The IBS and constipation agents are most commonly associated with gastrointestinal-related adverse events.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Amitiza (lubiprostone)	Capsules	Oral	Treatment of CIC in adults and OIC: twice daily Treatment of IBS-C in women ≥ 18 years of age: twice daily	• Safety and efficacy have not been established in pediatric patients. • Dose should be adjusted in moderate and severe hepatic impairment.
Ibsrela (tenapanor)	Tablets	Oral	IBS-C in adults: twice daily	• Safety and efficacy have not been established in pediatric patients. • Doses should be administered immediately prior to breakfast and dinner. • Maternal use is not expected to result in fetal or breastfed infant exposure due to minimal systemic absorption.
Linzess (linaclotide)	Capsules	Oral	IBS-C: once daily CIC: once daily	• Safety and efficacy have not been established in pediatric patients. • Capsule contents may be administered with applesauce or water if a patient is unable to swallow.
Lotronex (alosetron)	Tablets	Oral	Women with severe IBS-D: twice daily	• Data in pregnant women are insufficient to determine risk for maternal or fetal outcomes. • Safety and efficacy have not been established in pediatric patients. • Caution should be used in patients ≥ 65 years of age due to risk for constipation. • Caution should be used in patients with mild or moderate impairment;

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				use should be avoided in severe hepatic impairment. • Treatment should be discontinued in patients who have not had adequate control of IBS symptoms after 4 weeks of treatment with 1 mg twice daily.
Motegrity (prucalopride)	Tablets	Oral	CIC in adults: once daily	• Safety and efficacy have not been established in pediatric patients. • Dose should be adjusted for severe renal impairment (CrCl < 30 mL/min).
Movantik (naloxegol)	Tablets	Oral	OIC in chronic non-cancer pain: once daily	• Safety and efficacy have not been established in pediatric patients. • Tablet may be crushed for patients who are unable to swallow the tablet whole; crushed tablets may also be administered via a nasogastric tube. • Tablets should be taken 1 hour before the first meal of the day or 2 hours after the meal. • Use should be avoided in patients with severe hepatic impairment (Child-Pugh Class C). • Dose should be adjusted for renal impairment (CrCl < 60 mL/min). • Maintenance laxative therapy should be discontinued prior to initiating therapy. • Movantik should be discontinued when opioid pain medication is discontinued.
Relistor (methylnaltrex-one)	Single-use vials, single-use pre-filled syringes, tablets	Oral, SC injection	OIC in chronic non-cancer pain: SC injection once daily, or oral tablet(s) once daily in the morning OIC in advanced illness: Weight-based SC injection once every other day, as needed (maximum of once daily)	• Safety and efficacy have not been established in pediatric patients. • SC injection should be administered in the upper arm, abdomen, or thigh; injection sites should be rotated. • Oral dose should be adjusted in moderate and severe hepatic impairment; adjustment of SC injection dose should be considered in severe hepatic impairment. • Dose should be adjusted in moderate to severe renal impairment. • Maintenance laxative therapy should be discontinued prior to initiating therapy. • Tablets should be taken with water 30 minutes before the first meal of the day.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				• Relistor should be discontinued when opioid pain medication is discontinued.
Symproic (naldemedine)	Tablets	Oral	OIC in chronic non-cancer pain: once daily	• Safety and efficacy have not been established in pediatric patients. • Use should be avoided in patients with severe hepatic impairment (Child-Pugh Class C). • Symproic should be discontinued when opioid pain medication is discontinued.
Trulance (plecanatide)	Tablets	Oral	CIC and IBS-C: once daily	• Tablet may be crushed for patients who are unable to swallow the tablet whole; crushed tablets may also be administered via a nasogastric tube.
Viberzi (eluxadoline)	Tablets	Oral	Treatment of IBS-D in adults: twice daily	• Safety and efficacy have not been established in pediatric patients. • Dose should be adjusted in patients who are unable to tolerate the 100 mg dose, are receiving concomitant OATP1B1 inhibitors, or have mild or moderate hepatic impairment. • Use should be avoided in patients with severe hepatic impairment (Child-Pugh Class C).
Xifaxan (rifaximin)	Tablets	Oral	IBS-D: 3 times daily for 14 days TD: 3 times daily for 3 days Hepatic encephalopathy: twice daily	• Safety and efficacy have not been established in pediatric patients < 12 years of age with TD or patients < 18 years of age for hepatic encephalopathy and IBS-D. • Patients with IBS-D who experience recurrence may be retreated up to 2 times with the same regimen. • Should not be used in patients with TD complicated by fever or blood in the stool or diarrhea due to pathogens other than *E. coli*. • Caution should be used in patients with severe hepatic impairment (Child-Pugh Class C).
Zelnorm (tegaserod)	Tablets	Oral	IBS-C: twice daily	• Tablets should be taken 30 minutes before a meal. • Zelnorm should be discontinued if no response is seen after 4 to 6 weeks of treatment.

See the current prescribing information for full details.

CONCLUSION

- There are currently no head-to-head trials comparing the available agents used in the treatment of CIC, OIC, IBS-C, and IBS-D.
- IBS is a gastrointestinal disorder with symptoms of abdominal pain, discomfort and bloating, and abnormal bowel habits with bouts of diarrhea and/or constipation (*Andresen et al 2008, Ford et al 2018, Quigley et al 2012, WGO 2015*). IBS has 4 subtypes depending on the change in bowel habits: IBS-D, IBS-C, IBS-M, or IBS-U.
  - Most patients with mild disease are managed with disease state education and support, coupled with lifestyle modifications, including diet changes and stress reduction and, when possible, symptom control (*Andresen et al 2008, Ford et al 2009*).
  - Amitiza (lubiprostone), Ibsrela (tenapanor), Linzess (linaclotide), Trulance (plecanatide), and Zelnorm (tegaserod) are indicated for the treatment of IBS-C. Amitiza is a selective chloride channel activator, Linzess and Trulance are guanylate cyclase-C agonists, and Ibsrela is a sodium/hydrogen exchanger 3 inhibitor. Zelnorm is a 5-HT_4 agonist that was re-introduced to the market in March 2019.
  - Lotronex (alosetron), Viberzi (eluxadoline), and Xifaxan (rifaximin) are indicated for the treatment of IBS-D.
    - Viberzi is a mu-opioid receptor agonist and a schedule IV controlled substance.
    - Xifaxan is a rifamycin antibacterial. Patients with IBS-D who experience recurrence with Xifaxan treatment may be retreated up to 2 times with the same regimen.
    - Lotronex is limited to use in females with chronic, severe IBS-D who have not responded to conventional therapy. Due to serious safety concerns, Lotronex has a boxed warning regarding risk of gastrointestinal adverse events including ischemic colitis, and also has a REMS program.
  - The 2018 ACG monograph on the management of IBS strongly recommends that Linzess and Amitiza are superior to placebo for the treatment of IBS-C, and Trulance is effective in IBS-C; they weakly recommend that Xifaxan is effective in reducing IBS symptoms and bloating in IBS-D, Lotronex is effective in females with IBS-D, and Viberzi is superior to placebo in IBS-D (*Ford et al 2018*).
- The 2014 ACG monograph on the management of CIC and IBS notes that linaclotide and lubiprostone are each effective for the treatment of CIC, and prucalopride is more effective than placebo in improving symptoms of CIC (*Ford et al 2014*).
  - Additional guidelines on management of constipation suggest increased fiber intake and osmotic laxatives (*AGA 2013, Bharucha et al 2013, Lindberg et al 2010*). Stimulant laxatives are to be used as needed or as “rescue agents.” Amitiza and Linzess can be considered when symptoms of constipation do not respond to laxatives.
  - Amitiza, Linzess, Motegrity (prucalopride), and Trulance are indicated for the treatment of CIC.
  - Motegrity is a selective 5-HT_4 receptor agonist that stimulates colonic peristalsis. Amitiza, Linzess, and Trulance are intestinal secretagogues and there is no reported evidence indicating that these agents induce peristalsis.
- For management of OIC, the AGA recommends laxatives as a first-line treatment (*Crockett et al 2019*). For patients with laxative refractory OIC, Symproic (naldemedine) or Movantik (naloxegol) are recommended over no treatment. Relistor (methylnaltrexone) is suggested over no treatment, but authors note that evidence supporting the use of this agent for OIC is low. The AGA does not make any recommendations for the use of Amitiza or Motegrity for OIC due to lack of evidence.
  - Amitiza, Movantik, Relistor, and Symproic are approved for treatment of OIC in patients with chronic non-cancer pain, and in those chronic pain related to prior cancer or its treatment in those who do not require frequent (eg, weekly) opioid dosage escalation. Relistor injection is also approved in patients with advanced illness or pain caused by active cancer who require opioid dosage escalation for palliative care.
  - Movantik, Relistor, and Symproic are PAMORAs.
- TD is a type of acute diarrhea that develops after the consumption of contaminated food or water during periods of travel. For the prevention of TD, guidelines recommend prophylaxis with rifaximin in high-risk groups. If rifaximin is used as prophylaxis, azithromycin should also be provided to patients in case of need for break-through therapy. For the treatment of TD, antimicrobials such as azithromycin, rifaximin, or a fluoroquinolone are recommended, with the travel destination guiding the drug(s) of choice (*Riddle et al 2017*).
- HE is a common complication of severe liver disease characterized by neuropsychiatric abnormalities that vary in presentation based on disease severity. The AASLD and EASL recommend rifaximin as adjunct therapy to lactulose for the prevention of overt HE recurrence and overt HE recurrence after the second episode (*Vilstrup et al 2014*).

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Publication Date: March 11, 2020

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] 2020[a])*.
- 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 2020[b])*.
- 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 *(Drugs@FDA 2020)*. 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 (U-300). Additionally, Basaglar (insulin glargine) was approved under the FDA 505(b)(2) pathway. *(Fierce Biotech FDA press release 2015, Drugs@FDA 2020)*.
- Insulin therapy is usually administered by subcutaneous (SC) injection, which allows for prolonged absorption and less pain compared to intramuscular (IM) injection. Humalog, Humalog Kwikpen, Novolog, Novolog PenFil, Novolog FlexPen,

Novolog Mix 70/30, and Novolog Mix FlexPen 70/30 have authorized generics, while the rest of the insulin products do not have a generic (*Lilly 2019[a], Lilly 2019[b], Novo Nordisk 2019*). 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 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, Fiasp PenFill (insulin aspart)	-
Humalog, Humalog KwikPen, Humalog Junior KwikPen, Humalog Tempo Pen (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 FlexPen, Novolin R ReliOn (insulin, regular, human recombinant)	-
Intermediate-Acting Insulins	
Humulin N, Humulin N Kwikpen (insulin, NPH human recombinant isophane)	-
Novolin N, Novolin N FlexPen, 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, 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, Novolog 70/30 PenFill (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)	-

*Eli Lilly launched an authorized generic of Humalog (vial and KwikPen) through its subsidiary, ImClone Systems (*Lilly 2019[a], Lilly 2019[b]*).

**Novo Nordisk launched an authorized generic of Novolog (vial, Penfil, and FlexPen) and Novolog Mix (vial and FlexPen) through its affiliate, Novo Nordisk Pharma Inc (*Novo Nordisk 2019*).

(Drugs@FDA 2020)

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.
¶ Indicated for patients 6 years and older with diabetes mellitus.

(Prescribing information: Admelog 2019, Afrezza 2018, Apidra 2019, Basaglar 2019, Fiasp 2019, Humalog 2019, Humalog Mix 50/50 2019, Humalog Mix 75/25 2019, Humulin 70/30 2019, Humulin N 2019, Humulin R U-100 2019, Humulin R U-500 2019, Lantus 2019, Levemir 2019, Novolin 70/30 2019, Novolin N 2019, Novolin R 2019, Novolog 2019, Novolog Mix 70/30 2019, Toujeo 2019, Tresiba 2019)

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 non-inferior 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 non-inferiority to Novolog in HbA1c lowering (ETD -0.02%; p < 0.0001). Onset 3 *(Rodbard et al 2017[b])* 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-confirmed hypoglycemic episodes (RR, 8.24; p < 0.0001) and modest weight gain.
- In 2020, Fiasp's indication was expanded to include children with diabetes based on results from the Onset 7 Trial *(Bode et al 2019*). This trial demonstrated noninferiority of Fiasp to Novolog in 519 patients 1 to 17 years of age with T1DM. The estimated change from baseline to week 26 in HbA1c at meal time was −0.17% (95% CI −0.30 to −0.03) and post meal it was 0.13% (95% CI, −0.01 to 0.26); the change from baseline in HbA1c at meal time was statistically significant between groups in favor of Fiasp.
- The safety and efficacy of Admelog, the first "follow-on" rapid-acting insulin, were evaluated in two 26-week, 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 non-inferior 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 adults, adolescents, and children 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, Danne et al 2013, 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, Herwig et al 2007, 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, Schober et al 2002, 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, AC, 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 2019*).

- 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)*.
- A meta-analysis of 15 trials with 16,694 patients that compared Tresiba to Lantus found that Tresiba was associated with improved mean reduction in fasting plasma glucose (weighted mean difference, -5.2 mg/dL; 95% CI, -7.34 to -3.07; $p < 0.00001$) and less nocturnal hypoglycemia (RR, 0.81; 95% CI, 0.75 to 0.88; $p < 0.0001$). However, fewer patients achieved HbA1c ≤ 7% with Tresiba compared with Lantus (RR, 0.92; 95% CI, 0.86 to 0.98; $p = 0.01$). The meta-analysis showed no statistically significant differences between Tresiba and Lantus for HbA1c reduction, body weight gain, and serious adverse events (AEs) (*Zhou et al 2019*).
- 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 (MC), 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, detemir, 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).*
  - The safety of Tresiba was compared to Toujeo in the 2019 CONCLUDE trial that included 1609 patients with T2DM. In this trial, the rate of overall symptomatic hypoglycemia, the primary endpoint, was similar between Tresiba and Toujeo (RR, 0.88; 95%, CI 0.73 to 1.06). However, the rates of nocturnal symptomatic hypoglycemia and severe hypoglycemia (both of which were exploratory endpoints) were lower with Tresiba vs Toujeo (RR, 0.63; 95% CI, 0.48 to 0.84 and RR, 0.20; 95% CI 0.07 to 0.57, respectively) (*Philis-Tsimikas et al 2020*).
- In 2019, Toujeo's indication was expanded to include children with diabetes mellitus as young as 6 years of age based on results of the EDITION JUNIOR trial. In this study, Toujeo demonstrated non-inferiority to Lantus for the primary endpoint of change in HbA1c from baseline to week 26 (mean reduction, 0.4% in both groups; 95% CI, –0.17 to 0.18) with comparable numbers of patients experiencing ≥ 1 episode of hypoglycemia *(Danne et al 2019).*

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 AEs 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, 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).*
  - T2DM patients uncontrolled on basal insulin and/or OADs:

- The DUAL I trial was a 3-treatment arm, OL study in 1,663 T2DM patients that compared fixed-dose combination of insulin degludec/liraglutide (n = 834) to insulin degludec (n = 414) and liraglutide (n = 415) components. Prior to randomization, patients were receiving metformin ± pioglitazone. The HbA1c reduction from baseline after 26 weeks of treatment was -1.8% for fixed-dose combination insulin degludec/liraglutide, -1.4% for insulin degludec, and -1.2% for liraglutide. The ETD for HbA1c showed that the fixed-dose combination insulin degludec/liraglutide is non-inferior to insulin degludec (ETD, -0.47%; 95% CI -0.58 to -0.36; p < 0.0001) and superior to liraglutide (ETD, -0.64%; 95% CI, -0.75 to -0.53, p < 0.0001) (*Gough et al 2014*).
- 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 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 IV trial was a DB study in 435 T2DM patients that compared insulin degludec/liraglutide (n = 289) to placebo (n = 146). Prior to randomization, uncontrolled patients were receiving sulfonylurea ± metformin. The HbA1c reduction from baseline after 26 weeks of treatment was -1.5% for insulin degludec/liraglutide and -0.5% for placebo. The ETD for HbA1c statistically favored insulin degludec/liraglutide over placebo (ETD, -1.02%; 95% CI, -1.18 to -0.87; p < 0.001) (*Rodbard et al 2017[a]*).
- 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).*
- The DUAL VI trial was a 32-week, OL, non-inferiority study in 420 T2DM patients that compared insulin degludec/liraglutide titrated once weekly (n = 210) to insulin degludec/liraglutide titrated twice weekly (n = 210). Prior to randomization, patients were receiving metformin ± pioglitazone. The mean HbA1c reduction from baseline after 32 weeks was -2% with once-weekly titration and -2% with twice-weekly titration. The ETD revealed a non-inferiority between the 2 treatment regimens (ETD, 0.12%; 95% CI -0.04 to 0.28) (*Harris et al 2017*).
- The DUAL VII trial was a 2-treatment, OL study in 506 T2DM patients that compared insulin degludec/liraglutide (n = 252) to insulin glargine + insulin aspart (n = 254). Prior to randomization, patients were receiving metformin and insulin glargine. The HbA1c reduction from baseline after 26 weeks of treatment was -1.5% for insulin degludec/liraglutide and -1.5% for insulin glargine with insulin aspart. The ETD revealed non-inferiority between the 2 treatments (ETD, -0.02%; 95% CI -0.16 to 0.12) (*Billings et al 2018*).
- The DUAL VIII trial was a 26-week, OL, randomized study in patients with T2DM that compared once daily insulin degludec/liraglutide (n=506) with insulin glargine (n=506) (*Aroda et al 2019*). Prior to randomization, patients were uncontrolled on stable doses of oral antidiabetic agents. Results demonstrated that patients who received insulin degludec/liraglutide had a longer time to initiation of therapy intensification (met when HbA1c was ≥ 7% at 2 consecutive visits after 26 weeks of treatment) compared to insulin glargine (>2 years vs 1 year).
- The DUAL IX trial was a 26-week, OL, randomized study that compared once daily insulin degludec/liraglutide (n=210) with insulin glargine (n=210) in patients with T2DM uncontrolled with SGLT2 inhibitors (*Philis-Tsimikas et al 2019*). The results of this study demonstrated that treatment with insulin degludec/liraglutide was non-inferior to insulin glargine with respect to the primary outcome of change in HbA1c from baseline to week 26 (-1.9% and -1.7%, respectively). In a confirmatory analysis, insulin degludec/liraglutide was also found superior to insulin glargine for the primary outcome with an estimated treatment difference of -0.36% (95% CI, -0.50 to -0.21).

○ 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 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 non-inferiority; 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 2020[b], Chiang et al 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 2020[b], Buse et al 2020, Garber et al 2020, 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 2020[b], Buse et al 2020, Garber et al 2020, 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 is > 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 2020).*
    - 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 2020 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. For patients with T2DM and established ASCVD, the level of evidence for MACE benefit is greatest for GLP-1 agonists. GLP-1 agonists are also suggested for patients without CVD but with indicators of high risk. Due to the progressive nature of the disease, patients may eventually require insulin therapy (*ADA 2020[b], Buse et al 2020*).
    - 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 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 et al 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 consider liraglutide as the preferred GLP-1 agent (*ADA 2020[b], Das et al 2018*).
- The Endocrine Society released a guideline for the treatment of diabetes in older adults. The general recommendations focus on selecting treatment that would minimize hypoglycemia in patients 65 years and older with diabetes. The guideline does not provide specific targets. Metformin with lifestyle changes is the preferred initial treatment in patients without significant kidney function impairment. Patients who are not able to achieve glycemic targets with metformin and lifestyle changes can receive add-on therapy with oral or injectable agents and/or insulin. The guideline advises using insulin sparingly to decrease the risk for hypoglycemia in patients 65 years and older. The addition of a long-acting

insulin may be the initial step to control fasting glucose. Insulin degludec and insulin glargine U-300 may cause less hypoglycemia compared to insulin glargine U-100. Older adults typically have more postprandial hyperglycemia rather than fasting hyperglycemia. Therefore, adding a premeal insulin may be more optimal than titrating a long-acting basal insulin in certain cases (*LeRoith et al 2019*).

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.
  - Changes in insulin regimen, including insulin manufacturer, type, strength, injection site, or method of administration, may affect glycemic control and lead to hypoglycemia or hyperglycemia. Frequent glucose monitoring and close medical supervision is recommended when making changes to a patient's insulin regimen.
  - 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 than 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.
- 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 Interactions:
  - 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.

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.
- 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	Inhalation	Generally given 3 times daily at the beginning of a meal.	Safety and efficacy in pediatric patients or in renal or hepatic

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
	Available in cartons with a single dosage and in titration packs with multiple dosages			dysfunction have not been established.
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.	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, Tempo Pen, 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: cartridge, 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: well-controlled studies in children not available. Dosing in pediatric patients must be individualized.

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
			U-500: Generally given 2 to 3 times daily before meals. U-100: Often used concomitantly with intermediate- or long-acting insulin when administered by SC injection.	Dose conversion should not be performed when using the U-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 (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 (insulin, NPH, human recombinant isophane)	100 U/mL: Vial, Flexpen	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

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
				impairment who rely on audible clicks to dial their dose.
Levemir (insulin detemir)	100 U/mL: FlexTouch pen, vial	SC	Daily to twice daily 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.	Safety and efficacy in children < 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 May be administered at any time of day, but at the same time every day.	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				

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
Humalog Mix 50/50 Humalog Mix 75/25 (insulin lispro protamine/insulin lispro)	100 U/mL: KwikPen, vial	SC	Administer within 15 minutes before meals. Typically dosed twice daily.	Safety and efficacy in children have not been established. 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: cartridge, 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 (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 hepatic impairment or severe renal impairment. Use with caution in patients with visual impairment who rely on audible clicks to dial their dose.

Abbreviations: BG = blood glucose, IV = intravenous, SC = subcutaneous, T1DM = type 1 diabetes mellitus, T2DM = type 2 diabetes mellitus, U = unit
*Dose and frequency of insulin products should be individualized per patient needs.

(Clinical Pharmacology 2020)

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. Humalog, Humalog Kwikpen, Novolog, Novolog PenFil, Novolog FlexPen, Novolog Mix 70/30, and Novolog Mix FlexPen 70/30 have authorized generics, while the rest of the insulin products do not have a generic (*Lilly 2019[a], Lilly 2019[b], Novo Nordisk 2019*).
- 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 2020[b], 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 2020[b], Buse 2020, Garber et al 2020, 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 2020[b], Davies 2018, Garber et al 2020, 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. For patients with T2DM and established ASCVD, the level of evidence for MACE benefit is greatest for GLP-1 agonists. GLP-1 agonists are also suggested for patients without CVD but with indicators of high risk. 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 2020[b], Buse 2020*).

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 fewer 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 HbA1c > 10% and/or if above the target HbA1c by more than 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 2020[b], Buse 2020).*

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Publication Date: April 1, 2020

Therapeutic Class Overview
Anticonvulsants

INTRODUCTION

- Epilepsy is a disease of the brain defined by any of the following (*Fisher et al 2014*):
  - At least 2 unprovoked (or reflex) seizures occurring > 24 hours apart;
  - 1 unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after 2 unprovoked seizures, occurring over the next 10 years;
  - Diagnosis of an epilepsy syndrome.
- Types of seizures include generalized seizures, focal (partial) seizures, and status epilepticus (*Centers for Disease Control and Prevention [CDC] 2018, Epilepsy Foundation 2016*).
  - Generalized seizures affect both sides of the brain and include:
    - Tonic-clonic (grand mal): begin with stiffening of the limbs, followed by jerking of the limbs and face
    - Myoclonic: characterized by rapid, brief contractions of body muscles, usually on both sides of the body at the same time
    - Atonic: characterized by abrupt loss of muscle tone; they are also called drop attacks or akinetic seizures and can result in injury due to falls
    - Absence (petit mal): characterized by brief lapses of awareness, sometimes with staring, that begin and end abruptly; they are more common in children than adults and may be accompanied by brief myoclonic jerking of the eyelids or facial muscles, a loss of muscle tone, or automatisms.
  - Focal seizures are located in just 1 area of the brain and include:
    - Simple: affect a small part of the brain; can affect movement, sensations, and emotion, without a loss of consciousness
    - Complex: affect a larger area of the brain than simple focal seizures and the patient loses awareness; episodes typically begin with a blank stare, followed by chewing movements, picking at or fumbling with clothing, mumbling, and performing repeated unorganized movements or wandering; they may also be called “temporal lobe epilepsy” or “psychomotor epilepsy”
    - Secondarily generalized seizures: begin in 1 part of the brain and spread to both sides
  - Status epilepticus is characterized by prolonged, uninterrupted seizure activity.
- Seizure classifications from the International League against Epilepsy (ILAE) were updated in 2017. The ILAE classification of seizure types is based on whether the seizure has a focal, generalized, or unknown onset; has a motor or non-motor onset; and whether the patient is aware or has impaired awareness during the event (for focal seizures). Additional classification details may also be used (*Fisher et al 2017A, Fisher et al 2017B*).
  - There is variation between the ILAE classifications and many of the Food and Drug Administration (FDA)-approved indications for antiepileptic drugs (AEDs). For example, a “focal aware” seizure corresponds to the prior term “simple partial seizure,” and a “focal impaired awareness” seizure corresponds to the prior term “complex partial seizure.”
- A number of epilepsy syndromes have also been described; these are defined by groups of features that tend to occur together such as having a similar seizure type, age of onset, part of the brain involved, and electroencephalogram (EEG) pattern (*Epilepsy Foundation 2013*). An example is a childhood epilepsy syndrome called Lennox-Gastaut syndrome (LGS), which is characterized by several seizure types including tonic (stiffening) and atonic (drop) seizures. In LGS, there is a classic EEG pattern seen and intellectual development is usually impaired (*Epilepsy Foundation 2020*).
- Epilepsy management is focused on the goals of 1) controlling seizures, 2) avoiding treatment-related adverse effects (AEs), and 3) maintaining or restoring quality of life. Management options vary based on the seizure type. It is usually appropriate to refer patients to a neurologist to establish the epilepsy diagnosis and formulate the management strategy (*Schachter 2019*).
  - A correct diagnosis is essential to proper treatment selection. For example, absence seizures are commonly confused with complex partial seizures. However, drugs that reduce absence seizures are generally ineffective for complex partial seizures, and the most effective drugs for complex partial seizures may be ineffective against or even increase the frequency of absence seizures (*Epilepsy Foundation 2016*).
- When possible, monotherapy with a single AED is the preferred treatment approach. Combination therapy may be associated with decreased patient adherence to therapy and an increased incidence of AEs and drug interactions. When

combination therapy is needed, it is recommended to select products with different mechanisms of action and AE profiles. There is little comparative clinical data to support the use of specific combinations (*Schachter et al 2019*).

- Several broad classes of AEDs are available, including barbiturates, benzodiazepines, hydantoins, and miscellaneous agents (see Table 1).
- Cannibidiol (Epidiolex) was FDA-approved in June 2018 for use in pediatric patients 2 years of age and older with LGS or Dravet syndrome (*FDA news release 2018*). It is the first FDA-approved drug for treatment of patients with Dravet syndrome and is the first approved drug that contains a purified substance, cannabidiol, derived from marijuana. Cannabidiol is a schedule V controlled substance (*Epidiolex prescribing information 2018*).
- Stiripentol (Diacomit) capsules and powder for oral suspension were FDA-approved in August 2018 for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam.
- Everolimus tablets for oral suspension (Afinitor Disperz) received an expanded indication in April 2018 for use in partial-onset seizures associated with tuberous sclerosis complex (TSC). This product is a kinase inhibitor that also has several oncology indications.
- Midazolam nasal spray (Nayzilam) was approved in May 2019 for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 12 years of age (*Nayzilam prescribing information 2019*). In January 2020, diazepam nasal spray (Valtoco) was approved for the same indication in patients as young as 6 years of age (*Valtoco prescribing information 2020*).
- Several of the AEDs are used for additional indications beyond the management of epilepsy, including (but not limited to) bipolar disorder, migraine prophylaxis, and several types of neuropathic pain. These additional indications are listed in Table 2; however, this review primarily focuses on the use of AEDs for the management of epilepsy. Additionally, brands and formulations FDA-approved and marketed only for non-epilepsy indications are not included within this review; these include gabapentin tablets (Gralise), FDA-approved only for the management of postherpetic neuralgia, gabapentin enacarbil extended-release tablets (Horizant), FDA-approved only for management of postherpetic neuralgia and treatment of moderate-to-severe restless leg syndrome, and pregabalin extended-release tablets (Lyrica CR), FDA-approved only for the management of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia.
- Medispan class: Antianxiety agents, benzodiazepines; Anticonvulsants, AMPA glutamate receptor antagonists; Anticonvulsants, anticonvulsants – misc; Anticonvulsants, carbamates; Anticonvulsants, GABA modulators; Anticonvulsants, hydantoins; Anticonvulsants, succinimides; Anticonvulsants, valproic acid; Hypnotics/Sedatives/Sleep Disorder Agents, barbiturate hypnotics

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Barbiturates	
Pentobarbital (Nembutal)	✔
Phenobarbital* (Luminal†, Solfoton†)	✔
Primidone (Mysoline)	✔
Benzodiazepines	
Clobazam (Onfi; Sympazan)	✔ ***
Clonazepam (Klonopin§)	✔
Clorazepate (Tranxene T-Tab§)	✔
Diazepam (Diastat¶, Valium,§ Valtoco)	✔ ‖
Midazolam (Nayzilam)	-
Hydantoins	
Ethotoin (Peganone)	-
Fosphenytoin (Cerebyx)	✔
Phenytoin (Dilantin§, Phenytek)	✔ ‖
Miscellaneous	
Brivaracetam (Briviact)	-
Cenobamate (Xcopri¶¶)	-
Cannabidiol (Epidiolex)	-
Carbamazepine (Carbatrol, Epitol**, Equetro, Tegretol§, Tegretol-XR)	✔

Drug	Generic Availability
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	✔
Eslicarbazepine (Aptiom)	-
Ethosuximide (Zarontin)	✔
Everolimus (Afinitor Disperz)	-
Felbamate (Felbatol)	✔
Gabapentin (Neurontin)	✔
Lacosamide (Vimpat)	-
Lamotrigine (Lamictal, Lamictal ODT, Lamictal XR, Subvenite**)	✔
Levetiracetam (Keppra, Keppra XR, Roweepra**, Roweepra XR**, Spritam, Elepsia XR)	✔ ‖
Methsuximide (Celontin)	-
Oxcarbazepine (Oxtellar XR, Trileptal)	✔ ‖
Perampanel (Fycompa)	-
Pregabalin (Lyrica)	✔
Rufinamide (Banzel)	-
Stiripentol (Diacomit)	-
Tiagabine (Gabitril)	✔ ‖
Topiramate (Topamax, Topamax Sprinkle, Topiragen††, Trokendi XR, Qudexy XR¶)	✔ ‖
Valproic acid/valproate sodium (Depacon, Depakene)	✔ ‖
Vigabatrin (Sabril, Vigadrone**)	✔ ‖
Zonisamide (Zonegran§)	✔

* Not FDA approved
† Brand product not currently marketed; generic is available
§ Brand marketing status may vary by strength and/or formulation
‖ Generic availability may vary by strength and/or formulation
¶ Authorized generic available; no A-rated generics approved via abbreviated new drug application
** Branded generic
†† Branded generic; not currently marketed
***Generic available for Onfi tablets and oral suspension; only brand name available for Sympazan oral film.
¶¶ FDA-approved product, but not yet marketed.
(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

- Tables 2A and 2B provide an overview of anticonvulsant indications. Except where noted, only FDA-approved products and indications are included. For items marked with an asterisk, there is additional information about the indication provided in the box following the tables.
- Acute-care indications that are not related to convulsive disorders (for example, pre-procedural use of benzodiazepines in hospital settings) are not included.

Table 2A. Indications for anticonvulsants (Part 1 of 2)

Indications	Brivaracetam	Cannabidiol	Carbamazepine	Cenobamate	Clobazam	Clonazepam	Clorazepate	Diazepam	Divalproex Sodium	Eslicarbazepine	Ethosuximide	Ethotoin	Everolimus	Felbamate	Fosphenytoin	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam
Partial seizures (simple partial, complex partial and/or secondarily generalized)	✔ *		✔ *	✔ *			A		✔, A*	✔, A*		✔ *		✔, A*		A*	✔ *	✔, A*	✔ *
Primary generalized tonic-clonic seizure (grand mal)			✔									✔			✔ *			A*	A*
Absence seizure (petit mal)						✔ *			✔, A*		✔								
Multiple seizure types that include absence seizures									A										
Seizures of Lennox-Gastaut syndrome (LGS)		✔ *			A*	✔, A								A*				A*	
Seizures of Dravet syndrome		✔ *																	
Juvenile myoclonic epilepsy (JME)																			A*
Emergency/acute/short-term use for seizure control (see notes)								✔ *							✔ *				
Akinetic and myoclonic seizures						✔, A													
Convulsive disorders (see notes)								A*											
Certain mixed seizure patterns or other partial or generalized seizures			✔ *																
Migraine prophylaxis									✔ *										
Trigeminal neuralgia			✔ *																
Postherpetic neuralgia																✔ *			
Bipolar disorder			✔ *						✔ *									✔ *	
Panic disorder, with or without agoraphobia						✔													
Anxiety disorder; short-term relief of anxiety symptoms							✔	✔											
Symptomatic relief of acute alcohol withdrawal							✔	✔											

Indications	Brivaracetam	Cannabidiol	Carbamazepine	Cenobamate	Clobazam	Clonazepam	Clorazepate	Diazepam	Divalproex Sodium	Eslicarbazepine	Ethosuximide	Ethotoin	Everolimus	Felbamate	Fosphenytoin	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam
Relief of skeletal muscle spasm, spasticity, athetosis, and stiff-man syndrome								A											
Partial-onset seizures associated with tuberous sclerosis complex (TSC)													A*						

✓ = monotherapy (or not specified); A = adjunctive therapy

Table 2B. Indications for Anticonvulsants (Part 2 of 2)

Indications	Midazolam	Methsuximide	Oxcarbazepine	Pentobarbital	Perampanel	Phenobarbital†	Phenytoin	Pregabalin	Primidone	Rufinamide	Stiripentol	Tiagabine	Topiramate	Valproic acid	Vigabatrin	Zonisamide
Partial seizures (simple partial, complex partial and/or secondarily generalized)			✔, A*		✔*		✔*	A*	✔, A*			A*	✔, A*	✔, A*	A*	A*
Primary generalized tonic-clonic seizure (grand mal)					A*		✔*		✔, A*				✔, A*			
Absence seizure (petit mal)		✔*												✔, A*		
Multiple seizure types which include absence seizures														A*		
Seizures of LGS										A*			A*			
Seizures of Dravet syndrome											A*					
Emergency/acute/ short-term use for seizure control (see notes)	✔*			✔*			✔*									
Infantile spasms															✔*	
Convulsive disorders (see notes)						✔*										
Migraine prophylaxis													✔*	✔*		

Indications	Midazolam	Methsuximide	Oxcarbazepine	Pentobarbital	Perampanel	Phenobarbital†	Phenytoin	Pregabalin	Primidone	Rufinamide	Stiripentol	Tiagabine	Topiramate	Valproic acid	Vigabatrin	Zonisamide
Postherpetic neuralgia								✔								
Bipolar disorder														✔ *		
Sedative for anxiety, tension, and apprehension																
Neuropathic pain associated with diabetic peripheral neuropathy								✔								
Neuropathic pain associated with spinal cord injury								✔								
Fibromyalgia								✔								

✓ = monotherapy (or not specified); A = adjunctive therapy
†Phenobarbital is not approved by the FDA.

***Notes: Additional Detail on Selected Anticonvulsant Indications**

- Brivaracetam:
  - Treatment of partial-onset seizures in patients ≥ 4 years of age (oral formulations); ≥ 16 years of age (IV formulation)
- Cannabidiol:
  - Treatment of seizures associated with LGS or Dravet syndrome in patients ≥ 2 years of age
- Carbamazepine:
  - Partial seizures with complex symptomatology (psychomotor, temporal lobe); patients with these seizures appear to show greater improvement than those with other types; generalized tonic-clonic seizures (grand mal); mixed seizure patterns which include the above, or other partial or generalized seizures
  - Absence seizures do not appear to be controlled; carbamazepine has been associated with increased frequency of generalized convulsions in these patients
  - Treatment of pain associated with true trigeminal neuralgia; beneficial results also reported in glossopharyngeal neuralgia
  - Bipolar indication is for an extended-release capsule formulation (Equetro) only: treatment of patients with acute manic or mixed episodes associated with bipolar I disorder
- Cenobamate:
  - Partial-onset seizures in adult patients
- Clobazam:
  - Seizures associated with LGS in patients ≥ 2 years of age
- Clonazepam:
  - In patients with absence seizures who have failed to respond to succinimides, clonazepam may be useful
- Diazepam:
  - Oral diazepam may be used adjunctively in convulsive disorders; it has not proved useful as sole therapy.
  - Rectal diazepam is indicated in the management of selected, refractory patients with epilepsy on stable regimens of AEDs who require intermittent use of diazepam to control bouts of increased seizure activity
  - Injectable diazepam is a useful adjunct in status epilepticus and severe recurrent convulsive seizures
  - Diazepam nasal spray is indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure

activity (ie, seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 6 years of age

- Divalproex sodium:
  - Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures (≥ 10 years of age for all formulations)
  - Monotherapy and adjunctive therapy in the treatment of simple and complex absence seizures (≥ 10 years of age for extended-release tablets; age not specified for tablets/sprinkle capsules)
  - The tablets and extended-release tablets have indications in bipolar disorder and migraine prophylaxis; the sprinkle capsule formulation does not. For bipolar disorder, safety and effectiveness for long-term use (> 3 weeks) has not been demonstrated in controlled clinical trials. Bipolar disorder indications are as follows:
    - Treatment of the manic episodes associated with bipolar disorder (tablets)
    - Treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features (extended-release tablets)
- Eslicarbazepine:
  - Treatment of partial-onset seizures in patients ≥ 4 years of age
- Ethotoin:
  - Complex partial (psychomotor) seizures
- Everolimus:
  - Adjunctive treatment of adult and pediatric patients ≥ 2 years of age with TSC-associated partial-onset seizures (tablets for oral suspension only)
- Felbamate:
  - Not first-line; recommended only in patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or renal failure is deemed acceptable
  - Monotherapy or adjunctive therapy in the treatment of partial seizures, with and without generalization, in adults with epilepsy
  - Adjunctive therapy of partial and generalized seizures associated with LGS in children (age not specified)
- Fosphenytoin:
  - Treatment of generalized tonic-clonic status epilepticus
  - Prevention and treatment of seizures occurring during neurosurgery
  - Can be substituted short-term for oral phenytoin when oral phenytoin administration is not possible
- Gabapentin:
  - Adjunctive therapy in the treatment of partial-onset seizures, with and without secondary generalization, in adults and pediatric patients ≥ 3 years of age with epilepsy.
  - Management of postherpetic neuralgia in adults
- Lacosamide:
  - Treatment of partial-onset seizures in patients ≥ 4 years of age (tablet and oral solution)
  - Treatment of partial-onset seizures in patients ≥ 17 years of age (injection)
- Lamotrigine immediate-release formulations:
  - Age ≥ 2 years for adjunctive therapy for partial-onset seizures, primary generalized tonic-clonic seizures, and generalized seizures of LGS
  - Age ≥ 16 years for conversion to monotherapy in patients with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single AED
  - Maintenance treatment of bipolar disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy (treatment of acute manic or mixed episodes is not recommended)
- Lamotrigine extended-release tablets:
  - Age ≥ 13 years for adjunctive therapy for primary generalized tonic-clonic seizures and partial-onset seizures with or without secondary generalization, and age ≥13 years for conversion to monotherapy in patients with partial-onset seizures who are receiving treatment with a single AED
  - The extended-release formulation is not FDA-approved for bipolar disorder
- Levetiracetam:
  - Tablets, oral solution, injection, and tablets for oral suspension:
    - Treatment of partial-onset seizures in patients ≥ 1 month of age (tablets, oral solution, and injection [Keppra]); adjunctive treatment for partial-onset seizures in patients ≥ 4 years of age and weighing > 20 kg

(tablets for oral suspension [Spritam])
    - Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents ≥ 12 years of age with JME
    - Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and children ≥ 6 years of age with idiopathic generalized epilepsy
  - The extended-release tablets are only indicated for the treatment of partial-onset seizures in patients ≥ 12 years of age
- Methsuximide:
  - Control of absence (petit mal) seizures that are refractory to other drugs
- Midazolam nasal spray:
  - Acute treatment of intermittent, stereotypic episodes of frequent seizure activity (ie, seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 12 years of age.
- Oxcarbazepine immediate-release formulations:
  - Monotherapy in the treatment of partial seizures in adults and children 4 to 16 years of age
  - Adjunctive therapy in the treatment of partial seizures in adults and children 2 to 16 years of age
- Oxcarbazepine extended-release tablets:
  - Treatment of partial-onset seizures in adults and children ≥ 6 years of age
- Pentobarbital:
  - In anesthetic doses in the emergency control of certain acute convulsive episodes, eg, those associated with status epilepticus, cholera, eclampsia, meningitis, tetanus, and toxic reactions to strychnine or local anesthetics
- Perampanel:
  - Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy ≥ 4 years of age
  - Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients with epilepsy ≥ 12 years of age
- Phenobarbital (not FDA-approved):
  - Phenobarbital tablets are indicated for use as an anticonvulsant; the elixir is indicated for the treatment of generalized and partial seizures; the injection is indicated as an anticonvulsant for the treatment of generalized tonic-clonic and cortical focal seizures, in the emergency control of certain acute convulsive episodes, and in pediatric patients as an anticonvulsant
- Phenytoin oral formulations:
  - Treatment of tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery (the oral suspension does not have the neurosurgery indication)
- Phenytoin injection:
  - Treatment of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery
  - Can be substituted as short-term use for oral phenytoin when oral phenytoin administration is not possible
- Pregabalin:
  - Adjunctive therapy for treatment of partial-onset seizures in patients ≥ 1 month of age
- Primidone:
  - Control of grand mal, psychomotor, and focal epileptic seizures; may control grand mal seizures refractory to other anticonvulsant therapy
- Rufinamide:
  - Adults and pediatric patients ≥ 1 year of age
- Stiripentol:
  - Treatment of seizures associated with Dravet syndrome in patients ≥ 2 years of age taking clobazam; no clinical data to support its use as monotherapy
- Tiagabine:
  - Adjunctive therapy in adults and children ≥ 12 years of age in the treatment of partial seizures
- Topiramate:
  - Initial monotherapy in patients with partial-onset or primary generalized tonic-clonic seizures (age ≥ 2 years for

tablets, immediate-release sprinkle capsules, and Qudexy XR extended-release capsules; age ≥ 6 years for Trokendi XR extended-release capsules)
  - Adjunctive therapy for adults and pediatric patients with partial-onset seizures or primary generalized tonic-clonic seizures and in patients with seizures associated with LGS (age ≥ 2 years for tablets, immediate-release sprinkle capsules, and Qudexy XR extended-release capsules; age ≥ 6 years for Trokendi XR extended-release capsules)
  - Prophylaxis of migraine headache in patients ≥ 12 years of age
- Valproic acid/valproate sodium:
  - Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures; sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types which include absence seizures
- Vigabatrin:
  - Adjunctive therapy for patients ≥ 2 years of age with refractory complex partial seizures who have responded inadequately to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss
  - Monotherapy for patients with infantile spasms 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss
- Zonisamide:
  - Adjunctive therapy in the treatment of partial seizures in adults with epilepsy

- 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 anticonvulsants have demonstrated efficacy for their FDA-approved uses. Clinical trial data demonstrating efficacy of the anticonvulsants for the treatment of epilepsy is described in the prescribing information for the individual products, particularly for anticonvulsants more recently approved by the FDA. However, the prescribing information for some older, conventional products (eg, benzodiazepines, carbamazepine, ethotoin, ethosuximide, methsuximide, phenytoin, and primidone) and non-FDA approved products (eg, phenobarbital) do not contain efficacy data in their prescribing information.
- No single AED is clearly the most effective. Comparative efficacy data for the management of epilepsy are limited, and trials have generally not shown significant differences among drugs in terms of efficacy. However, the quality of the data is limited and generally derived from short-term trials (*Karceski 2019*).
- When possible, monotherapy with a single AED is the preferred treatment approach. Combination therapy may be associated with decreased patient adherence to therapy and an increased incidence of AEs and drug interactions. (*Schachter et al 2019*). Most patients with epilepsy are treated with anticonvulsant monotherapy (*Nevitt et al 2017*).
- An evidence review summarized AED efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes (*Glauser et al 2013*). This publication provides conclusions based on a review of 64 randomized trials and 11 meta-analyses. Conclusions include the following:
  - As initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures:
    - Carbamazepine, levetiracetam, phenytoin, and zonisamide are established as efficacious/effective.
    - Valproate is probably efficacious/effective.
    - Gabapentin, lamotrigine, oxcarbazepine, phenobarbital, topiramate, and vigabatrin are possibly efficacious/effective.
    - Clonazepam and primidone are potentially efficacious/effective.
  - As initial monotherapy for children with newly diagnosed or untreated partial-onset seizures:
    - Oxcarbazepine is established as efficacious/effective.
    - Carbamazepine, phenobarbital, phenytoin, topiramate, valproate, and vigabatrin are possibly efficacious/effective.
    - Clobazam, carbamazepine, lamotrigine, and zonisamide are potentially efficacious/effective.
  - As initial monotherapy for elderly adults with newly diagnosed or untreated partial-onset seizures:
    - Gabapentin and lamotrigine are established as efficacious/effective.
    - Carbamazepine is possibly efficacious/effective.
    - Topiramate and valproate are potentially efficacious/effective.
  - As initial monotherapy for adults with newly diagnosed or untreated generalized-onset tonic-clonic seizures:

        - Carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate, and valproate are possibly efficacious/effective.
        - Gabapentin, levetiracetam, and vigabatrin are potentially efficacious/effective.
        - Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.
    - For children with newly diagnosed or untreated generalized-onset tonic-clonic seizures:
        - Carbamazepine, phenobarbital, phenytoin, topiramate, and valproate are possibly efficacious/effective.
        - Oxcarbazepine is potentially efficacious/effective.
        - Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.
    - As initial monotherapy for children with newly diagnosed or untreated absence seizures:
        - Ethosuximide and valproate are established as efficacious/effective.
        - Lamotrigine is possibly efficacious/effective.
        - Gabapentin is established as inefficacious/ineffective.
        - Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, tiagabine, and vigabatrin may precipitate or aggravate absence seizures (based on scattered reports).
    - As initial monotherapy for children with benign childhood epilepsy with centrotemporal spikes (BECTS):
        - Carbamazepine and valproate are possibly efficacious/effective.
        - Gabapentin, levetiracetam, oxcarbazepine, and sulthiame (not available in the United States) are potentially efficacious/effective.
    - For patients with newly diagnosed JME:
        - Topiramate and valproate are potentially efficacious/effective.
        - Carbamazepine, gabapentin, oxcarbazepine, phenytoin, tiagabine, and vigabatrin may precipitate or aggravate absence, myoclonic, and in some cases generalized tonic-clonic seizures. There has also been a report that lamotrigine may exacerbate seizures in JME.
    - There is a lack of well-designed randomized trials in epilepsy, particularly for generalized seizures and in the pediatric population.
- A Cochrane systematic review evaluated the efficacy of AED monotherapy for epilepsy (*Nevitt et al 2017*). The review included the use of carbamazepine, phenytoin, valproate, phenobarbital, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, and zonisamide for the treatment of partial-onset seizures (simple partial, complex partial or secondarily generalized) or generalized tonic-clonic seizures with or without other generalized seizure types.
    - This network meta-analysis showed that for the primary outcome, the time to withdrawal of allocated treatment:
        - For individuals with partial seizures, levetiracetam performed better than carbamazepine and lamotrigine; lamotrigine performed better than all other treatments (aside from levetiracetam); and carbamazepine performed better than gabapentin and phenobarbital.
        - For individuals with generalized onset seizures, valproate performed better than carbamazepine, topiramate and phenobarbital.
        - For both partial and generalized onset seizures, phenobarbital seems to perform worse than all other treatments.
    - For the secondary outcome, time to first seizure:
        - For individuals with partial seizures, phenobarbital performed better than both carbamazepine and lamotrigine; carbamazepine performed better than valproate, gabapentin, and lamotrigine; and phenytoin performed better than lamotrigine.
        - For both partial and generalized seizure types, phenytoin and phenobarbital generally performed better than other treatments.
    - Few notable differences were shown for either partial or generalized seizure types for the secondary outcomes of time to 6-month or 12-month remission of seizures.
    - Overall, direct evidence and network meta-analysis estimates were numerically similar, and effect sizes had overlapping confidence intervals.
    - Data for individuals with generalized seizures are still limited and additional randomized trials are needed.
- The relative efficacy among valproate, lamotrigine, phenytoin, carbamazepine, ethosuximide, topiramate, levetiracetam, and phenobarbital as monotherapy for generalized (n = 7 studies) or absence seizures (n = 3 studies) was evaluated in a systematic review and network meta-analysis (*Campos et al 2018*). The outcomes analyzed were seizure freedom and withdrawal due to inefficacy. Compared to valproate, phenytoin had a lower odds of seizure freedom (odds ratio, 0.50; 95% credible Interval [CrI] 0.27 to 0.87) in patients with generalized tonic-clonic seizures. Lamotrigine had the highest

probability of seizure freedom and valproate had the highest probability of withdrawal due to inefficacy in these patients. For absence seizures, ethosuximide and valproate were found to have a higher probability of seizure freedom compared to lamotrigine.

- A meta-analysis estimated the comparative efficacy of achieving seizure freedom with 22 antiepileptic drugs and placebo in children and adolescents (*Rosati et al 2018*). For the treatment of newly diagnosed focal epilepsy (n = 4 studies), point estimates suggested superiority of carbamazepine and lamotrigine; however, this was not statistically significant. For refractory focal epilepsy (n = 9 studies), levetiracetam and perampanel were more effective than placebo in mixed comparisons. Ethosuximide and valproic acid were more effective than lamotrigine for absence seizures. The authors concluded that better designed comparative studies with appropriate length of follow-up, well-defined outcomes, and reliable inclusion criteria are needed to validate these results.
- A meta-analysis compared monotherapy with carbamazepine or phenytoin in children and adults with focal onset seizures (simple or complex focal and secondarily generalized), or generalized onset tonic-clonic seizures (with or without other generalized seizure types). Results demonstrated that the time to treatment failure (primary outcome) did not significantly differ between treatment groups. The time to first seizure after randomization and 6-month and 12-month remission were also similar between groups (*Nevitt et al 2019).*
- Approximately 20% to 40% of patients with epilepsy can be considered refractory to drug treatment, referred to as drug-resistant epilepsy. Treatment of drug-resistant epilepsy may include additional anticonvulsant drug trials, epilepsy surgery, vagal nerve stimulation, and dietary changes (the ketogenic diet) (*Sirven 2018*).
  - Combination AED regimens are an option for the treatment of drug-resistant epilepsy. However, robust clinical evidence of suitable combinations of AEDs has been difficult to generate due to the large number of possible combinations of drugs and doses. Examples of combinations for which there is some evidence of efficacy include valproate plus lamotrigine for partial-onset and generalized seizures, valproate plus ethosuximide for absence seizures, and lamotrigine plus topiramate for various seizure types; however, even this evidence is fairly limited. In general, when considering combination therapy, it is recommended to combine medications with different mechanisms of action, and to be mindful of the overall drug load to minimize AEs. Two-drug therapy should be attempted before considering addition of a third drug, and higher numbers of drugs should be avoided as they are associated with a very low likelihood of additional seizure reduction (*Kwan et al 2011*).
  - A meta-analysis examined the efficacy of newer AEDs (eslicarbazepine, brivaracetam, perampanel, and lacosamide) versus levetiracetam as adjunctive therapy for uncontrolled partial-onset seizures. Most patients in this meta-analysis were on at least 2 other AEDs at the time of treatment. In this analysis, eslicarbazepine, lacosamide, and brivaracetam were non-inferior to levetiracetam in terms of efficacy, but all newer AEDs except brivaracetam had worse tolerability profiles than levetiracetam at high doses (*Zhu et al 2017*).
  - A network meta-analysis examined the efficacy of AEDs (including brivaracetam, eslicarbazepine acetate, gabapentin, lacosamide, levetiracetam, lamotrigine, oxcarbazepine, pregabalin, perampanel, rufinamide, tiagabine, topiramate, vigabatrin, and zonisamide) for adjunctive use in patients with refractory partial-onset seizures while using monotherapy (*Zhao et al 2017*). The efficacy outcomes studied were 50% responder rate and state of seizure freedom. The authors concluded that topiramate, levetiracetam, pregabalin, and oxcarbazepine were preferable for their relatively high efficacy and low risk of AEs. Rufinamide was the least preferable medication due to its low efficacy and high risk of AEs.
  - A network meta-analysis was conducted to evaluate the efficacy of 17 newer AEDs for treatment of refractory partial-onset epilepsy with or without secondary generalization (*Hu et al 2018*). The primary outcome was seizure freedom, which was defined as a 100% seizure reduction in the maintenance or double-blind treatment period of the trial. Safety was assessed by the withdrawal rate due to treatment-emergent AEs. Based on results of 54 studies that evaluated the efficacy outcome, the most effective agents included tiagabine, brivaracetam, and valproic acid, and the least effective agents included rufinamide, lamotrigine, and zonisamide. Products with favorable safety included levetiracetam, brivaracetam, and perampanel, while those with the least favorable safety included retigabine (not available in the United States), oxcarbazepine, and rufinamide. The authors stated that agents with the best outcomes in terms of efficacy and safety included levetiracetam, vigabatrin, valproic acid, and brivaracetam.
  - Cannabidiol (Epidiolex) was approved in June 2018 for use in pediatric patients 2 years of age and older with LGS or Dravet syndrome (*FDA news release 2018*). It is the first FDA-approved drug for treatment of patients with Dravet syndrome and is the first approved drug that contains a purified substance, cannabidiol, derived from marijuana. Its approval for these 2 indications was based on 3 placebo-controlled trials in patients refractory to other treatments. Epidiolex, along with use of other agents, demonstrated a significant reduction in seizure frequency compared to

placebo (*Thiele et al 2018*; *Devinsky et al* 2018; *Devinsky et al* 2017). To date, no comparative trials have been published.
- Everolimus tablets for oral suspension (Afinitor Disperz) received an expanded indication for adjunctive use in TSC-associated partial-onset seizures in April 2018. Results of a randomized, double-blind, placebo-controlled study of 366 patients with inadequately controlled seizures on 2 or more AEDs demonstrated a significant reduction in seizure frequency compared to placebo (*French et al 2016*).
- In August 2018, the FDA approved a second drug, stiripentol (Diacomit), for use in the treatment of seizures associated with Dravet syndrome. Two multicenter placebo-controlled studies evaluated the addition of stiripentol to clobazam and valproate therapy in patients 3 years to less than 18 years of age with Dravet syndrome. Responder rates (seizure frequency reduced by 50%) with respect to generalized tonic-clonic seizures were significantly lower with stiripentol compared to placebo (*Diacomit prescribing information 2018).*
- In May 2019, a nasal spray formulation of midazolam (Nayzilam) was approved for the acute treatment of cluster seizures in adults and adolescents. In one randomized controlled trial in patients with seizure clusters while receiving a stable AED regimen, the proportion of patients who experienced treatment success (seizure termination within 10 minutes and no recurrence for the next 6 hours) was significantly higher with midazolam nasal spray compared to placebo (53.7% vs 34.4%, p = 0.0109) with similar tolerability (*Detyniecki et al 2019*).
- Cenobamate was approved in late 2019 and its efficacy has yet to be compared to other AEDs. The approval of this agent was based on 2 multicenter, randomized, double-blind, placebo-controlled studies that enrolled 655 adults with partial-onset seizures with or without generalization who were not adequately controlled with 1 to 3 other AEDs. The results of these trials demonstrated that cenobamate significantly reduced the frequency of seizures occurring in a 28-day period. In the first trial, the median percent change in seizure frequency from baseline was -55.6% with cenobamate and -21.5% with placebo. In the second trial, the median percent change ranged from -36.3% to -55.3% with cenobamate and was -24.3% with placebo (*Xcopri package insert 2019, Krauss et al 2020*).
- A 2019 randomized controlled trial of children and adults with benzodiazepine-refractory convulsive status epilepticus compared the efficacy of intravenous levetiracetam (n = 145 patients), fosphenytoin (n = 118), or valproate (n = 121) in this setting. Results demonstrated that each agent led to seizure cessation and improved alertness by 1 hour in approximately 50% of patients, with no significant differences between groups (*Kapur et al 2019*).

CLINICAL GUIDELINES

- **Efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy**. American Academy of Neurology and American Epilepsy Society (*French et al 2004A, Kanner et al, 2018A*).
  - A 2018 update to the 2004 guideline focuses on treatment of new-onset epilepsy with second and third generation AEDs. The 2004 publication summarizes the efficacy, tolerability, and safety of gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide for the treatment of children and adults with newly diagnosed partial and generalized epilepsies.
  - The recommendations from the 2004 guideline include the following:
    - Patients with newly diagnosed epilepsy who require treatment can be initially treated with standard AEDs such as carbamazepine, phenytoin, valproic acid, or phenobarbital, or on the newer AEDs lamotrigine, gabapentin, oxcarbazepine, or topiramate. Choice will depend on individual patient characteristics.
    - Lamotrigine can be included in the options for children with newly diagnosed absence seizures.
  - The 2018 recommendations include the following:
    - As monotherapy in adult patients with new-onset focal epilepsy or unclassified generalized tonic-clonic seizures:
      - Lamotrigine use should be considered to decrease seizure frequency.
      - Lamotrigine use should be considered and gabapentin use may be considered to decrease seizure frequency in patients aged ≥ 60 years.
      - Levetiracetam and zonisamide use may be considered to decrease seizure frequency.
      - Vigabatrin appears to be less efficacious than carbamazepine immediate-release and may not be offered; furthermore, the toxicity profile precludes vigabatrin use as first-line therapy.
      - Pregabalin 150 mg per day is possibly less efficacious than lamotrigine 100 mg per day.
      - There is insufficient evidence to consider use of gabapentin, oxcarbazepine, or topiramate over carbamazepine.

        - There is insufficient evidence to consider use of topiramate instead of phenytoin in urgent treatment of new-onset or recurrent focal epilepsy, unclassified generalized tonic-clonic seizures, or generalized epilepsy presenting with generalized tonic-clonic seizures.
        - Data are lacking to support or refute use of third-generation AEDs (eslicarbazepine, ezogabine [no longer marketed], lacosamide, perampanel, pregabalin, and rufinamide), clobazam, felbamate, or vigabatrin for new-onset epilepsy.
        - Data are lacking to support or refute use of newer AEDs in treating unclassified generalized tonic-clonic seizures.
    - Ethosuximide or valproic acid should be considered before lamotrigine to decrease seizure frequency in children with absence epilepsy. An exception would be if there are compelling AE-related concerns with use of ethosuximide or valproic acid.
    - The guideline does not address newly approved agents including cannabidiol, everolimus, or stiripentol.
- **Efficacy and tolerability of the new antiepileptic drugs II: treatment of refractory epilepsy**. American Academy of Neurology and American Epilepsy Society (*Kanner et al 2018B*, *French et al 2004B*).
    - A 2018 update to the 2004 guideline focuses on management of treatment-resistant epilepsy with second and third generation AEDs. The 2004 publication summarizes the efficacy, tolerability, and safety of gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide for the treatment of children and adults with refractory partial and generalized epilepsies.
    - Recommendations from the 2004 guideline include the following:
        - It is appropriate to use gabapentin, lamotrigine, tiagabine, topiramate, oxcarbazepine, levetiracetam, and zonisamide as add-on therapy in patients with refractory epilepsy.
        - Oxcarbazepine, topiramate, and lamotrigine can be used as monotherapy in patients with refractory partial epilepsy.
        - Topiramate may be used for the treatment of refractory generalized tonic-clonic seizures in adults and children.
        - Gabapentin, lamotrigine, oxcarbazepine, and topiramate may be used as adjunctive treatment of children with refractory partial seizures.
        - Topiramate and lamotrigine may be used to treat drop attacks associated with LGS in adults and children.
    - Recommendations from the 2018 guideline include the following:
        - As adjunctive therapy in patients with treatment-resistant adult focal epilepsy (TRAFE):
            - Immediate-release pregabalin and perampanel are established as effective to reduce seizure frequency.
            - Lacosamide, eslicarbazepine, and extended-release topiramate should be considered to decrease seizure frequency.
            - Vigabatrin and rufinamide are effective for decreasing seizure frequency, but are not first-line agents.
            - Ezogabine (no longer marketed) use should be considered to reduce seizure frequency, but carries a serious risk of skin and retinal discoloration.
            - Clobazam and extended-release oxcarbazepine may be considered to decrease seizure frequency.
        - As monotherapy in patients with TRAFE:
            - Eslicarbazepine use may be considered to decrease seizure frequency.
            - Data are insufficient to recommend use of second- and the other third-generation AEDs.
        - For add-on therapy for generalized epilepsy, immediate-release and extended-release lamotrigine should be considered as add-on therapy to decrease seizure frequency in adults with treatment-resistant generalized tonic-clonic seizures secondary to generalized epilepsy. Levetiracetam use should be considered to decrease seizure frequency as add-on therapy for treatment-resistant generalized tonic-clonic seizures and for treatment-resistant juvenile myoclonic epilepsy.
        - Rufinamide is effective to reduce seizure frequency as add-on therapy for LGS. Clobazam use should be considered as add-on therapy for LGS.
        - For add-on therapy in pediatric patients with treatment-resistant focal epilepsy:
            - Levetiracetam use should be considered to decrease seizure frequency (ages 1 month to 16 years).
            - Zonisamide use should be considered to decrease seizure frequency (age 6 to 17 years).
            - Oxcarbazepine use should be considered to decrease seizure frequency (age 1 month to 4 years).
            - Data are unavailable on the efficacy of clobazam, eslicarbazepine, lacosamide, perampanel, rufinamide, tiagabine, or vigabatrin.
        - The guideline does not address newly approved agents including cannabidiol, everolimus, or stiripentol.

- **Evidence-based guideline: management of an unprovoked first seizure in adults.** Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society (*Krumholz et al 2015; reaffirmed in 2018*).
  - This practice guideline makes recommendations based on a consideration of the evidence for prognosis and treatment of adults with an unprovoked first seizure.
  - Recommendations include the following:
    - Adults presenting with an unprovoked first seizure should be informed that the chance for a recurrent seizure is greatest within the first 2 years after a first seizure (21% to 45%).
    - Clinicians should also advise such patients that clinical factors associated with an increased risk of seizure recurrence include a prior brain insult such as a stroke or trauma, an EEG with epileptiform abnormalities, a significant brain-imaging abnormality, or a nocturnal seizure.
    - Clinicians should advise patients that, although immediate AED therapy, as compared with delay of treatment pending a second seizure, is likely to reduce the risk of a seizure recurrence in the 2 years subsequent to a first seizure, it may not improve quality of life.
    - Clinicians should advise patients that over the longer term (> 3 years), immediate AED treatment is unlikely to improve the prognosis for sustained seizure remission.
    - Patients should be advised that their risk for AED AEs ranges from 7% to 31% and that these AEs are predominantly mild and reversible.
  - Immediate AED therapy after an unprovoked first seizure is likely to reduce seizure recurrence risk. A reduction in risk may be important, particularly for adults, for whom seizure recurrences may cause serious psychological and social consequences such as loss of driving privileges and limitations on employment. However, immediate AED treatment is not well accepted and is debated. Decisions should be based on weighing the risk of recurrence against the AEs of AED therapy, and should take patient preferences into account.
  - It is accepted that when a patient has a second or additional seizures, an AED should be initiated because the risk of subsequent seizures is very high.
- **Evidence-based guideline: treatment of convulsive status epilepticus in children and adults.** Guideline Committee of the American Epilepsy Society (*Glauser et al 2016*).
  - This publication provides conclusions and a treatment algorithm based on a structured literature review of randomized trials of anticonvulsant treatments for seizures lasting longer than 5 minutes. A total of 38 trials were included.
  - For treatment in the adult population, conclusions included the following:
    - Intramuscular (IM) midazolam, intravenous (IV) lorazepam, IV diazepam (with or without phenytoin), and IV phenobarbital are established as efficacious at stopping seizures lasting at least 5 minutes.
    - IV lorazepam is more effective than IV phenytoin in stopping seizures lasting at least 10 minutes.
    - There is no difference in efficacy between IV lorazepam followed by IV phenytoin, IV diazepam plus phenytoin followed by IV lorazepam, and IV phenobarbital followed by IV phenytoin.
    - IV valproic acid has similar efficacy to IV phenytoin or continuous IV diazepam as second therapy after failure of a benzodiazepine.
    - Insufficient data exist in adults about the efficacy of levetiracetam as either initial or second therapy.
    - In adults with status epilepticus without established IV access, IM midazolam is established as more effective compared with IV lorazepam.
    - No significant difference in effectiveness has been demonstrated between lorazepam and diazepam in adults with status epilepticus.
  - For treatment in the pediatric population, conclusions included the following:
    - IV lorazepam and IV diazepam are established as efficacious at stopping seizures lasting at least 5 minutes.
    - Rectal diazepam, IM midazolam, intranasal midazolam, and buccal midazolam are probably effective at stopping seizures lasting at least 5 minutes.
    - Insufficient data exist in children about the efficacy of intranasal lorazepam, sublingual lorazepam, rectal lorazepam, valproic acid, levetiracetam, phenobarbital, and phenytoin as initial therapy.
    - IV valproic acid has similar efficacy but better tolerability than IV phenobarbital as second therapy after failure of a benzodiazepine.
    - Insufficient data exist in children regarding the efficacy of phenytoin or levetiracetam as second therapy after failure of a benzodiazepine.

        - In children with status epilepticus, no significant difference in effectiveness has been established between IV lorazepam and IV diazepam.
        - In children with status epilepticus, non-IV midazolam (IM/intranasal/buccal) is probably more effective than diazepam (IV/rectal).
    - Conclusions included the following (age not specified):
        - Insufficient data exist about the comparative efficacy of phenytoin and fosphenytoin. Fosphenytoin is better tolerated compared with phenytoin. When both are available, fosphenytoin is preferred based on tolerability, but phenytoin is an acceptable alternative.
    - The overall treatment algorithm directs that:
        - A benzodiazepine (IM midazolam, IV lorazepam, or IV diazepam) is recommended as the initial therapy of choice in the first phase of treatment (5 to 20 minutes after the beginning of the seizure). Although IV phenobarbital is established as efficacious and well tolerated as initial therapy, its slower rate of administration positions it as an alternative initial therapy. For prehospital settings or where first-line benzodiazepine options are not available, rectal diazepam, intranasal midazolam, and buccal midazolam are reasonable initial therapy alternatives.
        - In the second phase of treatment (from 20 to 40 minutes after the beginning of the seizure), reasonable options include fosphenytoin, valproic acid, and levetiracetam. There is no clear evidence that any of these options is better than the others. Because of AEs, IV phenobarbital is a reasonable second-therapy alternative if none of the 3 recommended therapies are available.
        - There is no clear evidence to guide therapy in the third phase of therapy (≥ 40 minutes after the beginning of the seizure).
- **Evidence-based guideline update: medical treatment of infantile spasms.** Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (*Go et al 2012*; reaffirmed in 2018)
    - This publication provides updated recommendations for the treatment of infantile spasms. The literature review included an evaluation of 26 published articles on this topic.
    - Recommendations include the following:
        - Evidence is insufficient to recommend the use of prednisolone, dexamethasone, and methylprednisolone as being as effective as adrenocorticotropic hormone (ACTH) for short-term treatment of infantile spasms.
        - Low-dose ACTH should be considered as an alternative to high-dose ACTH for treatment of infantile spasms.
        - ACTH or vigabatrin may be offered for short-term treatment of infantile spasms; evidence suggests that ACTH may be offered over vigabatrin.
        - Evidence is insufficient to recommend other therapies (valproic acid, vitamin B6, nitrazepam [not available in the United States], levetiracetam, zonisamide, topiramate, the ketogenic diet, or novel/combination therapies) for treatment of infantile spasms.
        - Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to vigabatrin in infants with cryptogenic infantile spasms, to possibly improve developmental outcome.
        - A shorter lag time to treatment of infantile spasms with either hormonal therapy or vigabatrin may be considered to improve long-term cognitive outcomes.
    - There is a lack of sufficient randomized trials to provide definitive answers to key questions related to treatment of infantile spasms.
- **Practice parameter: treatment of the child with a first unprovoked seizure.** Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (*Hirtz et al 2003*; reaffirmed in 2018)
    - This parameter reviews published literature relevant to the decision to begin treatment after a child or adolescent experiences a first unprovoked seizure and presents evidence-based practice recommendations. Treatment during the neonatal period is not addressed.
    - Recommendations include the following:
        - Treatment with AEDs is not indicated for the prevention of the development of epilepsy.
        - Treatment with AEDs may be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the risks of pharmacologic and psychosocial AEs.

- The majority of children who experience a first unprovoked seizure will have few or no recurrences. Treatment with AEDs after a first seizure as opposed to after a second seizure has not been shown to improve prognosis for long-term seizure remission.
- Treatment has been shown in several studies combining both children and adults to reduce the risk of seizure recurrence; however, there is a relative paucity of data from studies involving only children after a first seizure.

- **Summary of recommendations for the management of infantile seizures**. Task force report for the ILAE Commission of Pediatrics (*Wilmshurst et al 2015*).
  - This publication recommends an approach to the standard and optimal management of infants with seizures. When possible, recommendations are evidence-based; however, when no evidence was available, recommendations are based on expert opinion and standard practice.
  - Recommendations/findings include the following:
    - There is no indication for initiation of chronic AEDs for simple febrile seizures. However, in the acute treatment of febrile seizures, it is important to treat seizures lasting 10 minutes or longer.
    - In an otherwise healthy infant, a policy of "wait and see" is reasonable after the first afebrile seizure. However, this is a rare event and close monitoring is essential.
    - Treatment options with established or probable efficacy include the following:
      - Focal seizures: levetiracetam
      - Epileptic spasms: High-dose or low-dose ACTH
      - Dravet syndrome: stiripentol
    - Treatment options with possible efficacy include the following:
      - Generalized seizures: levetiracetam, valproate, lamotrigine, topiramate, clobazam
      - Epileptic spasms: prednisone, vigabatrin
      - Benign infantile convulsions: carbamazepine, phenobarbital, valproate
      - Dravet syndrome: topiramate, zonisamide, valproate
      - Benign myoclonic epilepsy of infancy: valproate, topiramate, lamotrigine, clonazepam
      - Provoked or situational seizures: carbamazepine
    - There is no clear evidence supporting an optimal duration of treatment; this is dependent on seizure type.
- **Guidelines on neonatal seizures**. World Health Organization (WHO) (*WHO 2011*).
  - This document was prepared based on a systematic review of the literature and involved cooperation between the WHO, the ILAE, and the International Bureau of Epilepsy (IBE).
  - Recommendations include the following:
    - Phenobarbital should be used as the first-line agent for treatment of neonatal seizures and should be made readily available in all settings.
    - In neonates who continue to have seizures despite administering the maximum tolerated dose of phenobarbital, either a benzodiazepine, phenytoin, or lidocaine may be used as the second-line agent for control of seizures (use of phenytoin or lidocaine requires cardiac monitoring).
    - In neonates with a normal neurological examination and/or normal EEG, stopping AEDs may be considered if the neonate has been seizure-free for > 72 hours; the drug(s) should be reinstituted if seizures recur.
    - In neonates in whom seizure control is achieved with a single AED, the drug can be discontinued abruptly without tapering the dose. In neonates requiring > 1 AED for seizure control, the drugs may be stopped one at a time, with phenobarbital being the last drug to be withdrawn.
- **Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes.** Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society (*Harden et al 2009A*; reaffirmed in 2013; Update in progress)
  - This publication summarizes evidence for selected issues regarding the clinical management of women with epilepsy (WWE) who are pregnant or planning to be pregnant.
  - Recommendations include the following:
    - If possible, avoidance of the use of valproate as part of polytherapy during the first trimester of pregnancy should be considered to decrease the risk of major congenital malformations (MCMs).
    - If possible, avoidance of the use of valproate monotherapy during the first trimester of pregnancy may be considered to decrease the risk of MCMs.

        - To reduce the risk of MCMs, the use of valproate during the first trimester of pregnancy should be avoided, if possible, compared to the use of carbamazepine.
        - To reduce the risk of MCMs, avoidance of the use of polytherapy with valproate during the first trimester of pregnancy, if possible, should be considered, compared to polytherapy without valproate.
        - To reduce the risk of MCMs, avoidance of the use of valproate during the first trimester of pregnancy, if possible, may be considered, compared to the use of phenytoin or lamotrigine.
        - To reduce the risk of MCMs, avoidance of the use of AED polytherapy during the first trimester of pregnancy, if possible, compared to monotherapy should be considered.
        - Limiting the dosage of valproate or lamotrigine during the first trimester, if possible, should be considered to lessen the risk of MCMs.
        - Avoidance of the use of valproate, if possible, should be considered to reduce the risk of neural tube defects and facial clefts, and may be considered to reduce the risk of hypospadias.
        - Avoidance of phenytoin, carbamazepine, and phenobarbital, if possible, may be considered to reduce the risk of specific MCMs: cleft palate for phenytoin use, posterior cleft palate for carbamazepine use, and cardiac malformations for phenobarbital use.
        - Carbamazepine exposure probably does not produce cognitive impairment in offspring of WWE.
        - Avoiding valproate in WWE during pregnancy, if possible, should be considered to reduce the risk of poor cognitive outcomes.
        - Avoiding phenytoin and phenobarbital in WWE during pregnancy, if possible, may be considered to reduce the risk of poor cognitive outcomes.
        - Monotherapy should be considered in place of polytherapy, if possible, for WWE who take AEDs during pregnancy to reduce the risk of poor cognitive outcomes.
        - For WWE who are pregnant, avoidance of valproate, if possible, should be considered compared to carbamazepine to reduce the risk of poor cognitive outcomes.
        - For WWE who are pregnant, avoidance of valproate, if possible, may be considered compared to phenytoin to reduce the risk of poor cognitive outcomes.
    - Valproate has the most data showing an association with risk from in utero exposure. If a change from valproate to another AED is planned, it is prudent to make this change well before pregnancy.
    - Although many of the recommendations in this parameter suggest minimizing AED exposure during pregnancy, for most WWE, discontinuing AEDs is not a reasonable or safe option. Discontinuing AEDs may expose the mother and fetus to physical injury from accidents due to seizure activity.
- **Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding.** Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society (*Harden et al 2009B*; reaffirmed in 2013; Update in progress)
    - This publication summarizes evidence for selected issues regarding the clinical management of WWE who are pregnant or planning to be pregnant.
    - Recommendations include the following:
        - The fact that phenobarbital, primidone, phenytoin, carbamazepine, levetiracetam, valproate, gabapentin, lamotrigine, oxcarbazepine, and topiramate cross the placenta may be factored into the clinical decision regarding the necessity of AED treatment for a woman with epilepsy.
        - Monitoring of lamotrigine, carbamazepine, and phenytoin levels during pregnancy should be considered.
        - Monitoring of levetiracetam and oxcarbazepine (as monohydroxy derivative) levels during pregnancy may be considered.
        - There is insufficient evidence to support or refute a change in phenobarbital, valproate, primidone, or ethosuximide levels related to pregnancy, but this lack of evidence should not discourage monitoring levels of these AEDs during pregnancy.
        - Valproate, phenobarbital, phenytoin, and carbamazepine may not transfer into breast milk to as great an extent as primidone, levetiracetam, gabapentin, lamotrigine, and topiramate.
    - Although many of the AEDs were shown to cross the placenta or enter breast milk, studies were limited in duration and did not systematically evaluate neonatal symptoms.

- Guidelines also support the use of AEDs for several common non-epilepsy indications:
  - The American Academy of Neurology and American Headache Society state that AEDs with established efficacy for migraine prevention include valproate, divalproex sodium, and topiramate; carbamazepine is noted to be possibly effective (*Silberstein et al 2012;* reaffirmed in 2015; Update in progress). An American Academy of Neurology guideline for pediatric migraine prevention noted that children and adolescents with migraine receiving topiramate are probably more likely than those receiving placebo to have a reduction in migraine or headache day frequency, whereas there was insufficient evidence to support the efficacy of extended-release divalproex sodium for reducing frequency (*Oskoui et al 2019*).
  - The American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation state that, for relief of painful diabetic neuropathy, pregabalin is established as effective, and gabapentin and valproate are probably effective (*Bril et al 2011*; Update in progress).
  - A retired guideline from The American Academy of Neurology states that gabapentin and pregabalin are of benefit in reducing pain from postherpetic neuralgia (*Dubinsky et al 2004; retired February 27, 2018*).
  - American Psychiatric Association guidelines describe the key role of AEDs in the management of bipolar disorder, including the following (*Hirschfeld et al 2002*):
    - First-line pharmacological treatment for more severe manic or mixed episodes is either lithium plus an antipsychotic or valproate plus an antipsychotic; for less ill patients, monotherapy with lithium, valproate, or an antipsychotic may be sufficient. For mixed episodes, valproate may be preferred over lithium. Carbamazepine and oxcarbazepine are alternatives.
    - First-line pharmacological treatment for bipolar depression is either lithium or lamotrigine. When an acute depressive episode of bipolar disorder does not respond to first-line medication treatment, the next steps include adding lamotrigine, bupropion, or paroxetine.
    - The initial treatment for patients who experience rapid cycling should include lithium or valproate; an alternative is lamotrigine.
    - The medications with the best empirical evidence to support their use in maintenance treatment include lithium and valproate; possible alternatives include lamotrigine, carbamazepine, or oxcarbazepine.
    - Note: This guideline was published in 2002 and cannot be assumed to be current; however, AEDs continue to be recommended for both acute (mania or hypomania) and maintenance phases of bipolar disorder *(Post 2017, Stovall 2018).*

SAFETY SUMMARY

- Tolerability and safety are as important as efficacy in determining the overall effectiveness of epilepsy treatment (*Schachter 2019*).
- Common AEs among AEDs include the following (*Schachter 2019*).
  - Systemic AEs:
    - nausea, vomiting, constipation, diarrhea, anorexia
    - rash
    - hyponatremia (carbamazepine, eslicarbazepine, oxcarbazepine)
    - weight gain (pregabalin, perampanel, valproate), weight loss (felbamate, topiramate, stiripentol)
  - Neurologic AEs:
    - headache
    - somnolence, sedation, drowsiness, lethargy, fatigue
    - dizziness, vertigo
    - tremor, anxiety, nervousness, insomnia
    - aggression, irritability, hyperactivity
    - depression, mood alteration
    - confusion
    - ataxia
    - blurred or double vision
- Examples of rare but serious AEs include the following (*Schachter 2019, individual package inserts*):
  - suicidal ideation and behavior (AEDs as a class, except everolimus)

- neutropenia, leukopenia, pancytopenia, agranulocytosis, thrombocytopenia, and/or aplastic anemia (brivaracetam, carbamazepine, ethosuximide, felbamate, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, phenobarbital, primidone, stiripentol, valproate, vigabatrin, zonisamide)
- anaphylaxis or angioedema (brivaracetam, fosphenytoin, gabapentin, levetiracetam, phenytoin, pregabalin)
- severe skin rashes, Stevens-Johnson syndrome (SJS), and/or toxic epidermal necrolysis (TEN) (carbamazepine, clobazam, eslicarbazepine, fosphenytoin, ethosuximide, lamotrigine, levetiracetam, oxcarbazepine, phenytoin, phenobarbital, primidone, rufinamide, tiagabine, valproate, zonisamide)
- hepatic failure (carbamazepine, ethosuximide, felbamate, phenytoin, phenobarbital, primidone, valproate)
- hepatocellular injury (cannabidiol)
- prolonged PR interval, atrioventricular block, and/or changes in QT interval (cenobamate, eslicarbazepine, lacosamide, rufinamide)
- serum sickness (carbamazepine, ethosuximide, phenytoin, phenobarbital, primidone, valproate)
- multiorgan hypersensitivity (carbamazepine, cenobamate, ethosuximide, gabapentin, lacosamide, lamotrigine, oxcarbazepine, perampanel, phenytoin, rufinamide, valproate, zonisamide)
- severe neuropsychiatric effects/hostility/aggression (brivaracetam, levetiracetam, perampanel)
- hemophagocytic lymphohistiocytosis (HLH) (lamotrigine)
- Cardiac AEs, including bradycardia and cardiac arrest (phenytoin)
- Abnormal magnetic resonance imaging signals in infants (vigabatrin)
- Intramyelinic edema (vigabatrin)

- A number of AEDs carry boxed warnings related to potentially serious AEs; these include the following:
  - Carbamazepine:
    - Serious and sometimes fatal dermatologic reactions, including TEN and SJS, have been reported. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. Patients with ancestry in genetically at-risk populations (across broad areas of Asia) should be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine.
    - Aplastic anemia and agranulocytosis have been reported. If a patient exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely, and discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.
  - Clobazam, clonazepam, clorazepate, diazepam, and midazolam:
    - Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Concomitant prescribing should be reserved for use in patients for whom alternative treatment options are inadequate, and patients should be followed for signs and symptoms of respiratory depression and sedation.
  - Felbamate:
    - Use is associated with a marked increase in the incidence of aplastic anemia. Felbamate should only be used in patients whose epilepsy is so severe that the risk of aplastic anemia is deemed acceptable. Routine blood testing cannot be reliably used to reduce the incidence of aplastic anemia, but it will in some cases allow detection of hematologic changes before the syndrome declares itself clinically. Felbamate should be discontinued if any evidence of bone marrow depression occurs.
    - Cases of acute liver failure have been reported. Felbamate should not be prescribed for anyone with a history of hepatic dysfunction. Treatment should be initiated only in individuals without active liver disease and with normal baseline serum transaminases. It has not been proven that periodic serum transaminase testing will prevent serious injury, but it is generally believed that early detection of drug-induced hepatic injury along with immediate withdrawal of the suspect drug enhances the likelihood for recovery. Serum transaminases should be monitored at baseline and periodically thereafter. Felbamate should be discontinued if either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) become increased to ≥ 2 times the upper limit of normal, or if clinical signs and symptoms suggest liver failure, and should not be considered for retreatment.
  - Fosphenytoin and phenytoin:
    - There is a cardiovascular risk associated with rapid IV infusion rates. The rate of administration should not exceed recommendations, and careful cardiac monitoring is required.

- Lamotrigine:
  - Cases of life-threatening serious skin rashes, including SJS and TEN, and/or rash-related death have been caused by lamotrigine. Benign rashes are also caused by lamotrigine; however, it is not possible to predict which rashes will prove to be serious. Lamotrigine should be discontinued at the first sign of a rash, unless the rash is clearly not drug related.
- Perampanel:
  - Serious or life-threatening psychiatric and behavioral AEs including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported. Patients should be monitored for these reactions and for changes in mood, behavior, or personality. The dose should be reduced if these symptoms occur, and it should be discontinued if symptoms are severe or worsening.
- Valproic acid and divalproex sodium:
  - Hepatotoxicity, including fatalities, have been reported, usually during the first 6 months of treatment. Serum liver tests are required and patients should be monitored closely. There is an increased risk of valproate-induced acute liver failure and resultant deaths in patients with mitochondrial disease. Valproic acid and divalproex sodium are contraindicated in patients known to have mitochondrial disorders caused by polymerase gamma (POLG) gene mutations, and in children < 2 years of age who are suspected of having a mitochondrial disorder.
  - There is a risk to fetuses exposed in utero, particularly neural tube defects, other major malformations, and decreased intelligence quotient (IQ). Valproate should not be given to a woman of childbearing potential unless the drug is essential to the management of her medical condition, and women should use effective contraception while using valproate.
  - Pancreatitis, including fatal hemorrhagic cases, has occurred. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation.
- Vigabatrin:
  - Vigabatrin can cause permanent bilateral concentric visual field constriction, including tunnel vision that can result in disability. In some cases, vigabatrin may also damage the central retina and may decrease visual acuity. Baseline and periodic vision assessment are recommended. However, this assessment cannot always prevent vision damage, and once detected, vision loss due to vigabatrin is not reversible. Vigabatrin should be withdrawn from patients who fail to show substantial clinical benefit.
  - Due to the risks of vision loss, vigabatrin is available only through a risk evaluation and mitigation strategy (REMS) program (*FDA REMS 2020*). Healthcare providers who prescribe vigabatrin and pharmacies that dispense the product must be specially certified. Each patient must be enrolled in the REMS program. Prescribers must ensure that periodic visual monitoring is performed and report any AE suggestive of vision loss to the vigabatrin REMS program.

- Everolimus is an antineoplastic, immunosuppressant agent associated with several adverse reactions.
  - The most common AE that occurred in trials for TSC-associated partial-onset seizures was stomatitis.
  - More serious AEs include:
    - non-infectious pneumonitis
    - infections
    - hypersensitivity reactions
    - angioedema (when taken with an angiotensin-converting enzyme inhibitor)
    - renal failure
    - impaired wound healing
    - myelosuppression
    - reduced immune response with vaccination
    - hyperglycemia
    - hyperlipidemia
    - embryo-fetal toxicity

DOSING AND ADMINISTRATION

- General dosing information is provided in Table 3. Dosing may vary based on the specific indication, interacting medications, and the patient's age and renal and hepatic function. Additionally, some medications are recommended to be titrated during initial treatment. Please refer to the prescribing information of the individual products for more detailed information.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Barbiturates				
Pentobarbital (Nembutal)	injection	IV, IM	Single dose	Acute use only. If needed, additional small increments may be given after the initial dose.
Phenobarbital* (Luminal†, Solfoton†)	tablets, elixir, injection	oral, IV, IM	2 to 3 times per day	
Primidone (Mysoline)	tablets	oral	3 to 4 times per day	
Benzodiazepines				
Clobazam (Onfi, Sympazan)	tablets, oral suspension, oral film	oral	1 or 2 times per day	Daily doses > 5 mg should be given in divided doses 2 times per day. Sympazan should be applied on top of the tongue where it adheres and dissolves.
Clonazepam (Klonopin)	tablets, orally disintegrating tablets (wafers)	oral	3 times per day	
Clorazepate (Tranxene T-Tab)	tablets	oral	2 to 3 times per day	
Diazepam (Diastat, Valium, Valtoco)	tablets, oral solution, oral concentrate, rectal gel, injection, nasal spray	oral, rectal, IV, IM, intranasal	2 to 4 times per day	For the rectal gel (for acute use), a second dose may be given 4 to 12 hours after the initial dose when required. The injection and nasal spray are also for short-term acute use. For the nasal spray, a second dose may be given 4 hours after the initial dose when required. The product should be used to treat no more than 1 episode every 5 days and no more than 5 episodes per month.
Midazolam (Nayzilam)	nasal spray	intranasal	Up to 2 doses per seizure cluster, with the second dose given at least 10 minutes after the first dose	Should be used to treat no more than 1 episode every 3 days and no more than 5 episodes per month.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Hydantoins				
Ethotoin (Peganone)	tablets	oral	4 to 6 times per day	
Fosphenytoin (Cerebyx)	injection	IV, IM	2 times per day or other divided doses based on drug levels	Generally used in acute situations as a loading dose; may be given in divided doses when substituted for oral phenytoin.
Phenytoin (Dilantin, Phenytek)	extended-release capsules, chewable tablets, oral suspension, injection	oral, IV, IM	2 to 4 times per day	Capsules are extended-release and may be suitable for once-daily dosing in some adults.
Miscellaneous				
Brivaracetam (Briviact)	tablets, oral solution, injection	oral, IV	2 times per day	The injection may be used when oral administration is temporarily not feasible.
Cannabidiol (Epidiolex)	oral solution	oral	2 times per day	The provided oral syringe should be used to measure an accurate dose.
Carbamazepine (Carbatrol, Epitol, Equetro, Tegretol, Tegretol-XR)	tablets, chewable tablets, oral suspension, extended-release tablets, extended-release capsules	oral	2 to 4 times per day	Immediate-release tablets are given 2 to 3 times per day and the suspension is given 4 times per day. Carbatrol and Equetro are twice-daily extended-release capsule formulations; these capsules may be opened and sprinkled on soft food. Tegretol-XR is a twice-daily extended-release tablet formulation; these tablets must be swallowed whole.
Cenobamate (Xcopri)¶	tablets	oral	once daily	The recommended titration schedule should not be exceeded.
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	delayed-release tablets, delayed-release sprinkle capsules, extended-release tablets	oral	2 to 3 times per day (once daily for extended-release tablets)	Delayed-release tablets and extended-release tablets should be swallowed whole. Sprinkle capsules may be opened and sprinkled on soft food. Delayed-release tablet and capsule doses > 250 mg per day should be given in divided doses.
Eslicarbazepine (Aptiom)	tablets	oral	once daily	Tablets may be crushed.
Ethosuximide (Zarontin)	capsules, oral solution/syrup	oral	once daily or in divided doses	
Everolimus (Afinitor Disperz)	tablets for oral suspension	oral	once daily	Should be taken at the same time each day with or without food.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Suspension should be prepared using water only and administered immediately after preparation. The suspension should be discarded if not taken within 60 minutes of preparation. Dose adjustments are made based on trough drug concentration.
Felbamate (Felbatol)	tablets, oral suspension	oral	3 or 4 times per day	
Gabapentin (Neurontin)	tablets, capsules, oral solution	oral	3 times per day	Capsules should be swallowed whole.
Lacosamide (Vimpat)	tablets, oral solution, injection	oral, IV	2 times per day	
Lamotrigine (Lamictal, Lamictal ODT, Lamictal XR, Subvenite)	tablets, chewable dispersible tablets, orally disintegrating tablets, extended-release tablets	oral	2 times per day (once daily for extended-release tablets)	Only whole tablets should be administered. Extended-release tablets must not be chewed or crushed.
Levetiracetam (Keppra, Keppra XR, Roweepra, Roweepra XR, Spritam, Elepsia XR)	tablets, tablets for oral suspension, oral solution, extended-release tablets, injection	oral, IV	2 times per day (once daily for extended-release tablets)	Tablets and extended-release tablets should not be chewed or crushed. Tablets for oral suspension (Spritam) can be dissolved in liquid and swallowed or allowed to disintegrate in the mouth.
Methsuximide (Celontin)	capsules	oral	3 to 4 times per day (*Lexicomp 2020*)	
Oxcarbazepine (Oxtellar XR, Trileptal)	tablets, oral suspension, extended-release tablets	oral	2 times per day (once daily for extended-release tablets)	In conversion of oxcarbazepine immediate-release to Oxtellar XR, higher doses of Oxtellar XR may be necessary. Extended-release tablets must not be chewed or crushed.
Perampanel (Fycompa)	tablets, oral suspension	oral	once daily at bedtime	
Pregabalin (Lyrica)	capsules, oral solution	oral	2 to 3 times per day	
Rufinamide (Banzel)	tablets, oral suspension	oral	2 times per day	Tablets can be administered whole, as half tablets, or crushed.
Stiripentol (Diacomit)	capsules, powder for oral suspension	oral	2 to 3 times per day	Capsules must be swallowed whole with a glass of water during a meal. Powder should be mixed with water and taken immediately after mixing during a meal.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Tiagabine (Gabitril)	tablets	oral	2 to 4 times per day	
Topiramate (Topamax, Topamax Sprinkle, Topiragen, Trokendi XR, Qudexy XR)	tablets, sprinkle capsules, extended-release capsules, extended-release sprinkle capsules	oral	2 times per day (once daily for extended-release capsule formulations)	Sprinkle capsules may be opened and sprinkled on soft food. Extended-release capsules (Trokendi XR) must not be chewed or crushed, but extended release sprinkle capsules (Qudexy XR) may be sprinkled on soft food.
Valproic acid/ valproate sodium (Depakene, Depacon)	capsules, oral solution/ syrup, injection	oral, IV	1 to 3 times per day (*Lexicomp 2020*)	Capsules should be swallowed whole without chewing to avoid local irritation of the mouth and throat. If the total dose exceeds 250 mg, it should be given in divided doses.
Vigabatrin (Sabril, Vigadrone)	tablets, powder for oral solution	oral	2 times per day	Powder for oral solution is supplied in individual dose packets to be mixed with water before administration.
Zonisamide (Zonegran)	capsules	oral	1 or 2 times per day	Capsules must be swallowed whole.

* Not FDA approved
† Brand product not currently marketed; generic is available
¶ FDA-approved product, but not yet marketed

CONCLUSION

- Several classes of AEDs are available, including barbiturates, benzodiazepines, hydantoins, and miscellaneous agents. These products vary in terms of their indications for specific seizure types and indications other than epilepsy.
- Overall, the anticonvulsants have demonstrated efficacy for their FDA-approved uses. When possible, monotherapy with a single AED is the preferred treatment approach.
- Patients who are refractory to monotherapy may be treated with combination therapy. When considering combination therapy, it is recommended to combine medications with different mechanisms of action and AE profiles.
- Comparative efficacy data for the management of epilepsy are limited.
- Tolerability and safety are as important as efficacy in determining the overall effectiveness of epilepsy treatment. Both systemic AEs and neurologic AEs commonly occur. Some AEDs are associated with rare but serious AEs, and careful patient selection and monitoring are required.
- Epilepsy management can be complex and is often performed by neurologists. A variety of AEDs should be available to allow clinicians to select the most clinically appropriate agent for individual patients.
- Anticonvulsants are also established as effective for several non-epilepsy indications, including (but not limited to) bipolar disorder, migraine prophylaxis, and neuropathic pain.

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Publication Date: March 19, 2020.

Therapeutic Class Overview
Ophthalmic Corticosteroids

INTRODUCTION

- Most ophthalmic corticosteroids are indicated to treat various steroid-responsive inflammatory ocular conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctuate keratitis, herpes zoster keratitis, iritis, and cyclitis. Other indications include postoperative inflammation following various ocular surgeries; anterior uveitis; ocular allergies; corneal injury from chemical, radiation or thermal burns; and penetration of foreign bodies.
  - Dexamethasone sodium phosphate solution is also approved for otic use; however, this review will only cover ophthalmic indications.
- Ocular corticosteroids are thought to act by the induction of phospholipase A_2 inhibitory proteins; these proteins control the biosynthesis of inflammatory mediators (eg, prostaglandins and leukotrienes) by inhibiting the release of the common precursor arachidonic acid. Arachidonic acid is released from membrane phospholipids by phospholipase A_2 (*Facts & Comparisons 2018*).
  - Steroids inhibit edema, cellular infiltration, fibrin deposition, capillary dilation, leukocyte migration, capillary and fibroblast proliferation, collagen deposition, and scar formation associated with inflammation.
- So-called “soft” ophthalmic corticosteroids (eg, loteprednol etabonate, fluorometholone, rimexolone [discontinued in the US]) have been designed with certain structural modifications in an effort to retain anti-inflammatory efficacy, while reducing the risk of typical corticosteroid adverse effects (AEs). Soft corticosteroids are metabolized at the target site or near the application site and are claimed to produce a low rate of AEs in relation to their anti-inflammatory potency (*Bielory et al 2010, Hamrah et al 2018, Pleyer et al 2002).*
- Ophthalmic steroids are available in various formulations including emulsions, ointments, solutions, and suspensions. Dexamethasone, fluorometholone, prednisolone acetate, and prednisolone sodium phosphate are currently available generically.
  - Prednisolone acetate 1% is available as 2 different branded products, Pred Forte, which contains both benzalkonimum chloride (BAK) preservative and the inactive ingredient, sodium bisulfite, and Omnipred, which contains BAK preservative, but is free of sulfites (*Prescribing information: Omnipred 2007, Pred Forte 2017*).
  - Unlike all of the other commercially available corticosteroid ophthalmic drops, difluprednate does not contain BAK preservative (*Foster et al 2010*).
  - Fluorometholone differs structurally from other traditional corticosteroids in that it lacks a hydroxyl group in the 21st position; it undergoes local ocular metabolism in the cornea (*McGhee et al 2002*).
  - Loteprednol etabonate is a unique corticosteroid molecule that is structurally similar to other corticosteroids (eg, prednisolone), but has an ester group substituted for a ketone at the C-20 position, which results in a predictable transformation to an inactive metabolite (*Bielory et al 2010*).
  - Ointments are particularly useful for overnight treatment as an adjunct to daytime drops in certain inflammatory conditions (*McGhee et al 2002*). Disadvantages of ointments include transient blurred vision and more difficult administration (*Comstock et al 2011*).
- Medispan class: Ophthalmic steroids

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Maxidex (dexamethasone ophthalmic suspension, 0.1%)	-
dexamethasone sodium phosphate ophthalmic solution, 0.1%	✔
Durezol (difluprednate ophthalmic emulsion, 0.05%)	-
FML (fluoromethalone ophthalmic suspension, 0.1%)	✔
FML (fluoromethalone ophthalmic ointment, 0.1%)	-
FML Forte (fluoromethalone ophthalmic suspension, 0.25%)	-

Drug	Generic Availability
Flarex (fluoromethalone acetate ophthalmic suspension, 0.1%)	-
Alrex (loteprednol etabonate ophthalmic suspension, 0.2%)	-
Lotemax (loteprednol etabonate ophthalmic suspension, 0.5%)	-
Lotemax (loteprednol etabonate ophthalmic gel, 0.5%)	-
Lotemax (loteprednol etabonate ophthalmic ointment, 0.5%)	-
Pred Mild (prednisolone acetate ophthalmic suspension, 0.12%)	-
Omnipred, Pred Forte (prednisolone acetate ophthalmic suspension, 1%)	✔
prednisolone sodium phosphate ophthalmic solution, 1%	✔

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Maxidex (dexamethasone suspension); dexamethasone solution	Durezol (difluprednate)	FML, FML Forte (fluorometholone); Flarex (fluoromethalone acetate)	Alrex, Lotemax (loteprednol etabonate)	Pred Mild, Pred Forte, Omnipred (prednisolone acetate)	prednisolone sodium phosphate
Anterior uveitis, endogenous		✔				
Corneal injury from chemical, radiation or thermal burns	✔				✔ (Omnipred)	✔
Mild to moderate noninfectious allergic and inflammatory disorders of the lid, conjunctiva, cornea, and sclera (including chemical and thermal burns)					✔ (Pred Mild)	
Penetration of foreign bodies	✔				✔ (Omnipred)	✔
Postoperative inflammation and pain following ocular surgery		✔		✔ (Lotemax gel, ointment)		
Postoperative inflammation following ocular surgery				✔ (Lotemax suspension)		
Temporary relief of the signs and				✔ (Alrex)		

Indication	Maxidex (dexamethasone suspension); dexamethasone solution	Durezol (difluprednate)	FML, FML Forte (fluorometholone); Flarex (fluoromethalone acetate)	Alrex, Lotemax (loteprednol etabonate)	Pred Mild, Pred Forte, Omnipred (prednisolone acetate)	prednisolone sodium phosphate
symptoms of seasonal allergic conjunctivitis						
Steroid-responsive inflammatory ocular conditions	✔*		✔*	✔* (Lotemax suspension)	✔* (Pred Forte, Omnipred)	✔*

*Indicated for the treatment of steroid-responsive inflammatory ocular conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe, such as allergic conjunctivitis, acne rosacea, superficial punctuate keratitis, herpes zoster keratitis, iritis, cyclitis and selected infective conjunctivitides when the inherent risk of steroid use is accepted to obtain a diminution in edema and inflammation.

(*Prescribing information: Alrex 2016, dexamethasone sodium phosphate 2016, Durezol 2017, Flarex 2017, FML ointment 2013, FML suspension 2013, FML Forte 2013, Lotemax gel 2016, Lotemax ointment 2011, Lotemax suspension 2016, Maxidex 2017, Omnipred 2007, Pred Forte 2017, Pred Mild 2017, prednisolone sodium phosphate 2013*)

- 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

- Two double-blind (DB), multi-center (MC), randomized, active-controlled (AC) trials (*Loteprednol etabonate US Uveitis Study Group 1999*) compared the safety and efficacy of loteprednol etabonate 0.5% suspension with that of prednisolone acetate 1% suspension in reducing the ocular signs and symptoms associated with acute anterior uveitis. The first study involved up to 42 days of treatment, starting with a dose of 8 times per day. The second study involved up to 28 days of treatment, starting with a dose of 16 times per day. Efficacy was evaluated by the proportion of patients with anterior chamber cell score of 0 for key signs and symptoms of uveitis.
  - In Study 1 (N = 70), the proportion of patients achieving resolution of anterior chamber cell by the final visit was 74% for loteprednol etabonate vs 88% for prednisolone acetate (p = 0.194). In Study 2 (N = 175), the proportion of patients achieving resolution of anterior chamber cell by the final visit was 72% for loteprednol etabonate vs 87% for prednisolone acetate (p = 0.015).
  - In both studies, an intraocular pressure (IOP) increase > 10 mm Hg was observed in 7 patients receiving prednisolone acetate and 1 patient receiving loteprednol etabonate.
- A DB, MC, randomized, non-inferiority trial (N = 90) (*Foster et al 2010*) compared the safety and efficacy of difluprednate 0.05% emulsion dosed 4 times daily with prednisolone acetate 1% suspension dosed 8 times a day for the treatment of endogenous anterior uveitis. At day 14, mean anterior chamber cell grade improvement for difluprednate-treated patients was similar to that observed with prednisolone-treated patients (2.1 vs 1.9, respectively), demonstrating non-inferiority. Clinically significant IOP elevation occurred in 3 difluprednate-treated patients (6.0%) and 2 prednisolone-treated patients (5.0%).
- A DB, MC, AC, randomized, non-inferiority trial (N = 110) (*Sheppard et al 2014*) compared the efficacy of difluprednate 0.05% emulsion dosed 4 times daily with prednisolone acetate 1% suspension dosed 8 times a day or the treatment of endogenous anterior uveitis. At day 14, the mean change in anterior chamber cell grade with difluprednate was noninferior to that of prednisolone acetate (-2.2 vs -2.0, respectively; p = 0.16). There was a statistically significant difference in mean IOP increase at day 3 (2.5 mm Hg for difluprednate-treated patients vs 0.1 mm Hg for prednisolone acetate–treated patients, p = 0.0013), but not at other time points during the study.

- A DB, randomized controlled trial (RCT) (*Stewart 2004 [abstract]*) compared fluorometholone acetate 0.1% (Flarex) suspension with loteprednol etabonate 0.5% suspension in 30 patients undergoing cataract extraction. The treatment regimen for both groups included instillation of 1 drop 4 times daily for 14 days. Flare scores gradually decreased during the course of the study. On day 21, no flare was observed in any of fluorometholone patients while 3 loteprednol patients still showed signs of flare. However, no statistically significant differences in flare, anterior segment cell, or conjunctival hyperemia scores were observed between the 2 groups.
- An investigator-masked, MC, RCT (N = 88) (*Lane et al 2013*) evaluated the efficacy of loteprednol etabonate 0.5% 4 times daily vs prednisolone acetate 1% 4 times daily for the control of postoperative inflammation after cataract surgery. Throughout the 3-week follow-up, control of inflammation was equivalent between the treatment groups. Mean IOP was numerically higher in patients treated with prednisolone acetate vs loteprednol etabonate at each assessment; however, there were no statistically significant differences between the 2 groups.
- A DB, MC, randomized, contralateral-eye trial (N = 52) (*Donnenfeld et al 2011*) compared the effects of difluprednate 0.05% vs prednisolone acetate 1% suspension on corneal thickness and visual acuity after cataract surgery. The first eye randomly received 1 of the treatment drugs; the fellow eye received the alternative. At day 1, corneal thickness was 33 µm less in the difluprednate-treated eyes (p = 0.026). The mean IOP remained within the normal range for both groups at all study visits.
- A DB, MC, RCT (N = 73) (*Raizman et al 2007*) comparing 2 ophthalmic prednisolone acetate 1% formulations (Omnipred and Pred Forte) in adult patients who underwent cataract surgery found that there were no statistically significant differences in clinical efficacy between the treatment groups in terms of postoperative ocular pain, keratitis, aqueous cell counts, or aqueous flare on post-op days 1, 12, and 28.
- An investigator-masked, randomized study (N = 60) (*Oner et al 2012*) evaluating the safety and efficacy of loteprednol etabonate 0.5%, prednisolone acetate 1%, and fluorometholone acetate 0.1% for the treatment of vernal keratoconjunctivitis found that the baseline mean scores of signs and symptoms gradually improved for all groups except for pannus formation in the fluorometholone group; however, all signs and symptoms (with the exception of chemosis) were significantly less improved in the fluorometholone group compared to the other treatments. There was significant IOP elevation in the prednisolone group after the day 3 visit.

CLINICAL GUIDELINES

- **American Academy of Ophthalmology: Cataract in the Adult Eye Preferred Practice Pattern** (*Olson et al 2017*)
  - Postoperative follow-up
    - Postoperative regimens of topically applied antibiotics, corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), and oral analgesics vary among practitioners. Optimal regimens for the use of these agents have not been established; thus, the operating surgeon is responsible for making the decision whether to use any or all of the topical products alone or in combination.
    - Elevated IOP is a postoperative complication with corticosteroids.
  - Cystoid macular edema
    - Topical anti-inflammatory agents are used to prevent as well as to treat cystoid macular edema.
    - There is evidence that NSAIDs, alone or in combination with topical corticosteroids, decreases the risk of postoperative cystoid macular edema.
- **American Optometric Association: Care of the Adult Patient with Cataract** *(Murrill et al 2004*)
  - A combination of topical and oral anti-glaucoma, antibiotic, and anti-inflammatory medications may be administered to the patient before, during, and after an operation.
  - Topical corticosteroids may be used to suppress inflammation associated with cataract surgery.
  - To control inflammation associated with anterior uveitis, topical corticosteroids such as prednisolone acetate 1% may be used every 2 to 4 hours depending on the degree of inflammation.
  - When there is anterior chamber inflammation associated with cystoid macular edema, topical steroidal and nonsteroidal anti-inflammatory agents should be applied to the eye for up to a month.
- **American Academy of Ophthalmology: Refractive Errors & Refractive Surgery Preferred Practice Pattern** (*Chuck et al 2018*)
  - Surface ablation techniques
    - Postoperative regimens of topically applied antibiotics, corticosteroids, and oral analgesics vary among practitioners. It is the decision of the surgeon to use any or all of these products alone or in combination.
    - Topical corticosteroids are generally started immediately after surgery and tapered over a period of days to weeks, and sometimes months.

        - Periodic examinations are necessary to monitor ocular status and to check for corticosteroid-related side effects such as elevated IOP.
    - Laser in situ keratomileusis
        - Corticosteroids are generally used for a short time postoperatively.
        - Treatment of diffuse lamellar keratitis is commonly guided by the severity of the inflammation. Increasing the frequency of topical corticosteroid administration with a closer follow-up is practiced by most surgeons.
- **American Optometric Association: Care of the Patient with Anterior Uveitis** *(Alexander et al 2004*)
    - Available treatment options for the treatment of anterior uveitis include: topical ophthalmic corticosteroids, cyclopegics and mydriatics, oral steroids and NSAIDs, and other therapies such as immunosuppressants.
        - Steroids should be continued until the cellular reaction is minimal or absent, and then they should be tapered. The more potent and frequent the use of a topical steroid, the longer the tapering period required.
- **American Academy of Ophthalmology: Conjunctivitis Preferred Practice Pattern** (*AAO 2013a*)
    - Seasonal allergic conjunctivitis
        - Mild allergic conjunctivitis can be treated with an over-the-counter (OTC) antihistamine/vasoconstrictor or second-generation topical histamine H_1-receptor antagonist. If the condition is persistent, mast-cell stabilizers may be used.
        - A brief course (1 to 2 weeks) of a low-potency topical corticosteroid may be added if the symptoms are not adequately controlled. The lowest potency and frequency of corticosteroid administration that relieves the patient's symptoms should be used. If corticosteroids are used in chronic or recurrent conjunctivitis, periodic exams should be performed to monitor for cataract and glaucoma.
        - Ketorolac, an NSAID, is also approved for the treatment of allergic conjunctivitis. Additional measures include allergen avoidance and using cool compresses, oral antihistamines, and artificial tears.
    - Vernal/atopic conjunctivitis
        - General treatment measures include modifying the environment to minimize exposure to allergens or irritants and using cool compresses and ocular lubricants. Topical and oral antihistamines and topical mast-cell stabilizers may also be beneficial.
        - For acute exacerbations, topical corticosteroids are usually necessary to control severe symptoms. The minimal amount of corticosteroid should be used based on patient response and tolerance. Topical cyclosporine is effective as adjunctive therapy to reduce the amount of topical corticosteroid used to treat severe atopic keratoconjunctivitis.
        - If corticosteroids are prescribed, baseline and periodic measurement of IOP and papillary dilation should be performed to evaluate for glaucoma and cataract.
- **American Optometric Association: Care of the Patient with Conjunctivitis** *(Quinn et al 2007*)
    - The following agents are useful in treating allergic conjunctivitis (includes atopic keratoconjunctivitis, simple allergic conjunctivitis, seasonal or perennial conjunctivitis, vernal conjunctivitis, and giant papillary conjunctivitis): topical corticosteroids, topical vasoconstrictors/antihistamines, topical antihistamines, topical NSAIDs, topical mast cell stabilizers, topical antihistamines/mast cell stabilizers, immunosuppressants, and systemic antihistamines.
        - The use of topical corticosteroids should be limited to the acute suppression of symptoms because of the potential for AEs with prolonged use (eg, cataract formation and elevated IOP).
- **American Academy of Ophthalmology: Bacterial Keratitis Preferred Practice Pattern** (*AAO 2013b*)
    - Ophthalmic corticosteroid therapy may have a beneficial role in treating some cases of infectious keratitis due to the probable suppression of inflammation, which may reduce subsequent corneal scarring and associated visual loss.
    - Potential disadvantages of ophthalmic corticosteroid use include infection reoccurrence, local immunosuppression, inhibition of collagen synthesis predisposing to corneal melting, and increased IOP.
    - There is no conclusive evidence that ophthalmic corticosteroids alter clinical outcome.
    - Despite the risks, it is believed that the judicious use of ophthalmic corticosteroids can reduce morbidity. The minimum amount of ophthalmic corticosteroid required should be used to achieve control of inflammation.
    - Ophthalmic corticosteroids should not be used for presumed bacterial ulcers until the organism has been determined by cultures. Outcomes of corticosteroid therapy are likely to be poor for ulcers associated with *Acanthamoeba*, *Nocardia*, fungus, or herpes simplex virus.
    - IOP must be monitored frequently, and the patient should be examined within 1 to 2 days after initiation of ophthalmic corticosteroid therapy.
- **American Academy of Ophthalmology: Blepharitis Preferred Practice Pattern** (*AAO 2013c*)
    - Blepharitis is typically a chronic condition that cannot be cured. Optimal treatment regimens often require a trial and error approach.

- Treatments options, which are often used in combination, include the following:
  - Warm compresses
  - Eyelid hygiene
  - Antibiotics (topical and/or systemic)
  - Ophthalmic anti-inflammatory agents (eg, corticosteroids, cyclosporine)
- Ophthalmic corticosteroid eye drops or ointments are typically applied several times daily to the eyelids or ocular surface. Once the inflammation is controlled, the corticosteroid can be tapered and discontinued and then used intermittently to maintain patient comfort. The minimal effective dose should be used, and long-term therapy should be avoided if possible.
- Potential AEs of ophthalmic corticosteroid use, including the risk for developing increased IOP and cataracts may be minimized by using a site-specific ophthalmic corticosteroid such as loteprednol etabonate and ophthalmic corticosteroids with limited ocular penetration, such as fluorometholone.

- **American Academy of Ophthalmology: Dry Eye Syndrome Preferred Practice Pattern** (*AAO 2013d*)
  - Treatment options for patients with mild dry eye syndrome include: education and environmental modifications; discontinuation of any offending medications; aqueous enhancement using artificial tear substitutes, gels or ointments; eyelid therapy (warm compresses and eyelid hygiene); treatment of contributing ocular factors such as blepharitis or meibomianitis; and correction of eyelid abnormalities.
  - Treatments for moderate dry eye syndrome include (in addition to treatments for mild dry eye syndrome): anti-inflammatory agents (eg, topical corticosteroids and cyclosporine), systemic omega-3 fatty acid supplements, punctal plugs, and spectacle side shields and moisture chambers.
    - Low dose topical corticosteroids can be used at infrequent intervals for short-term (ie, several weeks) suppression of inflammation.
  - Treatments for severe dry eye syndrome include (in addition to treatments for mild and moderate dry eye syndrome): systemic anti-inflammatory agents, systemic cholinergic agonists, mucolytic agents, autologous serum tears, contact lenses, permanent punctal occlusion, and tarsorrhaphy.

SAFETY SUMMARY

- Contraindications for ophthalmic corticosteroids include hypersensitivity to any component of the formulation; most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella; mycobacterial infections of the eye; and fungal diseases of ocular structures.
  - Flarex (fluorometholone acetate 1%), Pred Forte (prednisolone acetate 1%), and Pred Mild (prednisolone acetate 0.12%) are also contraindicated with acute purulent untreated infections.
  - Prednisolone sodium phosphate 1% solution is contraindicated after uncomplicated removal of a superficial corneal foreign body.
- Warnings and precautions for ophthalmic corticosteroids include glaucoma, cataract formation, delayed healing after cataract surgery, risk of fungal infections and secondary bacterial infections, masking or enhancement of existing bacterial infections, exacerbation of viral infections, and contact lens wear.
  - Lotemax (loteprednol etabonate 0.5%) should not be used be used in children following ocular surgery, as it may hinder the child's ability to see out of the operated eye.
  - Some products contain sodium bisulfite, which may cause allergic-type reactions in susceptible patients.
- AEs associated with ophthalmic steroids include glaucoma with optic nerve damage, visual acuity and field defects, posterior subcapsular cataract formation, delayed wound healing, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Maxidex (dexamethasone, 0.1%)	Suspension	Topical ophthalmic	Mild disease: Up to 4 to 6 times daily Severe disease: May be used hourly and tapered to	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			discontinuation as inflammation subsides	
dexamethasone sodium phosphate, 0.1%	Solution	Topical ophthalmic	Every hour during the day and every 2 hours during the night as initial therapy; reduce to every 4 hours when a favorable response is observed; later, further reduction to 3 to 4 times daily may suffice to control symptoms	The duration of treatment will vary with the type of lesion and may extend from a few days to several weeks.
Durezol (difluprednate, 0.05%)	Emulsion	Topical ophthalmic	Anterior uveitis, endogenous 4 times daily for 14 days, followed by tapering as clinically indicated Postoperative inflammation following ocular surgery 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the post-operative period, followed by 2 times daily for 1 week, and then a taper based on response	
FML (fluoromethalone, 0.1%)	Suspension	Topical ophthalmic	2 to 4 times daily; during the initial 24 to 48 hours, the frequency may be increased to every 4 hours	Care should be taken not to discontinue therapy prematurely. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
FML (fluoromethalone, 0.1%)	Ointment	Topical ophthalmic	1 to 3 times daily; during the initial 24 to 48 hours, the frequency may be increased to every 4 hours	Care should be taken not to discontinue therapy prematurely. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
FML Forte (fluoromethalone, 0.25%)	Suspension	Topical ophthalmic	2 to 4 times daily; during the initial 24 to 48 hours, the frequency may be increased to every 4 hours	Care should be taken not to discontinue therapy prematurely. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Flarex (fluoromethalone acetate, 0.1%)	Suspension	Topical ophthalmic	4 times daily; during the initial 24 to 48 hours, the frequency may be increased every 2 hours	Care should be taken not to discontinue therapy prematurely. If there is no improvement after 2 weeks, the physician should be consulted.
Alrex (loteprednol etabonate, 0.2%)	Suspension	Topical ophthalmic	4 times daily	
Lotemax (loteprednol etabonate, 0.5%)	Suspension	Topical ophthalmic	Postoperative inflammation: 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the post-operative period Steroid responsive disease: 4 times daily; during the first week, the frequency may be increased up to every hour if needed	Steroid responsive disease: Care should be taken not to discontinue therapy prematurely. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
Lotemax (loteprednol etabonate, 0.5%)	Gel	Topical ophthalmic	4 times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period	
Lotemax (loteprednol etabonate, 0.5%)	Ointment	Topical ophthalmic	4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the post-operative period	
Pred Mild (prednisolone acetate, 0.12%)	Suspension	Topical ophthalmic	2 to 4 times daily; during the initial 24 to 48 hours, the frequency may be increased if necessary	Care should be taken not to discontinue therapy prematurely. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
Omnipred (prednisolone acetate, 1%)	Suspension	Topical ophthalmic	4 times daily	Care should be taken not to discontinue therapy prematurely. If signs and symptoms fail to improve after 2

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				days, the patient should be re-evaluated. In cases of bacterial infections, concomitant use of anti-infective agents is mandatory.
Pred Forte (prednisolone acetate, 1%)	Suspension	Topical ophthalmic	2 to 4 times daily; during the initial 24 to 48 hours, the frequency may be increased if necessary	Care should be taken not to discontinue therapy prematurely. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
prednisolone sodium phosphate, 1%	Solution	Topical ophthalmic	Every hour during the day and every 2 hours during the night as necessary as initial therapy; reduce to every 4 hours when a favorable response is observed; later, further reduction to 3 to 4 times daily may suffice to control symptoms	The duration of treatment will vary with the type of lesion and may extend from a few days to several weeks.

See the current prescribing information for full details

CONCLUSION

- Ophthalmic corticosteroids are used to treat a wide variety of ocular conditions of the conjunctiva, cornea, and anterior segment. These products exert anti-inflammatory activity against inciting agents of mechanical, chemical, or immunological nature.
- The anti-inflammatory potencies of the ophthalmic corticosteroid products depend on the pharmacokinetic and pharmacodynamic properties of both the drug and its formulation.
- Comparative data among the various ophthalmic corticosteroids are limited by the small numbers of trials, small sample sizes, and flaws in study design.
- Based on limited data, “soft” ophthalmic corticosteroids appear to be associated with less IOP-elevating potential compared with “strong” steroids, which are indicated for severe inflammation.
- Clinical guidelines address the use of ophthalmic corticosteroids post-operatively and for various conditions including anterior uveitis, bacterial keratitis, conjunctivitis, blepharitis, and dry-eye syndrome (*AAO 2013a, AAO 2013b, AAO 2013c, AAO 2013d, Alexander et al 2004, Chuck et al 2018, Murrill et al 2004, Olson et al 2017, Quinn et al 2007).*

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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 beta$_2$-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 2018, asthma affected an estimated 19.2 million adults and 5.5 million children in the United States (U.S.) (*Centers for Disease Control and Prevention [CDC] 2020, National Heart, Lung, and Blood Institute [NHLBI] 2020*).
- 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] 2020a*). COPD affects 6.4% of the U.S. population and is a major contributor to mortality from chronic lower respiratory diseases, the fourth leading cause of death in the U.S. (*CDC 2019*).
- 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	
Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol)	-

* Branded product DuoNeb is no longer marketed.

† Authorized generic
‡ Wixela Inhub is the generic of Advair Diskus
§The inhaled LABA and anticholinergic combination, Utibron Neohaler (indacaterol/glycopyrrolate), was discontinued by the manufacturer effective April 1, 2020 for business reasons. (*OINDP news 2020*). At the time of this review, Arcapta Neohaler was active in Medispan.

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2A. FDA-Approved Indications for Beta$_2$-agonist/Corticosteroid Combination Agents

Indication	Advair Diskus	Advair HFA	AirDuo RespiClick	Breo Ellipta	Dulera	Symbicort	Wixela Inhub
Treatment of asthma	✔ (age ≥ 4 years)	✔ (age ≥ 12 years)	✔ (age ≥ 12 years)	✔ (age ≥ 18 years)	✔ (age ≥ 5 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 2020, Breo Ellipta 2019, Dulera 2019, Symbicort 2019, Wixela Inhub 2019*)

Table 2B. FDA-Approved Indications for Beta$_2$-agonist/Anticholinergic Combination Agents

Indication	Anoro Ellipta	Bevespi Aerosphere	Combivent Respimat	Duaklir Pressair	ipratropium/ albuterol solution	Stiolto Respimat	Utibron Neohaler
Long-term, once-daily, maintenance treatment of patients with COPD	✔					✔	
Long-term, twice-daily, maintenance treatment of airflow obstruction in patients with COPD				✔			✔
Long-term, twice-daily, maintenance treatment of patients with COPD, including chronic bronchitis and/or emphysema		✔					
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 2019, Bevespi Aerosphere 2019, Combivent Respimat 2016, Duaklir Pressair 2020, ipratropium/albuterol solution 2018, Stiolto Respimat 2019, Utibron Neohaler 2019*)

Table 2C. FDA-Approved Indication for Triple Combination Agent

Indication	Trelegy Ellipta
Maintenance treatment of patients with COPD	✔

(*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*).
- A randomized, double-blind, double-dummy trial showed therapeutic bioequivalence of Wixela Inhub (generic fluticasone/salmeterol) to Advair Diskus (brand fluticasone/salmeterol) in 1227 patients with asthma. The trial revealed least-squares mean (LSM) Wixela Inhub to Advair Diskus ratios of 1.120 (90% confidence interval [CI], 1.016 to 1.237) for day 1 forced expiratory volume in 1 second (FEV_1) area under the curve and 1.069 (90% CI, 0.938 to 1.220) for day 29 trough FEV_1 (*Ng et al 2019*).
- 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 multicenter clinical trial (N = 181) compared mometasone furoate/formoterol 50 mcg/5 mcg to mometasone furoate 50 mcg in patients with asthma 5 to less than 12 years of age. The primary efficacy endpoint, defined as the change from baseline to week 12 in 60-minute morning post-dose % predicted FEV_1, was significantly improved with mometasone furoate/formoterol compared with mometasone furoate (5.21; 95% CI, 3.22 to 7.20) (*Dulera Prescribing Information 2019*).
- 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% 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*).
  - A 52-week randomized trial of adults with mild asthma (N = 675) revealed that budesonide/formoterol administered as needed was superior to albuterol as needed (relative rate, 0.49; 95% CI, 0.33 to 0.72; p < 0.001) and similar to budesonide with albuterol as needed (relative rate, 1.12; 95% CI, 0.70 to 1.79; p = 0.65) for prevention of asthma exacerbations. The rate of severe exacerbations was lower with budesonide/formoterol compared with albuterol as needed (relative risk, 0.40; 95% CI, 0.18 to 0.86) and budesonide with albuterol as needed (relative risk, 0.44; 95% CI, 0.20 to 0.96) (*Beasley et al 2019*).

<u>Comparisons between different ICS/LABA combinations</u>

- 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 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, Celli et al 2014, 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, Maltais et al 2019a, 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*).
- PINNACLE-4, a randomized phase 3 study of 1756 patients with moderate-to-severe COPD, showed that glycopyrrolate/formoterol significantly improved predose trough FEV_1 at week 24 compared with glycopyrrolate monotherapy, formoterol monotherapy, or placebo (all $p < 0.0001$). The combination therapy also improved other lung function endpoints compared with individual agents or placebo (*Lipworth et al 2018*).
- 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 post hoc pooled analysis of 3 studies (N = 1747) showed improved trough FEV_1 with umeclidinium/vilanterol compared with tiotropium ($p < 0.001$) in patients with COPD (*Maleki-Yazdi et al 2017*).
- 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*).
- In a meta-analysis of 6 randomized trials in patients with COPD, tiotropium/olodaterol resulted in similar changes in lung function and similar tolerability compared to tiotropium alone (*He and Lin 2020*).
- 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

- Several 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 24-week, double-blind, double-dummy, randomized phase 3 trial compared glycopyrrolate/formoterol and umeclidinium/vilanterol in 1119 patients with moderate-to-very severe COPD (*Maltais et al 2019b*). One of the primary endpoints, peak change from baseline in FEV_1 within 2 hours post-dose over 24 weeks, was similar between glycopyrrolate/formoterol and umeclidinium/vilanterol (LSM difference, -3.4 mL; 97.5% CI, -32.8 to 25.9). Glycopyrrolate/formoterol showed improved outcomes for another primary endpoint, change from baseline in morning pre-dose trough FEV_1 over 24 weeks, compared with umeclidinium/vilanterol (LSM difference, - 87.2 mL; 97.5% CI, -117.0 to - 57.4). The trial did not reveal any clinically meaningful differences in symptoms between the 2 treatments.
- 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.
- A network meta-analysis of 16 randomized controlled trials (N = 17,734) compared fixed-dose combinations of LABA/LAMA versus ICS/LABA. The analysis showed that umeclidinium/vilanterol, glycopyrrolate/indacaterol, and glycopyrrolate/formoterol were the most effective in improving FEV_1. Glycopyrrolate/indacaterol significantly decreased the risk of exacerbations compared with fluticasone/salmeterol (*Calzetta et al 2019*).

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 2020 Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention report also provides a stepwise approach to asthma management. It recommends as-needed low-dose ICS-formoterol as a preferred controller medication to prevent exacerbations and control symptoms in adult or adolescent patients with infrequent asthma symptoms (eg, < twice a month). If patients remain uncontrolled, an ICS or ICS/LABA is the next preferred controller options. The choice of a specific dose and combination depends on the age of the patient and step within the therapy. As-needed ICS-formoterol is also the preferred reliever medication for adults and adolescents, while as-needed SABAs are the only option for reliever medications in children; of note, a low dose ICS should be taken whenever a SABA is taken. At the highest step of therapy, the patient should be referred for add-on treatment (eg, tiotropium, azithromycin, omalizumab, mepolizumab, benralizumab, reslizumab, dupilumab) (*GINA 2019, GINA 2020*).
- The 2020 GINA report provides interim guidance on the management of asthma in the context of the coronavirus disease 2019 (COVID-19) pandemic. Patients with asthma should continue their prescribed asthma medications, including ICS with or without LABA and add-on therapies, during the pandemic. Use of nebulizers should be avoided when possible to prevent transmission of the virus to other patients or healthcare workers (*GINA 2020*).

- 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 does not recommend LABA medications for the management of acute asthma symptoms or exacerbations (*GINA 2020, 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 2020*). *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*).
- A European Respiratory Society/American Thoracic Society guideline on the management of severe asthma recommends the addition of tiotropium for patients with uncontrolled asthma despite GINA step 4 or 5 or NAEPP step 5 therapy, and a trial of chronic macrolide therapy to reduce exacerbations in patients who require additional control despite GINA step 5 or NAEPP step 5 therapy (*Holguin et al 2020*).

COPD

- The 2020 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. Of note, the 2020 GOLD guidelines no longer recognize the phrase "asthma-COPD overlap," instead, emphasize that asthma and COPD are unique disease states with some similar signs and symptoms. Key recommendations from the GOLD guidelines are as follows (*GOLD 2020a*):
  - 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, and for immediate relief of symptoms in patients already receiving long-acting bronchodilators for maintenance therapy.
  - 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.
    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. Long-term treatment with ICS may cause pneumonia in patients with severe disease.
  - Triple inhaled therapy of LAMA/LABA/ICS improves lung function, symptoms, and health status and reduces exacerbations compared to ICS/LABA, LABA/LAMA, or LAMA monotherapy.
- Treatment recommendations are given for patients with COPD based on their GOLD patient group (see Table 3).
  - 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.
  - 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 or blood eosinophil count ≥ 300 cells/µL.

- Follow-up treatments: The follow-up treatments apply to any patients receiving maintenance treatment irrespective of the patient GOLD group.
  - For persistent dyspnea: The use of 2 bronchodilators is recommended in patients receiving 1 long-acting bronchodilator and experiencing persistent breathlessness or exercise limitation. Patients with persistent dyspnea symptoms on LABA + ICS may benefit from LAMA + LABA + ICS.
  - For exacerbations: Patients with persistent exacerbations on long-acting bronchodilator monotherapy 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 or blood eosinophil count ≥ 300 cells/µL, ICS + LABA is preferred. In patients who develop further exacerbations on LAMA + LABA therapy, alternative pathways include escalation to a LAMA + LABA + ICS if eosinophil count ≥ 100 cells/µL or addition of roflumilast or azithromycin if eosinophil count < 100 cells/µL. In patients with additional exacerbations on LABA + ICS, patients should try LAMA + LABA + ICS therapy. 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.
- Patients with COPD should continue their usual therapy, including inhaled or oral corticosteroids during the coronavirus disease 2019 (COVID-19) pandemic (*GOLD 2020b*).

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 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. Anoro Ellipta, Bevespi Aerosphere, Duaklir Pressair, Stiolto Respimat, and Utibron Neohaler are contraindicated without ICS in patients with asthma.
- Anoro Ellipta, Bevespi Aerosphere, Duaklir Pressair, Stiolto Respimat, and Utibron Neohaler have a warning stating that LABAs 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 cytochrome P450 (CYP) 3A4 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.
- The 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 combination products is that their use ensures that patients are not using a LABA without a concomitant ICS.
  - In adults and adolescents, low dose ICS-formoterol is the preferred reliever medication. For chronic management of asthma, the preferred controller options consist of ICS-formoterol (on an as-needed basis), ICS, or ICS/LABA depending on the age of a patient and severity of symptoms.
- 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, 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 and COPD treatment guidelines do not recommend the use of one specific combination product over another. The 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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Publication Date: June 22, 2020

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

Therapeutic Class Overview
Cephalosporins, Third-generation

INTRODUCTION

- Cephalosporins are used to treat a variety of infections. They have a broad spectrum of activity, are usually well tolerated, and are easy to administer *(AHFS 2020).*
- The cephalosporins are grouped into generations based on their spectrum of activity.
  - Generally, the first- and second-generation cephalosporins are used in the treatment of infections caused by susceptible staphylococci or streptococci. Use of first-generation cephalosporins in the treatment of gram-negative infections is generally limited as compared to second- and third-generation agents *(AHFS 2020).*
  - Third-generation cephalosporins are less active than first and second-generation cephalosporins against gram-positive aerobic bacteria, especially staphylococci. These agents may be used for infections caused by the following susceptible gram-negative bacteria: *Escherichia coli*, *Haemophilus influenzae, Klebsiella pneumoniae, Proteus mirabilis, Enterobacter, Neisseria,* and *Serratia*, among others. Cefdinir, cefixime, and cefpodoxime are inactive against most strains of *Enterobacter (AHFS 2020).*
  - Fourth and fifth generation cephalosporins are available in injectable formulations. They provide expanded gram-negative coverage, especially against bacteria resistant to third-generation cephalosporins. In addition, they have improved gram-positive coverage than third-generation cephalosporins *(AHFS 2020).*
- Enterobacteriaceae continue to develop more β-lactamase–mediated resistance. Additionally, other modes of resistance to the third-generation cephalosporins are becoming more prevalent. These resistance patterns are threatening the utility of this class of drugs *(Lepak et al 2020).*
- This review will focus on the oral third-generation cephalosporins as listed in Table 1. Review of each drug will focus on its Food and Drug Administration (FDA)-approved indications.
- Medispan class: Cephalosporins – third-generation

Table 1. Medications Included Within Class Review

Drug*	Generic Availability
cefdinir†	✔
cefpodoxime‡	✔
Spectracef (cefditoren pivoxil)	✔
Suprax (cefixime) §	✔

* Cedax (ceftibuten) is an FDA-approved third-generation cephalosporin which has been discontinued.
† Branded product, Omnicef, is no longer marketed.
‡ Branded product, Vantin, is no longer marketed.
§ Generic available for cefixime capsule and oral suspension; Suprax chewable tablets remain a branded product.
(Drugs@FDA 2020; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020, Clinical Pharmacology 2020)

INDICATIONS

Table 2. FDA Approved Indications

Indication	cefdinir	cefpodoxime	Spectracef (cefditoren)	Suprax (cefixime)
Acute Bacterial Exacerbations of Chronic Bronchitis due to *H. influenzae* (including ß-lactamase-producing strains), *M. catarrhalis* (including ß-lactamase-producing strains), or *S. pneumoniae* (penicillin-susceptible strains only)	✔ *	✔ ‡	✔ *	✔ **

Indication	cefdinir	cefpodoxime	Spectracef (cefditoren)	Suprax (cefixime)
Acute Bacterial Otitis Media due to *H. influenzae* (including ß-lactamase-producing strains), *M. catarrhalis* (including ß-lactamase-producing strains), or *S. pyogenes*	✔ †	✔ §		✔
Acute Maxillary Sinusitis caused by *H. influenzae* (including β-lactamase producing strains), *S. pneumoniae* (penicillin-susceptible strains only), and *M. catarrhalis* (including β-lactamase producing strains)	✔	✔		
Acute, Uncomplicated Ano-rectal Infections in women due to *N. gonorrhoeae* (including penicillinase-producing strains)		✔		
Community-Acquired Pneumonia caused by *H. influenzae* (including ß-lactamase-producing strains), *H. parainfluenzae* (including ß-lactamase-producing strains), *S. pneumoniae* (penicillin-susceptible strains only), or *M. catarrhalis* (including ß-lactamase producing strains)	✔	✔ ‖	✔	
Pharyngitis and Tonsillitis due to *S. pyogenes*	✔	✔	✔	✔
Uncomplicated Gonorrhea (cervical/urethral) caused by *N. gonorrhoeae* (penicillinase- and non-penicillinase-producing strains)		✔		✔
Uncomplicated Skin and Skin-Structure Infections caused by *S. aureus* (including ß-lactamase-producing strains) or *S. pyogenes*	✔	✔	✔	
Uncomplicated Urinary Tract Infections caused by *E. coli* and *P. mirabilis*		✔ ¶		✔

* Also approved for *H. parainfluenzae* (including ß-lactamase producing strains)
† Approved for *S. pneumoniae* (penicillin-susceptible strains only), not for *S. pyogenes*
‡ *H. influenzae* (non-beta-lactamase-producing strains only)
§ Also approved for *S. pneumoniae* (excluding penicillin-resistant strains)
‖ Not for *H. parainfluenzae* or *M. catarrhalis*
¶ Also approved for *K. pneumoniae* or *S. saprophyticus*
** Not for *M. catarrhalis*

(Prescribing information: cefdinir powder for suspension 2020, cefdinir capsule 2020, cefpodoxime tablet 2018, cefpodoxime granule for suspension 2018, Spectracef 2013, Suprax 2020)

- 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

- Studies evaluating the third-generation cephalosporins for the treatment of acute exacerbations of chronic bronchitis did not consistently demonstrate significant differences in clinical response or eradication rate when compared to other cephalosporin agents *(Alvarez-Sala et al 2006, Fogarty et al 2000, Phillips et al 1993, Van Herwaarden et al 1999, Zuck et al 1999)*. A study compared cefixime and cephalexin in the treatment of hospitalized patients with exacerbations of chronic bronchitis and demonstrated significantly better clinical cure rates in patients treated with cefixime compared to cephalexin (70.8% vs 50%; $p < 0.05$). The incidence of diarrhea was higher in the cefixime group (*Verghese et al 1990*).
- In the treatment of gonorrhea, cefixime and cefpodoxime have generally demonstrated comparable efficacy in the rate of bacteriologic cure (> 90%) in open-label and dose-response studies; cefixime also demonstrated comparable efficacy when compared to ceftriaxone (*Handsfield et al 1991, Novak et al 1992, Plourde et al 1992, Portilla et al, 1992, Verdon et al 1993*). In a meta-analysis in pregnant women, there was no significant difference between intramuscular ceftriaxone and oral cefixime for gonococcal infection cure based on 1 study and very low-quality evidence (*Comunián-Carrasco et al 2018).*

- A study compared cefixime and cefpodoxime in the treatment of acute otitis media. By day 15, bacteriologic cure was reported in 83% and 81% of patients treated with cefpodoxime and cefixime, respectively (p = 0.541) *(Asmar et al 1994).* Other head-to-head studies of the third-generation cephalosporins in the treatment of acute otitis media demonstrated no statistically significant differences in efficacy between the agents *(Blumer et al 2000, MacLoughlin et al 1996, Piippo et al 1991)*. However, 1 study did show that high-dose amoxicillin/clavulanic acid for 10 days of therapy was more effective than 5 days of therapy with cefdinir (*Casey et al 2012*).
- Studies evaluating the use of the third-generation cephalosporins for the treatment of pharyngitis and/or tonsillitis have failed to consistently demonstrate "superiority" of any third-generation cephalosporins over penicillin or amoxicillin *(Adam et al 1995, Block et al 1992, Brook 2005, Nemeth et al 1999, Ozaki et al 2008, Pichichero et al 1994, Tack et al 1998a)*.
- In the treatment of lower respiratory tract infections including community-acquired pneumonia, no cephalosporin consistently demonstrated significant differences when the third-generation cephalosporins were compared with each other, cephalosporins in other generations, or amoxicillin/clavulanate *(Drehobl et al 1997, Fogarty et al 2002, Lodha et al 2013, Sengupta et al 2004, van Zyle et al 2002).*
- Studies evaluating the treatment of skin and soft tissue infections, sinusitis, and urinary tract infections did not consistently demonstrate the "superiority" of any third-generation cephalosporin when compared to 1 another or to cephalosporins in other generations *(Bucko et al 2002, Gehanno et al 1990, Ho et al 2001, Koning et al 2012, Leigh et al 2000, Stevens et al 1993, Tack et al 1997, Tack et al 1998b).* One trial determined that a switch from intravenous (IV) ceftriaxone to oral cefditoren provided similar clinical cure rates as continuation of IV ceftriaxone in treatment of acute pyelonephritis *(Monmaturapoj et al 2012)*.

CLINICAL GUIDELINES

- Organizations differ in their recommendations regarding the use of third-generation cephalosporins for the treatment of acute bacterial rhinosinusitis. The American College of Allergy, Asthma, and Immunology allows for the empiric use of third-generation cephalosporins for acute bacterial rhinosinusitis, while the Infectious Diseases Society of America discourages their use due to emerging resistance patterns *(Chow et al 2012, Peters et al 2014*). Combination therapy with clindamycin may be used as an alternative to amoxicillin in children and adults with non-type 1 hypersensitivity reactions to penicillins (*Chow et al 2012, Rosenfeld et al* 2015). Other authors state that third-generation cephalosporins and clindamycin are an appropriate alternative for treatment of acute bacterial rhinosinusitis in children with a history of any type of hypersensitivity reaction to amoxicillin *(Wald et al 2013).*
- For empiric treatment of outpatients with community acquired pneumonia, a ß-lactam plus a macrolide or doxycycline may be used as an alternative to a respiratory fluoroquinolone in patients with risk factors for drug-resistant *S. pneumoniae*. While high-dose amoxicillin and amoxicillin-clavulanate are the preferred ß-lactams, ceftriaxone, cefpodoxime, and cefuroxime are recommended alternatives (*Metlay et al 2019*).
- Although not first-line treatment, third-generation oral cephalosporins may also be considered as a part of the treatment regimen in patients with skin and soft-tissue diseases (*Stevens et al 2014*).
- For Group A streptococcal pharyngitis, penicillin or amoxicillin are the recommended therapies. In patients with penicillin allergies, first generation cephalosporins (non-anaphylaxis type reactions) for 10 days, clindamycin or clarithromycin for 10 days, or azithromycin for 5 days are recommended (*Shulman et al 2012*).
- Third-generation cephalosporins are also recommended as an alternative treatment for acute otitis media and acute cystitis (*Gupta et al 2011, Lieberthal et al 2013*). Cefixime is a treatment option for acute pyelonephritis in children > 1 month of age (*Strohmeier et al 2014*).
- Due to treatment failures, the CDC no longer recommends the routine use of cefixime as a first-line regimen for treatment of gonorrhea in the United States (*CDC 2015*). Cefixime should only be considered as an alternative regimen if ceftriaxone is not available, and only in combination with azithromycin. Other oral cephalosporins (eg, cefpodoxime) are not recommended because of inferior efficacy and less favorable pharmacodynamics.
- Third-generation cephalosporins may be an option for empiric treatment of bloody diarrhea in infants < 3 months of age and others with neurologic involvement *(Shane et al 2017)*.
- In treatment of uncomplicated pyelonephritis, cefpodoxime or ceftibuten may be used in combination with an initial IV dose of a long-acting parenteral antimicrobial; oral fluoroquinolones also comprise the suggested regimens if resistance is below 10% (*Bonkat et al 2020*).

SAFETY SUMMARY

- The most common adverse effects seen with the cephalosporins are gastrointestinal disturbances, with diarrhea and nausea reported most frequently. Female patients can develop vaginal yeast infections. Changes in laboratory parameters such as increased blood urea nitrogen (BUN) and creatinine, decreased hematocrit and hemoglobin, increased liver enzymes, and increased glucose levels may also be seen.
- Dose adjustment of third-generation cephalosporins is recommended in renal impairment.
- Cephalosporins should not be given to patients who have experienced a previous allergic reaction to a cephalosporin. Caution should be utilized if administering to penicillin-allergic patients; however, the risk of a cross-reaction is less than 10 percent with the third-generation cephalosporins (*The Medical Letter 2012*).
- Patients should be monitored for *Clostridium difficile*-associated diarrhea.
- Antacids and H_2-antagonists can inhibit the absorption of cephalosporins; administration should be separated by at least 2 hours.
- A false-positive reaction for ketones and glucose in the urine can be seen when using certain tests.
- Cefixime, cefdinir, cefditoren, and cefpodoxime 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).
- Cefixime chewable tablets contain aspartame, which may be harmful to patients with phenylketonuria.
- Cefditoren causes renal excretion of carnitine and is contraindicated in patients with carnitine deficiency or with inborn errors of metabolism that may result in carnitine deficiency.
- Cefditoren is contraindicated in patients with milk protein hypersensitivity.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
cefdinir	Capsule, suspension	Oral	Every 12 or 24 hours	Dosing adjustments are recommended in renal impairment
cefpodoxime	Tablet, suspension	Oral	Every 12 hours	
Spectracef (cefditoren)	Tablet	Oral	Every 12 hours	
Suprax (cefixime)	Capsule, chewable tablet, suspension	Oral	Every 12 or 24 hours	

See the current prescribing information for full details

CONCLUSION

- Current clinical evidence supports the efficacy of each third-generation cephalosporin for their FDA-approved indications, including the treatment of acute otitis media, upper and lower respiratory tract infections, pharyngitis, tonsillitis, uncomplicated urinary tract infections, and skin and soft-tissue infections.
- The safety and efficacy of the third-generation cephalosporins are generally comparable among agents, with the exception of variation in coverage of specific bacterial strains. No agent has consistently demonstrated superiority over another.
  - The overall place in therapy for third-generation cephalosporins in the treatment of various infections is limited by increasing resistance.
  - Local resistance patterns should be checked before prescribing a third-generation cephalosporin. More isolates of *H. influenzae, S. pneumonia, and N. gonorrhoeae* have become resistant.
- Cross-sensitivity reactions can occur with cephalosporins in patients with a penicillin allergy.

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Publication Date: June 22, 2020

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*).
  - 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*).
  - Additionally, for patients with PAH, the diagnosis requires a pulmonary vascular resistance (PVR) ≥ 3 Wood units (*Rubin et al 2019*).
  - 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*):
  - Group 1 – PAH
  - Group 2 – PH secondary to left heart disease
  - Group 3 – PH secondary to lung diseases and/or hypoxia
  - Group 4 – PH due to pulmonary artery obstructions
  - 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*):
  - Class I: No limitation of physical activity
  - Class II: Slight limitation of physical activity
  - Class III: Marked limitation of physical activity
  - 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.
  - 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 2020*).
  - 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).
  - Drugs active within the endothelin pathway are the endothelin receptor antagonists (ERAs) (oral ambrisentan, oral bosentan, and oral macitentan).
  - 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], Klinger et al 2019, McLaughlin et al 2009*).
- For patients who do not have a positive acute vasodilator response to testing and are considered at risk (NYHA Class II or III) based on clinical assessment, combination therapy with certain agents is preferred initially but monotherapy can be considered if combination therapy is not an option. Agents that can be used include ERAs, PDE-5 inhibitors, an 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. Add-on therapy may be considered if patients do not respond adequately to initial therapy (*Barst, 2009, Galiè et al 2015[b], Klinger et al 2019, McLaughlin et al 2009*).
- 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 is also FDA-approved 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 than 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*). Of the ERAs, Letairis is approved to be used in conjunction with Adcirca to reduce the risks of disease progression and hospitalization for worsening PAH and to improve exercise ability (*Klinger et al 2019, Letairis prescribing information 2019*). In addition to treatment of PAH (WHO Group I) in adults, Tracleer is approved for use in children 3 years and older with idiopathic or congenital PAH to improve pulmonary vascular resistance (*Tracleer prescribing information 2019*).
- 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 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

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	✔ ¶		✔ ≠				✔ ↂ			✔ Ω		✔ ₳	
Treatment of PAH (WHO Group I) to delay 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													✔ ¥
Treatment of PAH (WHO Group I) to delay disease progression and improve exercise capacity						✔ ¶¶							
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 studies that established effectiveness included predominantly patients with WHO FC II to III symptoms and etiologies of idiopathic or heritable PAH (66%) or PAH associated with connective tissue disease (26%).
ƨStudies 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 2019, Adempas 2018, Flolan 2019, Letairis 2019, Opsumit 2019, Orenitram 2019, Remodulin 2018, Revatio 2020, Tracleer 2019, Tyvaso 2017, Uptravi 2019, Veletri 2018, Ventavis 2019*)

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 (*Letairis prescribing information 2019).*

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, multicenter, 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 multicenter, 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*).
- The multicenter, randomized, double-blind FREEDOM-EV trial compared 3 times daily Orenitram to placebo in 690 patients who had recently started background therapy with sildenafil, tadalafil, bosentan, ambrisentan, macitentan, or riociguat. The primary endpoint was time to first adjudicated clinical worsening event. Patients receiving Orenitram were less likely to experience a clinical worsening event (HR, 0.74; 95% CI, 0.56 to 0.97; p = 0.028) (*White et al 2020*).

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, multicenter, 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:
  - o 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.
  - o 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:
  - o 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.
  - o 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]*).
- A 2019 meta-analysis of 17 randomized controlled trials evaluated the efficacy of PCAs (15 studies), including the prostacyclin receptor agonist Uptravi (2 studies), and demonstrated the following:
  - o WHO functional class was improved with prostanoids (OR, 2.39; 95% CI, 1.72 to 3.32), largely due to improvements after IV and inhaled therapy but not after oral therapy.
  - o IV prostanoid therapy improved 6MWD (19.5 m; 95% CI, 14.82 to 24.19).
  - o Mortality was reduced with IV prostanoid administration (OR, 0.29; 95% CI, 0.12 to 0.69) but not after administration by other routes.
  - o Compared to placebo, Uptravi improved 6MWD (12.62 m; 95% CI, 1.90 to 23.34) and clinical worsening (OR, 0.47; 95% CI, 0.37 to 0.60), but no difference in mortality was observed (risk difference, 0.02; 95% CI, 0.00 to 0.04) (*Barnes et al 2019[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:
  - o 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).
  - o 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*).
  - A network meta-analysis of 16 randomized controlled trials concluded that add-on therapy with Adcirca or Tyvaso improved 6MWD compared to ERAs alone, add-on therapy with Opsumit or Tracleer improved 6MWD compared to PDE-5 inhibitors alone, and add-on therapy with PDE-5 inhibitors improved 6MWD compared to epoprostenol alone. However, differences in all-cause mortality were not significant (*Petrovic et al 2020*).
  - 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 2018*).
  - 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[a]*). 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 2019 update on pharmacologic therapy for PAH recommends initial combination therapy rather than monotherapy, which is a change from the 2014 guideline (*Klinger et al 2019*).
    - Initial therapy: For patients in WHO FC II or III, combination therapy with Letairis and Adcirca is recommended to improve 6MWD. For patients unwilling or unable to take combination therapy, monotherapy with an ERA, PDE-5 inhibitor or sGC is recommended. WHO FC III patients with evidence of rapid progression or markers of poor prognosis, a parenteral PCA 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 and an oral PDE-5 inhibitor.

- Subsequent therapy: For patients in WHO FC III who have evidence of progression or markers of poor prognosis despite treatment with one or two classes of oral agents, 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.
- Due to limited evidence, the guideline does not provide recommendations for or against the use of Orenitram or Uptravi.

o 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.

o 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.

o 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 (endorsed by the Association for European Pediatric and Congenital Cardiology, the European Society for Pediatric Research, and the International Society of Heart and Lung Transplantation) recommends a PDE-5 inhibitor, ERA, or oral/inhaled prostacyclin agonist therapy for pediatric patients with low- or intermediate-risk PAH. Initial combination therapy with a PDE-5 inhibitor and an ERA may be considered for patients who are at intermediate risk. Higher-risk patients should be treated with intravenous epoprostenol or intravenous or subcutaneous treprostinil; early combination therapy with a PDE-5 inhibitor, an ERA, and a PCA may also be considered in these patients (*Hansmann et al 2019*).

SAFETY SUMMARY

- sGC Stimulator
  - o 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.
  - o 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.
  - o Adempas is contraindicated in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias.
  - o Additional contraindications for Adempas include co-administration with nitrates or nitric oxide donors and PDE-inhibitors (specific and non-specific).
  - o Warnings and precautions for Adempas include symptomatic hypotension, bleeding, and pulmonary edema in patients with veno-occlusive disease (if confirmed, treatment should be discontinued).
  - o 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 Ambrisentan and Opsumit REMS programs, respectively, are designed in the same manner as the Adempas REMS program described above.
  - The Bosentan REMS program requires healthcare professionals who prescribe or dispense this product to enroll and comply with requirements, which 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 additional contraindications for use with cyclosporine A or with glyburide.
  - 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.
  - 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).*
  - 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
  - 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 is contraindicated with strong CYP2C8 inhibitors.
  - 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. Remodulin inhibits platelet aggregation and thereby can increase the risk of bleeding. 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. Remodulin can cause symptomatic hypotension.
- 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. Veletri was associated with chills/fever/sepsis/flu-like symptoms in 25% of patients in controlled trials for idiopathic or heritable PAH.
- Ventavis solution should not be allowed to come into contact with skin or eyes, and ingestion should be avoided.
- 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.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
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, monthly during treatment, and one month after stopping 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.
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, monthly during treatment, and one month after stopping treatment.
Opsumit (macitentan)	Tablet: 10 mg	Oral	Once daily	Doses > 10 mg once daily are not recommended. Pregnancy test required prior to treatment initiation, monthly during treatment, and one month after stopping treatment.
Orenitram (treprostinil)	Extended-release tablet: 0.125, 0.25, 1, 2.5, and 5 mg	Oral	Twice or 3 times daily; maximum dose is determined by	Should be taken with food. Tablets should be swallowed whole.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			tolerability; titrate not more than every 3 to 4 days as tolerated	Coadministration with CYP2C8 inhibitors (eg, gemfibrozil) and the presence of mild hepatic impairment require a lower starting dose. Avoid use in moderate hepatic impairment; contraindicated in severe hepatic impairment.
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 been approved for use with Remodulin (Implantable System for Remodulin or ISR). Refer to the pump manufacturer's manual for specific instructions for use. Use a lower starting dose in patients with mild or moderate hepatic impairment.
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 of ritonavir; resume Tracleer 10 days following ritonavir 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 treatment. Initiation should be avoided in patients with aminotransferases > 3x ULN. Doses > 125 mg twice daily do not have additional benefit sufficient to offset the increased risk of hepatotoxicity.
Tyvaso (treprostinil)	Inhalation solution (solution, refill, and starter solution): 0.6	Inhale	3 breaths per treatment session, 4 times a day (4 hours apart); titrate by an	Inhalation system consists of an ultrasonic, pulsed delivery device and its accessories.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
	mg/mL (1.74 mg per 2.9 mL)		additional 3 breaths per session at 1 to 2 week intervals; maximum: 9 breaths per treatment session, 4 times daily	
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. Use a once-daily starting dose in patients with moderate hepatic impairment, and reduce dosing to once daily in patients taking concomitant moderate CYP2C8 inhibitors.
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/mL	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

- 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 ERAs, PDE-5 inhibitors, PCAs, a prostacyclin receptor agonist, and an sGC stimulator.
- All of the PAH agents have shown improved pulmonary hemodynamics and exercise capacity in PAH patients as compared to placebo. Meta-analyses have suggested statistically significant reduction in mortality with PDE-5 inhibitors and IV prostanoids (*Zheng et al 2014[a], Zheng et al 2014[b], Barnes et al 2019[b]*).

- 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, and some data are available on the use of combination therapy. Two trials evaluating combination therapy include the AMBITION and COMPASS-2 trials. The AMBITION trial 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]*). Results of this study are the primary driver of the change in the CHEST guidelines that recommend initial combination treatment with Letairis and Adcirca (*Klinger et al 2019*). 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 ET 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.
- 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. 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 2019 update to the 2014 CHEST Guideline and Expert Panel Report recommends initial combination therapy with Letairis plus Adcirca for treatment-naïve symptomatic patients with WHO class II and III PAH. Alternatives include monotherapy with PDE-5 inhibitors, ERAs, and the sGC stimulator. Intravenous PCAs are recommended as initial or add-on treatment for patients with rapid progression and/or poor prognosis or for patients with WHO class IV PAH. Inhaled PCA is recommended as an add-on therapy for patients who remain symptomatic despite oral treatment. The update does not provide recommendations for or against the use of Orenitram or Uptravi (*Klinger et al 2019*).

- 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 Letairis plus Adcirca has proven to be superior to initial monotherapy with either drug 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]*).
- 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]*). A 2019 expert consensus statement from the European Pediatric Pulmonary Vascular Disease Network (endorsed by the Association for European Pediatric and Congenital Cardiology, the European Society for Pediatric Research, and the International Society of Heart and Lung Transplantation) recommends a PDE-5 inhibitor, ERA, or oral/inhaled prostacyclin agonist therapy for pediatric patients with low- or intermediate-risk PAH. Initial combination therapy with a PDE-5 inhibitor and an ERA may be considered for patients who are at intermediate risk. Higher-risk patients should be treated with intravenous epoprostenol or intravenous or subcutaneous treprostinil; early combination therapy with a PDE-5 inhibitor, an ERA, and a prostacyclin agonist may also be considered in these patients (*Hansmann et al 2019*).
- A 2018 scientific statement on the evaluation and management of right-sided heart failure from the AHA summarizes data for the use of PCAs, PDE-5 inhibitors, and ERAs 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 the document.

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Publication Date: June 8, 2020

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, had a relative decline of 19.0%, from 21.0% of males and females infected with the virus to 17.0%. The prevalence in men declined most dramatically, from 17.0% to 11.2%, a 34.1% 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*). More recent data from a period between 1999 and 2016 showed that seroprevalence continued to decline, with the odds of HSV-2 infection declining by 2.23% and 2.89% per year among men and women, respectively (*Chemaitelly et al 2019*). 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 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

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 2018, Denavir 2018, Xerese 2019, 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, -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 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 2020*).

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

† Dosing for Abreva (docosanol 10% cream): Apply topically to affected area 5 times daily

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 2020*). 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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Publication Date: June 8, 2020

Therapeutic Class Overview
Electrolyte Depleters

INTRODUCTION

Phosphate Binders

- Hyperphosphatemia, an important and inevitable clinical consequence of advanced stages of chronic kidney disease (CKD), requires appropriate management due to the risk for secondary hyperparathyroidism and cardiovascular disease. Persistent or chronic hyperphosphatemia, along with an elevated calcium times phosphorus (Ca x P) product, is associated with an increased risk of vascular, valvular, and other soft-tissue calcification in patients with CKD. Elevated phosphorus levels may also directly influence several components of CKD-mineral and bone disorder such as secondary hyperparathyroidism, bone abnormalities, calcitriol deficiency, and extraskeletal calcification. In addition, there is evidence consistently demonstrating that hyperphosphatemia is a predictor of mortality in CKD stage 5 patients who are receiving dialysis. Because of these reasons, control of serum phosphorus levels in patients with CKD is an important component of care (*Kidney Disease Improving Global Outcomes [KDIGO] 2009, KDIGO 2017, National Kidney Foundation [NKF] 2003, Kestenbaum et al 2005, Voormolen et al 2007*).
- The 2 principal modalities used to control serum phosphorus levels in patients with CKD include restricting dietary phosphorus intake and administering phosphorus binders (or phosphorus depleters). When dietary phosphorus restriction is inadequate in controlling serum phosphorus levels, the administration of phosphorus binders is recommended. The phosphorus binders class can be divided into 2 subcategories: calcium- and non-calcium-containing products. Calcium-based phosphate binders include calcium carbonate and calcium acetate, and calcium-free binders include aluminum hydroxide, lanthanum carbonate, magnesium carbonate, sevelamer hydrochloride, sevelamer carbonate, ferric citrate, and sucroferric oxyhydroxide. Calcium carbonate's use as a phosphorus binder is off-label and therefore is not detailed in this review.
- The 2017 KDIGO guideline for the diagnosis, evaluation, prevention, and treatment of CKD-mineral and bone disorder (CKD-MBD) does not specifically recommend 1 type of phosphate-binder as first-line therapy, but suggests restricting the dose of calcium-based phosphate binders in adult patients with CKD stage 3a to 5 (with or without dialysis) receiving phosphate-lowering treatment. In children, it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels *(KDIGO 2017).*
- The sevelamer hydrochloride salt was the initial sevelamer formulation developed; however, because of the incidence of metabolic acidosis associated with its use, a buffered formulation was created. The sevelamer carbonate formulation has advantages compared to sevelamer hydrochloride because it does not lower a patient's bicarbonate level and does not result in the development of metabolic acidosis *(Perry and Plosker 2014)*. An advantage to the use of lanthanum carbonate is a decrease in the pill burden compared to other products (*Prescribing information: Fosrenol 2018, Renagel 2019, Renvela 2018*). Two iron-based, calcium-free phosphate binders are Velphoro (sucroferric oxyhydroxide) and Auryxia (ferric citrate). Velphoro may reduce the pill burden for those patients that require higher doses of sevelamer as demonstrated in trials (*Prescribing information: Auryxia 2019, Velphoro 2020; Wuthrich et al 2013*).
- Available evidence supports the efficacy of all of the phosphorus binders in controlling serum phosphorus levels. It is generally accepted that no one product is effective and acceptable to every patient. Although treatment guidelines recommend serum phosphorus levels to be maintained within or slightly above the normal range (depending on CKD stage), there is currently no evidence to demonstrate that lowering phosphorus to a specific target range results in improved clinical outcomes in patients with CKD. Despite this lack of evidence, it is still reasonable to use phosphorus binders to lower phosphorus levels in CKD patients with hyperphosphatemia to prevent the development of secondary hyperparathyroidism and cardiovascular disease.
- The main considerations for selection of phosphate binders include absorbability, adequate gastrointestinal tolerability, and cost or cost-effectiveness (*Frazão et al 2012*).
- Medispan Therapeutic Class: Phosphate Binder Agents

Table 1. Medications Included Within Class Review - Phosphate Binders

Drug	Generic Availability
Auryxia (ferric citrate)	-
Calphron (calcium acetate)*	✔
Fosrenol (lanthanum carbonate)	✔ †
PhosLo (calcium acetate)	✔
Phoslyra (calcium acetate)	-
Renagel (sevelamer hydrochloride)	✔
Renvela (sevelamer carbonate)	✔
Velphoro (sucroferric oxyhydroxide)	-

*This product is not intended to diagnose, treat, cure or prevent any disease. Calphron is available as an over-the-counter nutritional supplement.
†Fosrenol chewable tablets are available generically; however, the Fosrenol oral powder packet is not generically available.

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020; Calphron 2016*)

Potassium Removing Agents

- Hyperkalemia is a common clinical problem that is most often a result of impaired urinary potassium excretion due to acute or chronic kidney disease and/or disorders or drugs that inhibit the renin-angiotensin-aldosterone system (RAAS). The most serious manifestations of hyperkalemia are muscle weakness or paralysis, cardiac conduction abnormalities, and cardiac arrhythmias, including sinus bradycardia, sinus arrest, slow idioventricular rhythms, ventricular tachycardia, ventricular fibrillation, and asystole. These manifestations usually occur when the serum potassium concentration is ≥ 7 mEq/L with chronic hyperkalemia or possibly at lower levels with an acute rise in serum potassium or in patients with an underlying cardiac conduction disorder (*Mount 2019*).
- There are no clear guidelines regarding the appropriate setting for the treatment of hyperkalemia. The decision for hospital admission for continuous electrocardiograph (ECG) monitoring is a matter of clinical judgment in each case. Patients believed to have a rapid rise in potassium commonly need inpatient care, whereas patients whose hyperkalemia has developed over a period of weeks can often be managed in an outpatient setting with close follow-up (*Hollander-Rodriquez and Calvert 2006, NKF 2016, Rafique et al 2017*).
  - Urgent treatment of hyperkalemia includes 3 main phases: 1) antagonizing cardiac effects of potassium (using intravenous [IV] calcium gluconate); 2) redistributing potassium into cells (using insulin with dextrose, beta-2-adrenergic agonists, or sodium bicarbonate); and 3) removing excess potassium from the body (ie, using hemodialysis, loop diuretics, or cation exchange resins) (*Hollander-Rodriquez and Calvert 2006, Mount 2019, Raebel 2012*).
  - In patients who do not require urgent treatment, lowering total body potassium may be the only step necessary (*Hollander-Rodriquez and Calvert 2006, NKF 2016, Rafique et al 2017*).
- Long-term treatment or prevention of hyperkalemia should be tailored to correcting the underlying cause of hyperkalemia (*Hollander-Rodriquez and Calvert 2006*).
- Cation exchange resins are used in clinical practice for removing excess potassium from the body. Prior to 2015, Kayexalate (sodium polystyrene sulfonate) was the only potassium binding agent approved in the U.S. for the treatment of hyperkalemia; however, the use of sodium polystyrene sulfonate has been limited by tolerability and safety concerns (ie, colonic necrosis and sodium absorption leading to volume overload) and questions about efficacy (*Veltassa FDA Summary Review 2015*).
- In October 2015, the Food and Drug Administration (FDA) approved Veltassa (patiromer), a non-absorbed, cation exchange polymer that contains a calcium-sorbitol counterion, for the treatment of hyperkalemia.
- In May 2018, the FDA approved Lokelma (sodium zirconium cyclosilicate), a non-absorbed zirconium silicate, for the treatment of hyperkalemia in adults.
- Medispan Therapeutic Class: Potassium Removing Agents

Table 2. Medications Included Within Class Review - Potassium Removing Agents

Drug	Generic Availability
Lokelma (sodium zirconium cyclosilicate)	-
sodium polystyrene sulfonate*	✔
Veltassa (patiromer)	-

*Sodium polystyrene sulfonate is generically available; brand Kayexalate is no longer available; Kionex and SPS are branded generics.

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 3. FDA-Approved Indications for Phosphate Binders

Generic name	Reduce absorption of dietary phosphate	Reduce serum phosphate in end stage renal disease	Control serum phosphorus in patients with CKD on dialysis	Iron deficiency anemia in CKD in patients not on dialysis
calcium acetate	✔ (Calphron)	✔ (PhosLo, Phoslyra)		
ferric citrate			✔	✔
lanthanum carbonate		✔		
sevelamer carbonate			✔	
sevelamer hydrochloride			✔ *	
sucroferric oxyhydroxide			✔	

*Safety and efficacy in CKD patients who are not on dialysis have not been studied.

(Prescribing information: Auryxia 2019, Calphron 2016, Fosrenol 2020, PhosLo 2013, Phoslyra 2015, Renagel 2020, Renvela 2020, Velphoro 2020)

Table 4. FDA-Approved Indications for Potassium Removing Agents

Generic name	Treatment of hyperkalemia
patiromer	✔
sodium polystyrene sulfonate	✔
sodium zirconium cyclosilicate	✔

(Prescribing information: Lokelma 2020, sodium polystyrene sulfonate powder for suspension 2020, sodium polystyrene sulfonate suspension 2017, Veltassa 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

Phosphate Binders

Available evidence supports the efficacy of all of the phosphate binders controlling serum phosphorus levels (*Al-Baaj et al 2005, Almirall et al 2012, Bleyer et al 1999, Block et al 2015, Delmez et al 2007, Dwyer et al 2013, Evenepoel et al 2009, Fan et al 2009, Finn et al 2004, Finn et al 2005, Finn et al 2006, Fischer et al 2006, Fishbane et al 2010, Hervas et al 2003, Hutchison et al 2006, Hutchison et al 2008, Iwasaki et al 2005, Joy et al 2003, Kasai et al 2012, Ketteler et al 2008, Lewis et al 2015, Mehrotra et al 2008, Ouellet et al 2009, Pieper et al 2006, Qunibi et al 2004, Ruospo et al 2018, Shigematsu et al 2008, Shigematsu et al 2010, Sprague et al 2009, St. Peter et al 2008, Suki et al 2007, Wilson et al 2009*).

- In general, the true benefits of phosphorus lowering with respect to hard clinical outcomes have not been established, and most clinical trials evaluated surrogate endpoints. A systematic review of 18 studies evaluated the rate of all-cause mortality among those treated with non-calcium-based phosphate binders compared to calcium-based phosphate binders in patients with CKD (*Jamal et al 2013*). The non-calcium based group which included sevelamer and lanthanum had a statistically significant reduction of 22% in all-cause mortality compared to calcium-based phosphate binders (risk ratio 0.78, 95% confidence interval [CI]: 0.61 to 0.98, I^2 = 43%; 11 randomized clinical trials, N = 4622). Note that 2 observational studies and 1 cross-sectional study were included. No significant reduction in cardiovascular events was observed.
- Clinical trials have consistently demonstrated that sevelamer hydrochloride is effective at lowering phosphorus levels and maintaining phosphate control comparable to calcium acetate and calcium carbonate therapy (*Bleyer et al 1999, Evenepoel et al 2009, Hervas et al 2003, Pieper et al 2006, Qunibi et al 2004).* A 2018 systematic review concluded that sevelamer may lower death from all causes and significantly decrease the risk of hypercalcemia compared with calcium-based agents (*Ruospo et al 2018*). A 2016 meta-analysis of 25 studies with 88% of patients on hemodialysis found lower all-cause mortality with sevelamer (risk ratio 0.54, 95% CI: 0.32 to 0.93) compared to calcium-based binders, but no statistical difference for cardiovascular mortality was observed (*Patel et al 2016*).
- Clinical trials demonstrate that lanthanum carbonate and sevelamer show comparable efficacy in lowering phosphorous although limited studies have compared the 2 therapies for efficacy (*Kasai et al 2012*). Findings from a meta-analysis showed that, compared with calcium-based agents, lanthanum significantly decreased the risk for hypercalcemia but had similar effects on phosphate levels (*Ruospo et al 2018*). A randomized controlled trial also found similar effects on phosphorus levels with lanthanum compared to calcium acetate at the 1-year mark (*Kovesdy et al 2018*).
- The efficacy and safety of sucroferric oxyhydroxide were evaluated in 3 trials: a fixed dose study, a dose titration study, and a dose titration extension study. Sucroferric oxyhydroxide demonstrated efficacy by significantly reducing serum phosphorus in hemodialysis and peritoneal dialysis patients from 6 to 52 weeks (*Velphoro prescribing information 2020, Wuthrich et al 2013*).
  - In the fixed dose study, all sucroferric oxyhydroxide dose groups showed a significant decrease in serum phosphorus ($p \leq 0.02$), except the 250 mg/day group. The proportion of sucroferric oxyhydroxide-treated patients achieving goal phosphorus levels after 6 weeks of treatment ranged from 35 to 60% for 1000 to 2500 mg/day, and 42.1% in the sevelamer control arm. The median time to reach first controlled serum phosphorus levels was not different for sucroferric oxyhydroxide (1 week) vs the sevelamer (2 weeks) control arm ($p > 0.16$) (*Wuthrich et al 2013*).
  - In the dose titration study, sucroferric oxyhydroxide 1000 to 3000 mg/day was statistically superior to the sucroferric oxyhydroxide low dose (250 mg) control in maintaining the phosphorus-lowering effect in hemodialysis patients at week 27 ($p < 0.001$) (*Floege et al 2014*). In the extension trial, sucroferric oxyhydroxide demonstrated a greater change from baseline in serum phosphorus when compared to sevelamer carbonate from weeks 32 to 40. However, from weeks 44 to 52, changes in serum phosphorus between sevelamer carbonate and sucroferric oxyhydroxide were similar (*Floege et al 2015*). The greatest changes from baseline for serum phosphorus occurred up to week 12 for sevelamer carbonate and up to week 20 for sucroferric oxyhydroxide (*Velphoro prescribing information 2020*).
  - The most frequent adverse events were hypophosphatemia and discolored feces for the sucroferric oxyhydroxide groups. Sucroferric oxyhydroxide patients experienced more discolored feces, hypophosphatemia, muscle spasms, and constipation compared to sevelamer HCl in the active comparator trial (*Wuthrich et al 2013*).
- Ferric citrate is an iron-based, calcium-free phosphate binder that has been studied in several published trials. Ferric citrate is similarly safe and effective to 2 current first-line phosphate binders, calcium acetate and sevelamer (*Lewis et al 2015*). Ferric citrate offers a reduced pill burden vs sevelamer carbonate but not vs calcium acetate. In addition to reducing serum phosphorus, ferric citrate raises iron stores (evidenced by increased hemoglobin, serum ferritin, and serum transferrin saturation) and decreases IV iron and erythropoietin stimulating agent usage (*Auryxia Prescribing Information 2019, Block et al 2015, Lewis et al 2015, Umanath et al 2015*).

Potassium Removing Agents

- The FDA first approved sodium polystyrene sulfonate in 1958, 4 years before passage of the Kefauver-Harris Drug Amendment, which requires drug manufacturers to prove the effectiveness of their products before marketing (*Sterns et al 2010*).
  - In 1961, Scherr et al reported the largest clinical experience with sodium polystyrene sulfonate suspended in water in an uncontrolled study of hyperkalemic patients with acute and chronic renal failure, using the newly approved sodium polystyrene sulfonate. In 23 of 30 cases, the plasma potassium fell by at least 0.4 mEq/L in the first 24 hours. Two

patients with pre-treatment potassium levels of 6.1 and 7.4 mEq/L developed hypokalemia (3.3 and 2.3 mEq/L) while receiving 40 g/day of oral resin for 2 and 6 days. On the strength of this study and several smaller case series, the FDA's Drug Efficacy Study Implementation (DESI) Program, charged with reviewing pre-1962 drugs that were already on the market, ruled sodium polystyrene sulfonate powder "effective" (*Sterns et al 2010*).

- A randomized, double-blind, placebo-controlled, single-center study (n = 33) evaluated the safety and efficacy of a 7-day course of sodium polystyrene sulfonate in the treatment of mild hyperkalemia (potassium levels of 5.0 to 5.9 mEq/L) in patients with CKD (*Lepage et al 2015*).
  - Sodium polystyrene sulfonate was superior to placebo in the reduction of serum potassium levels (mean difference between groups: −1.04 mEq/L; 95% CI: −1.37 to −0.71). A higher proportion of patients in the sodium polystyrene sulfonate group attained normokalemia at the end of their treatment compared with those in the placebo group, but the difference did not reach statistical significance (73% vs 38%, p = 0.07).
- The safety and efficacy of patiromer were based primarily on 2 pivotal trials in hyperkalemic patients (potassium levels of 5.1 to < 6.5 mEq/L).
  - OPAL-HK was a 2-part, single-blind, Phase 3 study that evaluated the efficacy and safety of patiromer in 237 patients with CKD receiving RAAS inhibitors. During the initial treatment phase (Part A), patiromer therapy resulted in a mean (± standard error [SE]) change from baseline to week 4 in serum potassium of −1.01 ± 0.03 mEq/L (95% CI: −1.07 to −0.95; p < 0.001) (*Weir et al 2015*).
    - Patients with moderate to severe hyperkalemia at baseline who achieved a target potassium level with initial treatment during Part A were randomized to receive patiromer (n = 55) or placebo (n = 52) in Part B (randomized withdrawal phase). The median increase in potassium level from baseline of Part B through week 4 was greater with placebo compared with patiromer (0.72 mEq/L vs 0 mEq/L, 95% CI: 0.46 to 0.99; p < 0.001).
  - AMETHYST-DN was a long-term, Phase 2, randomized study in patients with CKD and diabetes mellitus receiving a RAAS inhibitor. Patiromer demonstrated a mean change from baseline to week 4 or at first patiromer dose titration in serum potassium of −0.35 mEq/L (95% CI: −0.22 to −0.48, p < 0.001) in patients with mild hyperkalemia receiving 8.4 g/day and −0.87 mEq/L (95% CI: −0.60 to −1.14, p < 0.001) in patients with moderate hyperkalemia receiving 16.8 g/day. The efficacy of patiromer was maintained for 1 year (*Bakris et al 2015*).
- The safety and efficacy of sodium zirconium cyclosilicate were based on data from 2 double-blind, placebo-controlled studies and 2 open-label studies in adult patients with hyperkalemia.
  - Study 1 was a 2-part, Phase 3, double-blind, randomized controlled trial in patients with hyperkalemia (> 5 mmol/L). Patients were randomly assigned to receive either sodium zirconium cyclosilicate (at a dose of 1.25 g, 2.5 g, 5 g, or 10 g) or placebo 3 times daily for 48 hours. Patients with normokalemia (serum potassium level, 3.5 to 4.9 mmol/L) at 48 hours were randomly assigned to receive either sodium zirconium cyclosilicate or placebo once daily on days 3 to 14 (maintenance phase). The primary endpoint was the exponential rate of change in the mean serum potassium level at 48 hours *(Packham et al 2015)*.
    - At 48 hours, the mean serum potassium level had decreased from 5.3 mmol/L at baseline to 4.9 mmol/L in the group of patients who received 2.5 g of sodium zirconium cyclosilicate, 4.8 mmol/L in the 5 g group, and 4.6 mmol/L in the 10 g group, for mean reductions of 0.5, 0.5, and 0.7 mmol/L, respectively (p < 0.001 for all comparisons) and to 5.1 mmol/L in the 1.25 g group and the placebo group (mean reduction, 0.3 mmol/L). In patients who received 5 g of sodium zirconium cyclosilicate and those who received 10 g of sodium zirconium cyclosilicate, serum potassium levels were maintained at 4.7 mmol/L and 4.5 mmol/L, respectively, during the maintenance phase, as compared with a level of more than 5.0 mmol/L in the placebo group (p < 0.01 for all comparisons).
  - Study 2 (HARMONIZE) was a Phase 3, randomized, double-blind, placebo-controlled trial evaluating sodium zirconium cyclosilicate in outpatients with hyperkalemia (serum potassium ≥ 5.1 mEq/L). Patients (n = 258) received 10 g of sodium zirconium cyclosilicate 3 times daily in the initial 48-hour open-label phase. Patients (n = 237) achieving normokalemia (3.5 to 5.0 mEq/L) were then randomized to receive sodium zirconium cyclosilicate, 5 g (n = 45 patients), 10 g (n = 51), or 15 g (n = 56), or placebo (n = 85) daily for 28 days *(Kosiborod et al 2014)*.
    - In the open-label phase, serum potassium levels declined from 5.6 mEq/L at baseline to 4.5 mEq/L at 48 hours, with 84% of patients (95% CI: 79 to 88) achieving normokalemia by 24 hours and 98% (95% CI: 96 to 99) by 48 hours. In the randomized phase, serum potassium was significantly lower during days 8 to 29 with all 3 sodium zirconium cyclosilicate doses vs placebo (4.8 mEq/L [95% CI: 4.6 to 4.9], 4.5 mEq/L [95% CI: 4.4 to 4.6], and 4.4 mEq/L [95% CI: 4.3 to 4.5] for 5 g, 10 g, and 15 g; 5.1 mEq/L [95% CI: 5.0 to 5.2] for placebo; p < 0.001 for all comparisons).

- Patients who completed the 28-day randomized withdrawal phase had the option to continue treatment with sodium zirconium cyclosilicate, in an open-label extension phase for up to 11 months (n = 123). The treatment effect on serum potassium was maintained during continued therapy *(Lokelma Prescribing Information, Roger et al 2019)*.
- The same study protocol was performed in Japan, Russia, South Korea, and Taiwan (HARMONIZE-Global). Maintenance of normokalemia was higher in the 5 g group (58.6%) and 10 g group (77.3%) compared to placebo (24%) (p<0.001 for all comparisons) (*Zannad et al 2020).*

- Sodium zirconium cyclosilicate was also evaluated in an open-label 12-month study in 751 hyperkalemic patients. The mean baseline potassium level in this study was 5.6 mEq/L. Following the acute phase treatment of sodium zirconium cyclosilicate 10 g 3 times a day, patients who achieved normokalemia (3.5 to 5.0 mEq/L) within 72 hours (n = 746; 99%) entered the maintenance phase. For maintenance treatment, the initial dosage was 5 g once daily and was adjusted to a minimum of 5 g every other day up to maximum of 15 g once daily, based on serum potassium level. The treatment effect on serum potassium was maintained during continued therapy, regardless of whether glomerular filtration rate was < 30 or ≥ 30 mL/min/1.73m^2 *(Lokelma Prescribing Information 2020, Spinowitz et al 2019, Roger et al 2020)*.
- The safety and efficacy of sodium zirconium cyclosilicate were evaluated in patients with end stage renal disease (ESRD) receiving hemodialysis through a double-blind, placebo-controlled, Phase 3b randomized clinical trial. A total of 196 patients with pre-dialysis hyperkalemia were randomized to receive either placebo or sodium zirconium cyclosilicate 5 g daily on non-dialysis days, with the option of titrating to 15 g daily. A total of 41.2% of patients receiving sodium zirconium cyclosilicate achieved a pre-dialysis potassium serum level between 4.0 and 5.0 mmol/L following 4 weeks of therapy compared to 1.0% in the placebo group (p<0.001) *(Fishbane et al 2019)*.

CLINICAL GUIDELINES

KDIGO - Clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of CKD-MBD *(KDIGO 2009, KDIGO 2017)*

- KDIGO published treatment guidelines in 2009 and these were updated again in 2017. The update revised recommendations for treatment of elevated phosphate levels. The recommendations include:
  - In patients with CKD stage 3a to 5 (with or without dialysis), KDIGO suggests lowering elevated phosphate levels toward the normal range. There is insufficient evidence that maintaining phosphate in the normal range is of clinical benefit to CKD stage 3a to stage 4 patients. Due to safety concerns with pharmacologic therapy, treatment should be reserved for overt hyperphosphatemia.
  - In patients with CKD stage 3 to stage 5 (with or without dialysis), decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphate. The broader term “phosphate-lowering” treatment is used instead of phosphate binding agents since all possible approaches (ie, binders, diet, or dialysis) can be effective.
  - In adult patients with CKD stage 3a to 5 (with or without dialysis) receiving phosphate-lowering treatment, KDIGO suggests restricting the dose of calcium-based phosphate binder. In children, it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels.

- **KDOQI – US Commentary on the 2017 KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of CKD-MBD** *(Isakova 2017)*
  - The KDOQI CKD-MBD work group published a commentary on the 2017 KDIGO guideline update recommendations.
  - The majority of the KDOQI work group supported the recommendation from the 2017 KDIGO guideline to limit calcium-based binders *when possible*, and discussed that there are multiple non-calcium phosphate-lowering therapies that are effective with similar adverse event profiles to calcium-based phosphate binders. The work group endorsed the recommendation to base the choice of phosphate-lowering therapy in children on serum calcium levels.

SAFETY SUMMARY

Phosphate Binders

- Sevelamer carbonate and sevelamer hydrochloride are contraindicated in patients with bowel obstruction. Cases of dysphagia, bowel obstruction and perforation, and esophageal tablet retention have been reported in association with use of the tablet formulation of sevelamer, some requiring hospitalization and intervention. Inflammatory disorders may resolve upon sevelamer discontinuation. The sevelamer suspension formulation should be considered in patients with a history of swallowing disorders. Adverse effects possibly related to sevelamer included nausea, vomiting, dyspepsia,

diarrhea, flatulence, abdominal pain, and constipation. Ciprofloxacin should be taken at least 2 hours before or 6 hours after sevelamer, and mycophenolate mofetil should be taken at least 2 hours before sevelamer.

- Calcium acetate is contraindicated in patients with hypercalcemia. Calcium supplements should be used with caution in patients with CKD due to the increased risk of developing hypercalcemia. The most common adverse effects include hypercalcemia, nausea, and vomiting. Diarrhea has been reported with calcium acetate oral solution. The administration of calcium acetate may decrease the bioavailability of tetracyclines or fluoroquinolones.
- Ferric citrate is contraindicated in patients with iron overload. Ferric citrate should be kept out of the reach of children to lower the risk of accidental overdose of iron. Adverse events reported in > 5% of patients treated with ferric citrate in clinical trials included diarrhea, nausea, constipation, vomiting, discolored feces, abdominal pain, hyperkalemia, and cough. Doxycycline should be taken at least 1 hour before ferric citrate. Ciprofloxacin should be taken at least 2 hours before or after ferric citrate.
- Bowel obstruction, ileus, and fecal impaction are contraindications to lanthanum carbonate therapy. Serious adverse events consisting of gastrointestinal obstruction, ileus, subileus, gastrointestinal perforation, and/or fecal impaction have been reported with this medication, and some of these events required surgery or hospitalization. Adverse events that were more commonly associated with lanthanum carbonate therapy included nausea, vomiting, and abdominal pain. Compounds that bind aluminum-, magnesium-, or calcium-based cationic antacids and thyroid hormone replacement therapy should be separated by at least 2 hours from lanthanum carbonate. Fluoroquinolones should be taken at least 1 hour before or 4 hours after lanthanum. Patients should be advised to chew lanthanum carbonate tablets completely and to not swallow them whole. Serious gastrointestinal complications have been associated with unchewed or incompletely chewed tablets.
- Sucroferric oxyhydroxide does not have any contraindications. Due to the potential for drug interactions, levothyroxine should be taken at least 4 hours before sucroferric oxyhydroxide. Doxycycline, acetylsalicylic acid, and cephalexin must be taken at least 1 hour before sucroferric oxyhydroxide. Common adverse events include dark/discolored feces, nausea, and diarrhea.

Potassium Removing Agents

- Patiromer is contraindicated in patients with known hypersensitivity to patiromer or any of its components. Warnings and precautions of patiromer include worsening of gastrointestinal motility and hypomagnesemia. The most common adverse effects (≥ 2%) with patiromer use were constipation, hypomagnesemia, diarrhea, nausea, abdominal discomfort, and flatulence.
- Sodium polystyrene sulfonate powder for suspension is contraindicated in patients with obstructive bowel disease and neonates with reduced gut motility. Sodium polystyrene sulfonate suspension is contraindicated in patients with hypokalemia, obstructive bowel disease, as oral administration in neonates, and in neonates with reduced gut motility. Warnings and precautions for sodium polystyrene sulfonate include intestinal necrosis; development of hypokalemia or other electrolyte disturbances; fluid overload in patients sensitive to high sodium intake; and risk of aspiration.
  - Sodium polystyrene sulfonate may cause some degree of gastric irritation. Anorexia, nausea, vomiting, and constipation may occur especially if high doses are given. Occasionally diarrhea develops.
- Sodium zirconium cyclosilicate does not have any contraindications. Warnings and precautions for sodium zirconium cyclosilicate include gastrointestinal adverse events in patients with motility disorders, edema, and hypokalemia in hemodialysis patients. The most common adverse effect was mild to moderate edema.

DOSING AND ADMINISTRATION

Table 5. Dosing and Administration of Phosphate Binders

Generic name	Available Formulations	Route	Usual Recommended Frequency	Comments
calcium acetate	Capsule, tablet, solution	Oral	Administered with each meal	--
ferric citrate	Tablet	Oral	Three times daily with meals	--

Generic name	Available Formulations	Route	Usual Recommended Frequency	Comments
lanthanum carbonate	Chewable tablet, powder	Oral	Administered with meals or immediately after meals	• Use is not recommended in children. In animal studies, lanthanum was deposited into developing bone including the growth plate. Consequences of lanthanum bone deposition are unknown.
sevelamer carbonate	Powder for oral suspension, tablet	Oral	Three times daily with meals	--
sevelamer hydrochloride	Tablet	Oral	Three times daily with meals	--
sucroferric oxyhydroxide	Chewable tablet	Oral	Three times daily with meals	--

See the current prescribing information for full details

Table 6. Dosing and Administration of Potassium Removing Agents

Generic name	Available Formulations	Route	Usual Recommended Frequency	Comments
patiromer	Powder for suspension	Oral	Once daily with or without food	• Administer at least 3 hours before or 3 hours after other oral medications. • Do not administer in its dry form.
sodium polystyrene sulfonate	Powder for suspension; suspension	Oral; rectal (enema)	Oral: 1 to 4 times daily Rectal: Every 6 hours	• Administer at least 3 hours before or 3 hours after other oral medications. • Patients with gastroparesis may require a 6-hour separation.
sodium zirconium cyclosilicate	Powder for suspension	Oral	Starting dose is 10 g administered 3 times daily for up to 48 hours; for maintenance, recommended dose is 10 g once daily or 5 g once daily on non-dialysis days for hemodialysis patients	• Other oral medications should be administered at least 2 hours before or 2 hours after sodium zirconium cyclosilicate.

CONCLUSION

Phosphate Binders

- The phosphorus binders (or phosphorus depleters) class is an important aspect of the medical management of patients with CKD; these agents are used to lower a patient's phosphorus level. If phosphorus levels remain elevated in this population, the patient is at a greater risk for the development of secondary hyperparathyroidism or cardiovascular disease. In addition, there is available evidence to demonstrate that hyperphosphatemia is a predictor of mortality in CKD stage 5 patients who are receiving dialysis. In patients with CKD stage 3 to stage 5 (with or without dialysis), decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphate. The broader term "phosphate-lowering" treatment is used instead of phosphate binding agents since all possible approaches (ie, binders, diet, or dialysis) can be effective (*NKF 2003, KDIGO 2009, KDIGO 2017*).
- The 2 subgroups of phosphorus binders currently available include the calcium and non-calcium containing products. Available evidence supports the efficacy of all of the phosphorus binders in controlling serum phosphorus levels. It is important to note that although the true benefits of these agents, with respect to hard clinical outcomes, have not been established, it is still reasonable to prescribe these products in patients with CKD who have elevated phosphorus levels to prevent the development of secondary hyperparathyroidism and cardiovascular disease.

- In adult patients with CKD stage 3a to 5 (with or without dialysis) receiving phosphate-lowering treatment, KDIGO suggests restricting the dose of calcium-based phosphate binder. In children, it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels *(KDIGO 2017).*
- Sevelamer, a non-calcium-containing phosphate binder, is available in 2 salt formulations: hydrochloride (Renagel) and carbonate (Renvela). The hydrochloride formulation was developed first, but due to the incidence of metabolic acidosis associated with its use, a buffered sevelamer formulation was later developed. The sevelamer carbonate product will most likely be preferred in this patient population due to a decrease in the incidence of metabolic acidosis associated with its use. Additionally, sevelamer carbonate is the only phosphate binder that is FDA-approved for use in children (6 years of age and older).
- Lanthanum carbonate (Fosrenol) is another non-calcium-containing phosphorus binder available. An advantage to this agent, in addition to not causing an increase in serum calcium levels, appears to be its decreased pill burden compared to the other products (*NKF 2003, KDIGO 2009*).
- Two iron-based, calcium-free phosphate binders are now available.
  - Sucroferric oxyhydroxide provides long-term control of hyperphosphatemia, as demonstrated by the 52-week extension trial (*Floege et al 2015*). Sucroferric oxyhydroxide may reduce the pill burden for those patients that require higher doses of sevelamer as demonstrated in trials (*Wuthrich et al 2013*).
  - Ferric citrate has shown to provide significant reductions in serum phosphate levels in 3 studies (*Block et al 2015, Dwyer et al 2013, Lewis et al 2015*). Based on secondary study endpoints, ferric citrate raises iron stores (evidenced by increased serum ferritin and serum transferrin saturation) and decreases IV iron and erythropoietin stimulating agent usage (*Lewis et al 2015, Umanath et al 2015*). Ferric citrate's effects may make it an attractive option for dialysis patients who require concomitant use of a phosphate binder and anemia treatments.
- The main considerations for selection of phosphate binders include absorbability, adequate gastrointestinal tolerability, and cost or cost-effectiveness (*Frazão et al 2012*).

Potassium Removing Agents

- Hyperkalemia is a common clinical problem that is most often a result of impaired urinary potassium excretion due to acute or chronic kidney disease and/or disorders or drugs that inhibit the RAAS may also cause hyperkalemia *(Mount 2019)*.
- Acute or urgent treatment of hyperkalemia includes 3 main phases: 1) antagonizing cardiac effects of potassium by using IV calcium gluconate; 2) redistributing potassium into cells using insulin with dextrose, beta-2-adrenergic agonists, or sodium bicarbonate; and 3) removing excess potassium from the body using hemodialysis, loop diuretics, or cation exchange resins (ie, sodium polystyrene sulfonate) (*Hollander-Rodriquez et al 2006, Mount 2019, Raebel 2012*).
  - In patients who do not require urgent treatment, lowering total body potassium may be the only step necessary (*Hollander-Rodriquez et al 2006*).
- In October 2015, the FDA approved Veltassa (patiromer), a non-absorbed, cation exchange polymer that contains a calcium-sorbitol counterion, for the treatment of hyperkalemia. Patiromer should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action.
- Patiromer has been shown to be effective in lowering serum potassium levels in patients with CKD receiving RAAS inhibitor therapy. Patiromer has also been shown to provide sustained reductions of serum potassium for up to 1 year.
  - Compared with sodium polystyrene sulfonate, patiromer has more robust prospective long-term data and may have a more favorable adverse event profile (sodium polystyrene sulfonate is associated with intestinal necrosis and sodium retention). Studies used for the approval of patiromer did not address the relative efficacy and safety of patiromer vs sodium polystyrene sulfonate.
  - In addition, the role of patiromer for the outpatient treatment of hyperkalemia is unknown, as chronic management of hyperkalemia is generally accomplished through dietary modifications, discontinuation or dose lowering of hyperkalemia-exacerbating agents, or the use of diuretics.
- In May 2018, the FDA also approved Lokelma (sodium zirconium cyclosilicate), a non-absorbed zirconium silicate that acts as a highly-selective potassium-removing agent, for the treatment of hyperkalemia. Similar to patiromer, sodium zirconium cyclosilicate should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action. The safety and efficacy of sodium zirconium cyclosilicate were based on data from 2 double-blind, placebo-controlled studies and 2 open-label studies in adult patients with hyperkalemia.

- The placebo-controlled studies demonstrated that patients treated with sodium zirconium cyclosilicate had significant reductions in serum potassium levels vs placebo-treated patients. The 2 open-label studies showed that the treatment effect of sodium zirconium cyclosilicate on serum potassium was maintained during continued therapy.

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Publication Date: June 22, 2020

Therapeutic Class Overview
Benign Prostatic Hyperplasia Agents

INTRODUCTION

- Benign prostatic hyperplasia (BPH) is a histologic diagnosis that refers to the proliferation of smooth muscle and epithelial cells of the prostate. A different but related term is benign prostatic enlargement, which is used when the prostate has an increased size (*McVary et al 2011*).
- BPH causes bladder outlet obstruction that leads to lower urinary tract symptoms (LUTS). The obstruction is caused by 2 main factors:
  - A static, structural component due to the bulk of the enlarged prostate impinging upon the urethra.
  - A dynamic, reversible component due to the tension of smooth muscle in the prostate (*McVary et al 2011*).
- LUTS include storage and voiding symptoms (*McVary 2019b, McVary et al 2011*).
  - Storage symptoms may include increased frequency of daytime urination, nocturia, urgency, and urinary incontinence.
  - Voiding symptoms may include a slow urinary stream, splitting or spraying of the urinary stream, intermittent urinary stream, hesitancy, straining to void, and terminal dribbling.
- The exact etiology of BPH is unknown (*McVary et al 2011*). Increased age is a major risk factor; the prevalence of BPH is 8% in men 31 to 40 years of age, 40% to 50% in men 51 to 60 years of age, and over 80% in men older than 80 years of age (*McVary 2019a*).
- The primary goals of treatment are to alleviate bothersome LUTS secondary to prostate enlargement, to alter the disease progression, and to prevent complications associated with BPH and LUTS (*McVary et al 2011*).
- Current treatment options include watchful waiting, surgical interventions, and pharmacological therapies (*Foster et al 2018, McVary et al 2011*).
  - Watchful waiting is the preferred management strategy for men with mild symptoms and for those with moderate to severe symptoms who are not bothered by their LUTS.
  - Surgical and minimally invasive therapies, such as transurethral resection of the prostate and transurethral microwave thermotherapy, are recognized as the most effective strategies for BPH management. Surgical therapy is an appropriate treatment alternative for patients with moderate-to-severe LUTS and for patients who have developed acute urinary retention or other complications.
  - Pharmacological therapies are appropriate for less frequent and severe symptom management. These therapies may include alpha $(\alpha)_1$-adrenergic blocking agents, 5-alpha (5-α)-reductase inhibitors, anticholinergic agents, and phosphodiesterase-5 (PDE5) inhibitors.
- This review focuses on the pharmacological agents that are Food and Drug Administration (FDA)-approved for the management of BPH and include the following drug classes:
  - α_1-adrenergic blocking agents: Cardura (doxazosin), Cardura XL (doxazosin extended-release), Flomax (tamsulosin), Hytrin (terazosin), Rapaflo (silodosin), and Uroxatral (alfuzosin)
    - Doxazosin and terazosin are non-uroselective α_1-adrenergic blocking agents. They cause relaxation in both the prostatic and vascular smooth muscles and are therefore associated with a higher incidence of orthostatic hypotension. Both agents are FDA-approved for the management of BPH and hypertension.
    - Cardura XL, an extended-release tablet, is only indicated for the management of BPH.
    - Tamsulosin, silodosin, and alfuzosin are uroselective α_1-adrenergic blocking agents and are therefore associated with a lower risk of orthostatic hypotension. They are FDA-approved for the management of BPH.
    - Minipress (prazosin) is also included in this review since it is an α_1-adrenergic blocking agent that could be used for the management of BPH, but it is only FDA-approved for the treatment of hypertension.
  - 5-α-reductase inhibitors: Avodart (dutasteride) and Proscar (finasteride)
    - Both agents are indicated for the treatment of BPH in men with enlarged prostate to improve symptoms, reduce the risk of acute urinary retention, and reduce the risk of BPH-related surgery. Finasteride is also indicated in combination with doxazosin to reduce the risk of symptomatic progression of BPH, and dutasteride is indicated in combination with tamsulosin for the treatment of symptomatic BPH in men with an enlarged prostate.
  - PDE5 inhibitor: Cialis (tadalafil)

  - In addition to the management of BPH symptoms in men with or without concomitant erectile dysfunction, Cialis is FDA-approved for the treatment of erectile dysfunction.
- Combination product: Jalyn (dutasteride/tamsulosin) is indicated for the treatment of symptomatic BPH in men with an enlarged prostate.

- Currently, doxazosin, prazosin, tamsulosin, terazosin, finasteride, dutasteride, alfuzosin, and the combination product dutasteride/tamsulosin are available generically. The brand product for Hytrin is no longer marketed; the product is only available generically.
- Medispan Therapeutic Class: Prostatic Hypertrophy Agents (tadalafil is classified with "Impotence Agents" but is also approved for BPH. Terazosin and doxazosin are classified with "antiadrenergic antihypertensives" but are also approved for BPH).

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single Entity Agents: α_1-Adrenergic Blocking Agents	
Cardura (doxazosin)	✔
Cardura XL (doxazosin extended-release)	-
Flomax (tamsulosin)	✔
Hytrin (terazosin)*	✔
Minipress (prazosin)	✔
Rapaflo (silodosin)	✔
Uroxatral (alfuzosin)	✔
Single Entity Agents: 5-α-Reductase Inhibitors	
Avodart (dutasteride)	✔
Proscar (finasteride)	✔
Single Entity Agents: PDE5 Inhibitors	
Cialis (tadalafil)	✔
Combination Product	
Jalyn (dutasteride/tamsulosin)	✔

*Brand product no longer marketed; product only available generically

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2a. FDA-Approved Indications: α_1-Adrenergic Blocking Agents

Indication	Cardura (doxazosin)	Cardura XL (doxazosin extended-release)	Flomax (tamsulosin)	Minipress (prazosin)	Hytrin (terazosin)	Rapaflo (silodosin)	Uroxatral (alfuzosin)
Treatment of signs and symptoms of BPH	✔	✔	✔		✔	✔	✔
Treatment of hypertension	✔			✔	✔		

(*Prescribing Information: Cardura 2019, Cardura XL 2017, Flomax 2019, Minipress 2016, Terazosin 2018, Rapaflo 2017, Uroxatral 2019*)

Table 2b. FDA-Approved Indications: 5-α-Reductase Inhibitors

Indication	Avodart (dutasteride)	Proscar* (finasteride)
Treatment of symptomatic BPH in men with an enlarged prostate to improve symptoms, reduce the risk of acute urinary retention, and to reduce the risk of need for BPH-related surgery	✔	✔
Treatment of symptomatic BPH in men with enlarged prostate in combination with tamsulosin	✔	

Indication	Avodart (dutasteride)	Proscar* (finasteride)
Reduction of the risk of symptomatic progression of BPH in combination with doxazosin		✔

*If finasteride is used with tadalafil to initiate BPH treatment, such use is recommended for up to 26 weeks because the incremental benefit of tadalafil decreases from 4 weeks until 26 weeks, and the incremental benefit of tadalafil beyond 26 weeks is unknown.

(*Prescribing information: Avodart 2020, Proscar 2013*)

Table 2c. FDA-Approved Indications: PDE5 Inhibitors

Indication	Cialis* (tadalafil)
Treatment of erectile dysfunction	✔
Treatment of signs and symptoms of BPH	✔
Treatment of signs and symptoms of BPH and erectile dysfunction	✔

*If tadalafil is used with finasteride to initiate BPH treatment, such use is recommended for up to 26 weeks because the incremental benefit of tadalafil decreases from 4 weeks until 26 weeks, and the incremental benefit of tadalafil beyond 26 weeks is unknown.

(*Cialis prescribing information 2018*)

Table 2d. FDA-Approved Indications: Combination Product

Indication	Jalyn (dutasteride/tamsulosin)
Treatment of symptomatic BPH in men with enlarged prostate	✔

(*Jalyn prescribing information 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

α_1-Adrenergic Blocking Agents

- Overall, doxazosin, Cardura XL, tamsulosin, terazosin, silodosin, and alfuzosin have been shown in clinical trials to decrease International Prostate Symptom Score (IPSS) and improve LUTS in men with BPH (*Chang et al 2010, Choo et al 2014, Chung et al 2018, Demir et al 2009, Kawabe et al 2006, Kojima et al 2012, Leungwattanakij et al 2010, Marks et al 2013, Matsukawa et al 2009, Permpongkosol et al 2011, Ren et al 2010, Song et al 2011, Sun et al 2010, Sun et al 2011, Yamanishi et al 2010, Yokoyama et al 2011*).
- Although some studies showed small differences among agents on selected efficacy endpoints, most randomized controlled trials and reviews demonstrated very similar efficacy among products.
- A meta-analysis of α_1-adrenergic blocking agents (doxazosin, tamsulosin, terazosin, and alfuzosin) in men with LUTS secondary to benign prostatic obstruction did not identify any difference among agents in improving total urinary symptom scores or maximum urinary flow rate. However, tamsulosin and alfuzosin were better tolerated than doxazosin and terazosin (*Djavan et al 1999*).
- A systematic review of studies comparing alfuzosin to doxazosin and tamsulosin showed that doxazosin was associated with the greatest improvement in IPSS (*MacDonald et al 2005*).
- Cardura XL was associated with greater improvement in IPSS compared to tamsulosin in 2 randomized controlled trials (*Chung et al 2011, Kirby et al 2003a*); however, 2 other randomized controlled trials showed no difference between the 2 agents in the improvement in IPSS, nocturia, or quality of life (*Xue et al 2007, Zhang et al 2011*).
- Other head-to-head studies comparing the various α_1-adrenergic blocking agents have demonstrated no difference among these agents in the improvement of BPH symptoms (*Kaplan et al 1995, Kaplan et al 1997, Karadag et al 2011, Kirby et al 2001, Lapitan et al 2005, Rahardjo et al 2006, Samli and Dincel 2004, Tsai et al 2007*).
- Results from a meta-analysis and 2 crossover studies demonstrated that the efficacy of silodosin was similar to tamsulosin in improving IPSS and maximum urinary flow rate (*Cui et al 2012, Miyakita et al 2010, Shirakawa et al 2013, Watanabe et al 2011*). A 2017 Cochrane review reported the efficacy of silodosin is similar to other α_1-adrenergic blockers (tamsulosin and alfuzosin), but it is associated with a higher rate of sexual adverse effects (*Jung et al 2017*).
- Another meta-analysis examined combination therapy with an anticholinergic medication (eg, tolterodine, oxybutynin ER, solifenacin, fesoterodine) plus an α_1-adrenergic blocker (eg, doxazosin, tamsulosin) versus α_1-adrenergic blocker monotherapy in men with BPH. Study results demonstrated the addition of an anticholinergic to an α_1-adrenergic blocker

slightly reduced storage symptoms and urinary frequency; however, this combination may increase the risk of acute urinary retention (*Filson et al 2013*).

- A systematic review of 48 studies concluded that older α_1-adrenergic blocking agents had similar outcomes as newer α_1-adrenergic blocking agents, PDE5 inhibitors, antimuscarinics, and combination therapy with agents from more than one medication class. However, older α_1-adrenergic blocking agents had more adverse events than comparators (*Dahm et al 2017*).

5-α-Reductase Inhibitors

- Dutasteride has been shown to reduce prostate volume in men with BPH (*Na et al 2012, Page et al 2011*). Dutasteride has also been demonstrated to reduce the incidence of clinical progression of BPH compared to placebo in men with enlarged prostates (*Toren et al 2013*). A 2-year randomized controlled trial in Asian men also found significant reduction in prostate volume, as well as improvements in IPSS, when dutasteride was added to background tamsulosin therapy (*Haque et al 2018*).
- In a Cochrane review, finasteride improved total BPH symptom scores compared to placebo (*Tacklind et al 2010*). One clinical study also showed that finasteride reduced the risk of clinical progression of BPH compared to placebo in men with large prostate volume (*Kaplan et al 2011*).
- The Enlarged Prostate International Comparator Study (N = 1630) showed that there was no significant difference between dutasteride and finasteride in reducing prostate volume and improving LUTS and maximum urinary flow rate in men with BPH over a period of 12 months (*Nickel et al 2011*). A smaller head-to-head study and a meta-analysis of 4 studies showed similar results (*Jun et al 2017, Ravish et al 2007*). A network meta-analysis of 21 studies found that dutasteride may improve BPH symptoms but not urinary flow or prostate volume compared to finasteride (*Yin et al 2017*). When compared to α_1-adrenergic blocking agents, one study showed finasteride to be comparable to tamsulosin in improving LUTS; however, improvements were seen earlier with tamsulosin compared to finasteride (*Lee 2002*).

Combination Therapy with an α_1-Adrenergic Blocking Agent Plus a 5-α-Reductase Inhibitor

- In men with an enlarged prostate, combination therapy may lead to improved symptom control compared to monotherapy with either an α_1-adrenergic blocking agent or a 5-α-reductase inhibitor (*Kaplan et al 2006*). However, available data are inconsistent in this area, with another study demonstrating symptom control with combination therapy to be no better than with α_1-adrenergic blocking monotherapy (*Kirby et al 2003b*).
- In the 4-year, double-blind, randomized, parallel-group study known as the Combination of Avodart and Tamsulosin (CombAT) trial (N = 4844), Jalyn significantly reduced the risk of acute urinary retention or BPH-related surgery compared to tamsulosin monotherapy and demonstrated significantly greater symptom benefit (*Roehrborn et al 2010*). Jalyn was also associated with greater reduction in voiding and storage symptoms compared to dutasteride or tamsulosin monotherapy (*Becher et al 2009*).
- The 2-year, open-label CONDUCT trial compared Jalyn to watchful waiting with the addition of tamsulosin if symptoms did not improve in treatment-naïve men with moderately symptomatic BPH. Jalyn was shown to significantly improve the rate of clinical progression, health-related quality of life, and IPSS scores compared to the watchful waiting/tamsulosin group (*Roehrborn et al 2015*).
- A meta-analysis examining 5 studies found that the combination of tamsulosin and dutasteride had a significantly greater effect on symptom scores, prostate volume, urine flow rate, post-void residual urine volume, and clinical progression compared to tamsulosin alone (*Zhou et al 2019*).

PDE5 Inhibitors

- A meta-analysis showed that PDE5 inhibitors (tadalafil, vardenafil [Levitra], and sildenafil [Viagra]) were safe and effective in improving IPSS and LUTS secondary to BPH. However, no statistically significant difference was detected in maximum urine flow rate (Q_{max}) or post-void residual urine volume (*Gacci et al 2016*).
- Several clinical studies have also demonstrated the efficacy of tadalafil in improving LUTS secondary to BPH in men with or without concomitant erectile dysfunction (*Broderick et al 2010, Dmochowski et al 2013, Donatucci et al 2011, Egerdie et al 2012, Goldfischer et al 2012, Oelke et al 2012, Porst et al 2011, Roehrborn et al 2008, Takahashi et al 2018*). A meta-analysis of 13 clinical studies also confirmed the efficacy of tadalafil in improving LUTS associated with BPH and treating erectile dysfunction over 12 weeks (*Wang et al 2018*).

Combination Therapy with a PDE5 Inhibitor

- A randomized, double-blind trial showed combination therapy with a 5-α-reductase inhibitor, finasteride, combined with the PDE5 inhibitor, tadalafil, was associated with modest improvements in urinary symptoms and significantly improved patient, but not clinician, global impression of improvement when compared with finasteride monotherapy (*Casabe et al 2014*). A Cochrane review supported these findings and showed that combination therapy with a PDE5 inhibitor and 5-α-

reductase inhibitor may slightly improve IPSS in the short term compared to a 5-α-reductase inhibitor alone (*Pattanaik et al 2018*).

- Four meta-analyses demonstrated that combination therapy with a PDE5 inhibitor and an α_1-adrenergic blocking agent statistically significantly improved IPSS compared to an α_1-adrenergic blocking agent alone (*Gacci et al 2012, Kallidonis et al 2019, Pattanaik et al 2018, Zhang 2019*). A small benefit was also found with the combination compared to monotherapy with a PDE5 inhibitor. However, no adverse event data was available comparing the combination to PDE5 inhibitor alone, and adverse events increased with the combination when compared to an α_1-adrenergic blocking agent (*Pattanaik et al 2018*).
- A randomized controlled trial with a primary objective of evaluating the occurrence of dizziness when tadalafil was added to α_1-adrenergic blocking therapy demonstrated that changes in hemodynamic signs and symptoms were similar for tadalafil- and placebo-treated patients. There was a trend toward increased hemodynamic signs and symptoms in men treated with concomitant tadalafil and non-uroselective α_1-adrenergic blocking agents. Notably, this study did not demonstrate increased effectiveness with combination therapy compared to α_1-adrenergic blocking agent monotherapy, with an IPSS reduction of 2.2 in the tadalafil group and 1.33 in the placebo group ($p = 0.13$) (*Goldfischer et al 2012*).
- A randomized trial comparing tamsulosin alone with tamsulosin plus tadalafil failed to find a significant benefit with combination therapy compared to monotherapy in patients with acute urinary retention due to BPH (*Baghani et al 2018*).

CLINICAL GUIDELINES

- The American Urological Association guideline, which was published in 2011 and confirmed in 2014, has noted no differences in efficacy among doxazosin, tamsulosin, terazosin and alfuzosin in the management of BPH (*McVary et al 2011*). The European Association of Urology guideline notes that all α_1-adrenergic blocking agents have similar efficacy at appropriate doses (*Gravas et al 2019*).
- The American Urological Association guideline notes that there is no evidence to suggest that the clinical efficacy of 5-α-reductase inhibitors differs when used for the appropriate indication (*McVary et al 2011*). Similarly, the European Association of Urology guideline notes that available evidence indicates that dutasteride and finasteride are equally effective in the treatment of LUTS (*Gravas et al 2019*).
- The American Urological Association guideline currently does not have a recommendation for the place in therapy for PDE5 inhibitors (*McVary et al 2011*); however, the European Association of Urology guideline suggests that PDE5 inhibitors are effective for reducing moderate-to-severe LUTS symptoms (*Gravas et al 2019*).

SAFETY SUMMARY

- α_1-adrenergic blocking agents:
  - Use of α_1-adrenergic blocking agents may lead to intraoperative floppy iris syndrome during cataract and glaucoma surgery and warrant modification in surgical techniques as needed.
  - Orthostatic hypotension may occur with all agents, but is more common with doxazosin, prazosin, and terazosin, especially after the first dose.
  - Doxazosin, prazosin, and Cardura XL are contraindicated in patients with hypersensitivity to quinazolines (eg, prazosin, terazosin).
  - Use of α_1-adrenergic blocking agents has been associated with priapism. Patients must be advised about the seriousness of this condition.
  - Tamsulosin may cause serious allergic reactions in patients allergic to sulfa.
  - Silodosin and alfuzosin are contraindicated in patients with severe hepatic impairment and in those who are taking strong cytochrome P450 (CYP) 3A4 inhibitors. Tamsulosin also should not be used with strong CYP3A4 inhibitors.
  - Silodosin is contraindicated in patients with creatinine clearance of less than 30 mL/minute. Silodosin may also increase the risk of QT prolongation. Silodosin should not be used with concurrent strong inhibitors of P-glycoprotein.
- 5-alpha (5-α)-reductase inhibitors:
  - Dutasteride and finasteride are contraindicated in women who are pregnant or have child-bearing potential; these agents should also be avoided in pediatric patients.
  - These agents may increase the risk of high-grade prostate cancer. Since these agents can decrease plasma prostate specific antigen (PSA) levels, a new PSA baseline should be obtained after at least 3 months of therapy and used for monitoring of prostate cancer.
  - Blood donation should be avoided during and for at least 6 months after therapy discontinuation.

- PDE5 inhibitors:
  - Tadalafil is contraindicated with regular or intermittent use of any form of organic nitrates. Tadalafil should not be used in patients using a guanylate cyclase inhibitor, such as riociguat.
  - Tadalafil may cause vasodilation and should be used with caution with alcohol and avoided in patients with preexisting cardiac conditions.
  - The lowest PDE5 inhibitor dose should be used when starting therapy with concurrent α_1-adrenergic blocking agents due to the risk of additive hypotension, although the manufacturer of tadalafil recommends against its use with concurrent α_1-adrenergic blocking agents for the treatment of BPH.
  - Patients should be advised to stop tadalafil and seek immediate medical attention if they experience sudden hearing or vision loss, which could be a sign of nonarteritic anterior ischemic optic neuropathy (NAION). In patients with a history of NAION, tadalafil should be used only if benefits outweigh the risks.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single Entity Agents: a_1-Adrenergic Blocking Agents				
Cardura (doxazosin)	Tablets	Oral	Daily	• Not recommended in severe hepatic impairment. • Should be used with caution and blood pressure should be monitored for hypotensive symptoms in patients with mild or moderate hepatic impairment.
Cardura XL (doxazosin extended-release)	Tablets (extended-release)	Oral	Daily	
Minipress (prazosin)	Capsules	Oral	Twice daily	
Flomax (tamsulosin)	Capsules	Oral	Daily	• Should be taken 30 minutes following the same meal each day. • Not indicated for use in women.
Hytrin (terazosin)	Capsules	Oral	Daily at bedtime	
Rapaflo (silodosin)	Capsules	Oral	Daily	• Contraindicated in severe renal and/or hepatic impairment. • Dosage adjustment required in moderate renal impairment.
Uroxatral (alfuzosin)	Tablets (extended-release)	Oral	Daily	• Contraindicated in moderate to severe hepatic impairment. • Caution should be used in patients with severe renal impairment.
Single Entity Agents: 5-α-Reductase Inhibitors				
Avodart (dutasteride)	Capsules	Oral	Daily	• Contraindicated for use in pregnancy because it may cause harm to the male fetus. • Not indicated for use in women.
Proscar (finasteride)	Tablets	Oral	Daily	• Pregnancy Category X* • Not indicated for use in women. • Should be used with caution in patients with hepatic impairment.
Single Entity Agents: PDE5 Inhibitors				
Cialis (tadalafil)	Tablets	Oral	Daily	• Dosage adjustment may be required in mild or moderate renal and/or hepatic impairment. Use is not recommended in severe renal or hepatic impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Combination Product				
Jalyn (dutasteride/tamsulosin)	Capsules	Oral	Daily	• Pregnancy Category X* • Not indicated for use in women. • Should be taken 30 minutes following the same meal each day.

*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.

See the current prescribing information for full details.

CONCLUSION

- BPH contributes to LUTS such as increased frequency of urination, nocturia, urinary hesitancy, and weak urinary streams (*McVary 2019b, McVary et al 2011*).
- Current treatment options include watchful waiting, surgical interventions, and pharmacological therapies (*McVary et al 2011*).
- α_1-adrenergic blocking agents are the most widely used agents for the management of BPH (*McVary et al 2011*).
  - Cardura (doxazosin), Minipress (prazosin), and Hytrin (terazosin) are non-uroselective and are associated with a higher risk of orthostatic hypotension; therefore, therapy should be started at the lowest possible dose and titrated to the maximally tolerated dose.
  - Flomax (tamsulosin), Rapaflo (silodosin), and Uroxatral (alfuzosin) are uroselective and are therefore associated with a lower risk of orthostatic hypotension.
  - The American Urological Association treatment guideline and a meta-analysis have indicated no differences in efficacy among doxazosin, tamsulosin, terazosin, and alfuzosin in the management of BPH (*Djavan et al 1999, McVary et al 2011*).
  - Silodosin was also shown to be similarly effective to tamsulosin in improving IPSS and LUTS secondary to BPH (*Choo et al 2014, Cui et al 2012, Jung et al 2017, Miyakita et al 2010, Shirakawa et al 2013, Watanabe et al 2011*).
- The 5-α-reductase inhibitors are FDA-approved for the management of BPH symptoms in men with an enlarged prostate and may be used to prevent clinical progression of BPH (*McVary et al 2011*).
  - Avodart (dutasteride) and Proscar (finasteride) are teratogenic and contraindicated in women. Therapy may increase the risk of high-grade prostatic cancer; therefore, evaluation for prostatic cancer should be performed prior to initiation of therapy and periodically during treatment.
  - Clinical trials have shown no significant differences between dutasteride and finasteride in reducing prostate volume and improving LUTS and maximum flow rate in men with BPH (*Nickel et al 2011*).
  - When compared to α_1-adrenergic blocking agents, 5-α-reductase inhibitors were associated with a slower onset of improvement in BPH symptoms (*Lee 2002*).
- Combination therapy with an α_1-adrenergic blocking agent and a 5-α-reductase inhibitor may be used in men with an enlarged prostate (*McVary et al 2011*).
  - In men with an enlarged prostate, combination therapy may lead to improved symptom control compared to monotherapy with either an α_1-adrenergic blocker or a 5-α-reductase inhibitor (*Kaplan et al 2006*). However, available data are inconsistent in this area, with another study demonstrating symptom control with combination therapy to be no better than with α_1-adrenergic blocker monotherapy (Kirby et al 2003b). A recent meta-analysis found benefit with the combination of dutasteride and tamsulosin, which was significant compared to tamsulosin alone (*Zhou et al 2019*).
  - Jalyn (dutasteride/tamsulosin) has been shown to reduce the risk of acute urinary retention or BPH-related surgery compared to tamsulosin monotherapy and watchful waiting (*Becher et al 2009, Roehrborn et al 2015*).
- Cialis (tadalafil), a PDE5 inhibitor, was approved by the FDA for the management of BPH. The American Urological Association treatment guideline currently does not have a recommendation for the place in therapy for PDE5 inhibitors (*McVary et al 2011*); however, the European Association of Urology treatment guideline suggests that PDE5 inhibitors are effective in patients with moderate-to-severe LUTS (*Gravas et al 2019*).
  - Tadalafil may cause hypotension and should not be administered within 48 hours of nitrate use.
  - Three meta-analyses and several other clinical studies have shown that tadalafil was safe and effective in improving IPSS and LUTS secondary to BPH in men with or without concomitant erectile dysfunction (*Broderick et al 2010,*

Dmochowski et al 2013, Donatucci et al 2011, Egerdie et al 2012, Gacci et al 2012, Gacci et al 2016, Goldfischer et al 2012, Oelke et al 2012, Porst et al 2011, Roehrborn et al 2008, Takahashi et al 2018, Wang et al 2018).
  - Combination therapy with the 5-α-reductase inhibitor finasteride and tadalafil was associated with modest improvements in urinary symptoms and significantly improved patient, but not clinician, global impression of improvement when compared with finasteride monotherapy (*Casabe et al 2014, Pattanaik et al 2018*). Guidance has been added to the tadalafil prescribing information regarding dosing for this combination.
  - Combination of a PDE5 inhibitor and an α_1-adrenergic blocking agent may have a small benefit on symptom score compared to monotherapy with an α_1-adrenergic blocking agent (*Gacci et al 2012, Kallidonis et al 2019, Pattanaik et al 2018, Zhang 2019*).
- Currently, Avodart, Cardura, Cialis, Minipress, Flomax, Hytrin, Jalyn, Proscar, Rapaflo, and Uroxatral are available generically. The brand product for Hytrin is no longer on the market; the product is only available generically.

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Publication Date: March 13, 2020

Therapeutic Class Overview
Urinary antispasmodics

INTRODUCTION

- Overactive bladder (OAB) is defined as urinary urgency, with or without urge incontinence, usually with frequency and nocturia. Urinary incontinence has been shown to greatly reduce quality of life in areas such as mental and general health in addition to physical and social functioning (*American Urological Association 2019, Coyne et al 2008, International Continence Society 2015).*
- Behavioral therapies (eg, bladder training, bladder control strategies, pelvic floor muscle training and fluid management) are considered first-line treatment in all patients with OAB *(American Urological Association 2019).*
- Urinary antispasmodics are used as first-line pharmacological therapy in OAB (*American Urological Association 2019, American College of Obstetricians and Gynecologists 2015, Blok et al 2019, Burkhard et al 2018*).
- The urinary antispasmodics used for the treatment of OAB belong to 2 classes of drugs, which include anticholinergic compounds known as muscarinic receptor antagonists, and the beta-3 adrenergic agonist, mirabegron. The anticholinergic agents act as antagonists of acetylcholine at muscarinic cholinergic receptors, thereby relaxing smooth muscle in the bladder and decreasing bladder contractions. Both immediate-release (IR) and extended-release (ER) formulations (LA, XL, and XR) are available for oxybutynin (Ditropan), tolterodine (Detrol), and trospium. Darifenacin (Enablex) and fesoterodine (Toviaz) are also supplied as ER tablets.
  - Oxybutynin is also formulated as a topical gel (Gelnique) and transdermal patch (Oxytrol).
  - Oxytrol for Women is an over-the-counter (OTC) product that was previously available as a prescription. Oxytrol for Women is an oxybutynin transdermal system applied every 4 days. It is specifically indicated for women ≥ 18 years of age with 2 or more of the following symptoms for at least 3 months: urinary frequency (the need to urinate more often than usual; typically more than 8 times in 24 hours), urinary urgency (a strong need to urinate right away), and urge incontinence (leaking or wetting yourself if you cannot control the urge to urinate) *(Oxytrol for Women Drug Facts 2016).*
- Myrbetriq (mirabegron) is an agonist of the human beta-3 adrenergic receptor (AR). Mirabegron relaxes the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle by activation of beta-3 AR, which increases bladder capacity.
- All urinary antispasmodics, with the exception of flavoxate, are Food and Drug Administration (FDA)-approved for the treatment of OAB. Flavoxate is FDA-approved for the relief of symptoms of cystitis, prostatitis, urethritis, or urethrocystitis/urethrotrigonitis. The IR oxybutynin formulation is also indicated for the relief of symptoms of neurogenic or reflex neurogenic bladder, and the ER tablet is approved for the treatment of detrusor overactivity.
- The anticholinergic urinary antispasmodics have demonstrated a similar safety and efficacy profile compared to one another; however, they primarily differ in their receptor selectivity and tolerability profiles. The M2 and M3 muscarinic receptor subtypes are highly concentrated in the bladder and are responsible for detrusor contraction, while M1, M4, and M5 are located throughout the body.
  - Preclinical studies suggested that solifenacin and darifenacin may be “uroselective” for the M3 receptor in the bladder; however, the clinical implications of this suggestion have not been established *(Brown et al 2018).*
- The development of ER formulations with more predictable pharmacokinetics has led to a lower incidence of anticholinergic adverse events (AEs). Oxybutynin undergoes first-pass metabolism to an active metabolite with a high incidence of dry mouth; however, transdermal oxybutynin formulations bypass this metabolism, maintaining the efficacy of oxybutynin with a lower incidence of AEs *(Dmochowski et al 2005).*
- Trospium, a water-soluble compound, has low penetration through the blood brain barrier and the gut; however, clinical studies have not demonstrated a lower incidence of AEs with trospium compared to other agents within the class.
- Fesoterodine, a prodrug, is rapidly metabolized by plasma esterases to 5-hydroxymethyl tolterodine, the same active metabolite as tolterodine.
- Botox injection (onabotulinumtoxinA) also has 2 FDA-approved indications for OAB. The OAB indications for BOTOX include the treatment of OAB with symptoms of urge urinary incontinence, urgency, and frequency in adults who have an inadequate response to or are intolerant of an anticholinergic medication; and the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (eg, spinal cord injury [SCI], multiple sclerosis [MS]) in adults who have an inadequate response to or are intolerant of an anticholinergic medication *(Botox prescribing information 2019).* Botox is not included in this review.

- 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. This review focuses on the use of the urinary antispasmodics for OAB.
- Medispan class: Urinary Antispasmodics

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Anti-muscarinic (Anticholinergic)	
Detrol (tolterodine)	✔
Detrol LA (tolterodine ER)	✔
Ditropan XL (oxybutynin ER)	✔
Enablex (darifenacin ER)	✔
Gelnique (oxybutynin) topical gel 10%	-†
oxybutynin	✔
Oxytrol (oxybutynin transdermal patch)	-
Oxytrol for Women (oxybutynin transdermal patch)*	-
trospium‡	✔
trospium ER‡	✔
Toviaz (fesoterodine)	-†
Vesicare (solifenacin)	✔
Beta-3 Adrenergic Agonists	
Myrbetriq (mirabegron)	-
Direct Muscle Relaxants	
flavoxate	✔

Abbreviations: ER = extended-release
*OTC product
†An oxybutynin topical gel that is AB rated to Gelnique has been approved by the FDA, but is not currently commercially available. Additionally, the FDA has approved a fesoterodine tablet that is AB rated to Toviaz, but it is currently commercially unavailable.
‡Branded product (Sanctura) is no longer available.

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Darifenacin (Enablex)	Fesoterodine (Toviaz)	Flavoxate	Mirabegron (Myrbetriq)	Oxybutynin (Ditropan XL, Gelnique, Oxytrol‡)	Solifenacin (Vesicare)	Tolterodine (Detrol and Detrol LA)	trospium
Treatment of OAB	✔*	✔*		✔*	✔* (patch, gel, XL)	✔*	✔*	✔*
Treatment of OAB in combination with solifenacin				✔*				
Treatment of detrusor overactivity					✔† (XL)			
Treatment of bladder instability in patients with uninhibited neurogenic or reflex neurogenic bladder					✔ (IR)			
Symptomatic relief of cystitis, prostatitis, urethritis, or urethrocystitis/urethrotrigonitis			✔					

Abbreviations: IR = immediate-release; OAB = overactive bladder; XL = extended-release
***** In patients with symptoms of urge urinary incontinence, urgency, and urinary frequency.

† In pediatric patients ≥ 6 years of age with symptoms of detrusor overactivity associated with a neurological condition.
‡ Oxytrol for Women is available OTC and is approved for women ≥ 18 years of age with ≥ 2 of the following symptoms for at least 3 months: urinary frequency, urinary urgency, and urge incontinence; Oxytrol is approved for overactive bladder in men.

(Oxytrol for Women Drug Facts 2016; Prescribing information: Detrol 2016, Detrol LA 2018, Ditropan XL 2019, Enablex 2016, flavoxate 2018, Gelnique 10% 2019, Myrbetriq 2018, oxybutynin tablets 2019, oxybutynin syrup 2018, Oxytrol 2017, Toviaz 2017, trospium tablets 2018, trospium extended-release capsules 2014, Vesicare 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

- A 2018 Agency for Healthcare Research and Quality (AHRQ) systematic review update of nonsurgical treatments for urinary incontinence in women concluded that behavioral therapy, alone or in combination with other interventions, is generally more effective than other first- or second-line interventions (including pharmacologic interventions) alone for both stress and urgency urinary incontinence (*Balk et al 2018*). For women with urgency urinary incontinence, anticholinergics were significantly more likely to result in "cure" (odds ratio [OR], 1.80; 95% confidence interval [CI], 1.29 to 2.52) or improvement (OR, 1.79; 95% CI, 1.18 to 2.7) as compared to placebo. Additionally, anticholinergics overall were found to improve quality of life compared with no treatment, but there was inconsistency both within and across studies regarding the comparative effect of these medications on various aspects of quality of life.
- Although used for urinary incontinence, flavoxate is no more effective than other drugs used for urge incontinence or related disorders *(Micromedex 2020).* No recent clinical trials have been published with flavoxate.
- The results from clinical studies have demonstrated each of the urinary antispasmodics to be more effective vs placebo with regard to improvements in micturition frequency, urgency and urge incontinence episodes *(Chapple et al 2004, Chapple et al 2007, Dmochowski et al 2003, Dmochowski et al 2008, Dmochowski et al 2010, Herschorn et al 2010(b), Kaplan et al 2011, Kay et al 2006, Khullar et al 2011, MacDiarmid et al 2011, Mattiasson et al 2010, Nitti et al 2007, Nitti et al 2013, Salinas-Casado et al 2015, Sand et al 2011, Staskin et al 2007, Staskin et al 2009, Wagg et al 2013, Zinner et al 2005).*
- Head-to-head studies with the urinary antispasmodics have not consistently found one agent to be superior to other agents within the class *(Anderson et al 1999, Anderson et al 2006, Appell et al 2001, Barkin et al 2004, Batista et al 2015, Chapple et al 2005, Chapple et al 2007, Davila et al 2001, Diokno et al 2003, Dmochowski et al 2003, Dmochowski et al 2010, Ercan et al 2015, Halaska et al 2003, Harvey et al 2001, Herschorn et al 2010(a), Herschorn et al 2010(b), Hsiao et al 2011, Kaplan et al 2011, Kay et al 2006, Kilic et al 2006, Kinjo et al 2018, Kobayashi et al 2018, Sand et al 2004, Versi et al 2000, Zellner et al 2009).*
- The evidence to support the efficacy and safety of the oxybutynin transdermal patch (Oxytrol for Women) as an OTC product was based on the completed studies with the prescription product *(Dmochowski et al 2002, Dmochowski et al 2003, FDA Oxytrol for Women Medical Review 2013*). The Oxytrol for Women transdermal patch is the same formulation and dose as the prescription Oxytrol transdermal patch.
- A 2012 Cochrane review reported that IR formulations of oxybutynin, tolterodine, and trospium have similar efficacy, but oxybutynin was associated with more AEs. In addition, solifenacin improved symptoms of OAB more than tolterodine IR, while fesoterodine was more effective than tolterodine ER *(Madhuvrata et al 2012).*
- Another review demonstrated that all anticholinergics for OAB showed similar small benefits. For urgency urinary incontinence, the drugs showed 20% or less difference from placebo in the rate of achieving urinary continence or improvement in urinary continence. The numbers needed to treat (NNT) to achieve continence in 1 woman were similar across drugs (range for NNT, 6 to 12). Dose-related efficacy effects were evident for fesoterodine, solifenacin, and oxybutynin. Small differences were apparent in the AEs among the anticholinergics. Dry mouth and constipation were the most common AEs. Treatment discontinuation due to AEs was greater than with placebo for all drugs except darifenacin and tolterodine (*Shamliyan et al 2012*).
- A network meta-analysis of 5 randomized controlled trials ranked the antispasmodics for treatment of OAB in women in the following order from highest to lowest efficacy: solifenacin 10 mg once daily, oxybutynin 3 mg 3 times daily, solifenacin 5 mg once daily, darifenacin 15 mg once daily, fesoterodine 8 mg once daily, darifenacin 7.5 mg once daily, and tolterodine 4 mg once daily. However, solifenacin 10 mg had the most AEs while darifenacin 7.5 mg once daily caused the least AEs. The authors concluded that solifenacin 5 mg once daily was preferred for OAB followed by oxybutynin 3 mg 3 times daily based on efficacy, AEs, and cost (*Nalliah et al 2017*).

- A network meta-analysis that compared solifenacin 5 mg/day to other antimuscarinic agents found that solifenacin was more effective than tolterodine 4 mg/day for incontinence and urgency. In addition, solifenacin had a lower risk of dry mouth compared to other antimuscarinics (*Nazir et al 2018*).
- A 2019 network meta-analysis of 128 studies of anticholinergics concluded that all the anticholinergic medications were better than placebo for patients with OAB; however, there was no clear best treatment for cure or improvement. In this analysis, transdermal oxybutynin was shown to cause less dry mouth than the other treatments (*Herbison et al 2019*).
- Three 12-week, randomized, placebo-controlled clinical trials evaluated the efficacy and safety of mirabegron 25 mg, 50 mg, or 100 mg once daily vs placebo. Mirabegron significantly reduced the mean number of incontinence episodes and the mean number of micturitions per 24 hours compared to placebo *(Nitti et al 2013).*
- Mirabegron compared with either tolterodine IR or tolterodine LA demonstrated comparable efficacy in 2 trials. However, tolterodine IR patients had more AEs *(Kuo et al 2015, Yamaguchi et al 2014).* A 2-period, 8-week crossover trial comparing mirabegron and tolterodine ER found greater tolerability with mirabegron; however, patient treatment preference and symptoms were similar between treatments (*Staskin et al* 2018). An indirect treatment comparison meta-analysis concluded that mirabegron had similar efficacy to most other antispasmodics; however, solifenacin demonstrated improved symptom control compared to mirabegron *(Obloza 2017).* Another systematic review and meta-analysis concluded that mirabegron demonstrated similar efficacy to tolterodine and solifenacin with regard to improvement in micturitions, incontinence, and nocturia with a lower incidence of dry mouth and no higher risk of hypertension (*Chen et al 2018*).
- A systematic review compared treatment with mirabegron 50 mg to several different active treatments (including darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium) in regard to micturitions, incontinence, and dry rate (*Kelleher et al 2018*). Mirabegron had similar efficacy to other active treatments with a few exceptions: solifenacin 10 mg monotherapy and solifenacin 5 mg plus mirabegron 50 mg were found to be more efficacious at reducing micturition frequency than mirabegron 50 mg; solifenacin 5 mg plus mirabegron 25/50 mg and fesoterodine 8 mg were found to be more efficacious at reducing urgency urinary incontinence than mirabegron 50 mg; and solifenacin 5 mg plus mirabegron 25/50 mg, trospium 60 mg, solifenacin 10 mg, and fesoterodine 8 mg were associated with an improved dry rate when compared to mirabegron 50 mg. In general, mirabegron was associated with a significantly lower frequency of AEs compared to other active treatments.
- Studies examining combination therapy of mirabegron and solifenacin have demonstrated decreased frequency of incontinence, urgency episodes, and/or micturition frequency with a similar AE profile to monotherapy *(Drake et al 2016, Herschorn et al 2017, Kosilov et al 2015, Yamaguchi et al 2015).* A 12-month long-term trial of mirabegron and solifenacin also found the combination to be well tolerated with greater improvement in OAB symptoms as compared to monotherapy with either agent (*Gratzke et al 2018*). Similarly, the combination of low-dose trospium and solifenacin has also resulted in decreased frequency of incontinence in elderly patients with moderate symptoms *(Kosilov et al 2014).*

CLINICAL GUIDELINES

- Current consensus guidelines recommend the use of urinary antispasmodics in patients with OAB symptoms caused by detrusor overactivity with or without urgency incontinence. Behavioral therapies should generally be used as initial treatment (eg, bladder training, bladder control strategies, pelvic floor muscle training, and fluid management) with urinary antispasmodics recommended as second-line therapy or in combination with behavioral therapy *(American Urological Association 2019, Burkhard et al 2018, Lightner et al 2019, Qaseem et al 2014).*
- The American Geriatrics Society recommends avoiding anticholinergics, including oral antimuscarinics and flavoxate, in elderly patients with delirium, dementia or cognitive impairment due to worsening central nervous system AEs *(American Geriatric Society 2019).*
- No one urinary antispasmodic is recommended over another; however, ER formulations are associated with lower incidences of AEs and similar efficacy as compared to IR products. Due to different tolerability profiles, patients experiencing an AE or inadequate efficacy (despite dose optimization) with one antispasmodic agent may be switched to another agent within the class *(American Urological Association 2019, Burkhard et al 2018).* The American College of Physicians recommends the choice of pharmacologic treatment be based on AEs, tolerability, convenience, and cost *(Qaseem et al 2014)*.

SAFETY SUMMARY

- The anticholinergic urinary antispasmodics are contraindicated with uncontrolled narrow angle glaucoma and urinary retention. Flavoxate is contraindicated in patients with achalasia, pyloric or duodenal obstruction, obstructive intestinal lesions or ileus, gastrointestinal hemorrhage, and obstructive uropathy.

- Warnings and precautions for most of the anticholinergic agents include the risk of angioedema, decreased gastrointestinal motility, urinary retention, and central nervous system effects such as dizziness, somnolence, confusion, and hallucinations. Anticholinergic agents should be used with caution in patients with myasthenia gravis or ulcerative colitis. Ditropan XL should be used with caution in patients with Parkinson's disease.
- In general, due to the anticholinergic mechanism of action of the urinary antispasmodics, these agents are commonly associated with anticholinergic-related AEs. The most common AEs include dry mouth and constipation. AEs for mirabegron include hypertension, nasopharyngitis, urinary tract infection, and headache.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Darifenacin	Tablet (ER)	Oral	Once daily	• Do not exceed 7.5 mg/day with moderate hepatic impairment (Child-Pugh B) or when co-administered with potent CYP3A4 inhibitors; not recommended for use in severe hepatic impairment (Child-Pugh C).
Fesoterodine	Tablet (ER)	Oral	Once daily	• Not recommended for use in severe hepatic impairment (Child-Pugh C). • Do not exceed 4 mg/day in severe renal impairment (CrCL < 30 mL/min) or when co-administered with potent CYP3A4 inhibitors.
Flavoxate	Tablet	Oral	3 to 4 times daily	• With improvement of symptoms, the dose may be reduced.
Mirabegron	Tablet (ER)	Oral	Once daily	• Not recommended for use in ESRD or severe hepatic impairment (Child-Pugh C). • Do not exceed 25 mg/day in patients with severe renal impairment (CrCL 15 to 29 mL/min) or moderate hepatic impairment (Child-Pugh B).
Oxybutynin	Tablet (IR), tablet (ER), syrup, gel, transdermal patch	Oral, transdermal	Tablet (IR), Syrup: twice to 3 times daily Tablet (ER): once daily Gel: once daily Patch: once every 3 to 4 days (Oxytrol); once every 4 days (Oxytrol for Women)	• FDA-approved for use in children ≥ 5 years (IR) and ≥ 6 years (ER) • Dose adjustment of tablets (IR) is recommended in the frail elderly due to prolonged elimination half-life.
Solifenacin	Tablet	Oral	Once daily	• Do not exceed 5 mg/day in patients with severe renal impairment (CrCL < 30 mL/min), when co-administered with potent CYP3A4 inhibitors, and in moderate hepatic impairment (Child-Pugh B). • Not recommended for use in severe hepatic impairment (Child-Pugh C).
Tolterodine	Capsule (ER), tablet	Oral	Capsule (ER): once daily Tablet: twice daily	• Dose adjustment is required for the capsule (ER) in patients with severe renal impairment, mild to moderate hepatic impairment, and those co-

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				administered potent CYP3A4 inhibitors (2 mg once daily); not recommended for use in severe hepatic impairment (Child-Pugh C). • Capsule (ER) is not recommended in patients with CrCL < 10 mL/min. • Dose adjustment is required for the tablet in patients with significantly reduced hepatic or renal function or those currently taking potent CYP3A4 inhibitors (1 mg twice daily).
Trospium	Capsule (ER), tablet	Oral	Capsule (ER): once daily Tablet: twice daily	• Should be administered at least 1 hour before meals or on an empty stomach. • Dose adjustment is recommended in severe renal impairment for the tablet (20 mg once daily); capsule (ER) not recommended for use in severe renal impairment (CrCL < 30 mL/min). • Should be used with caution in patients with moderate to severe hepatic dysfunction.

Abbreviations: CrCL = creatinine clearance, CYP = cytochrome P450, ER = extended-release, ESRD = end-stage renal disease, IR = immediate-release

See the current prescribing information for full details.

CONCLUSION

- The urinary antispasmodics are FDA-approved for the management of OAB, defined as urinary urgency, with or without urge incontinence, usually with frequency and nocturia.
  - In the absence of treatment, urinary incontinence has been shown to greatly reduce quality of life in areas such as physical and social functioning, as well as mental and general health *(Coyne et al 2008).*
- The urinary antispasmodics include 2 classes of medications: muscarinic receptor antagonists include darifenacin (Enablex), fesoterodine (Toviaz), flavoxate, oxybutynin, solifenacin (Vesicare), tolterodine (Detrol), and trospium (Sanctura); and the beta-3 adrenergic agonist, mirabegron (Myrbetriq). The anticholinergic agents antagonize the effects of acetylcholine at muscarinic cholinergic receptors, thereby relaxing smooth muscle tissue in the bladder and consequently decreasing bladder contractions. In an effort to reduce dosing frequency and AEs, ER (LA, XL, and XR) formulations are available for oxybutynin (Ditropan XL), tolterodine (Detrol LA), and trospium.
  - Oxybutynin is the only agent that is also available in a topical gel (Gelnique) and transdermal patch (Oxytrol). Oxytrol for Women is an OTC transdermal patch for women ≥ 18 years for OAB treatment.
  - Mirabegron has a different mechanism of action and AE profile.
- The results from clinical studies have demonstrated each of the urinary antispasmodics to be more effective compared to placebo in regard to improvements in micturition frequency, urgency, and urge incontinence episodes. Head-to-head studies with the urinary antispasmodics have not consistently found one agent to be superior to other agents within the class.
- A 2012 Cochrane review reported that IR formulations of oxybutynin, tolterodine, and trospium have similar efficacy, but oxybutynin was associated with more AEs. In addition, solifenacin improved symptoms of OAB more so than tolterodine IR, while fesoterodine was more effective than tolterodine ER *(Madhuvrata et al 2012).*
- A 2018 AHRQ systematic review update of nonsurgical treatments for urinary incontinence in women concluded that behavioral therapy, alone or in combination with other interventions, is generally more effective than other first- or second-line interventions (including pharmacologic interventions) alone for both stress and urgency urinary incontinence (*Balk et al* 2018). For women with urgency urinary incontinence, anticholinergics were significantly more likely to result in "cure" (OR, 1.80; 95% CI, 1.29 to 2.52) or improvement (OR, 1.79; 95% CI, 1.18 to 2.7) as compared to placebo.

- Current consensus guidelines recommend the use of urinary antispasmodics in patients with OAB symptoms caused by detrusor overactivity with or without urgency incontinence. Behavioral therapies should generally be used as initial treatment (eg, bladder training, bladder control strategies, pelvic floor muscle training, and fluid management) with urinary antispasmodics recommended as second-line therapy or in combination with behavioral therapy. Anticholinergics should be avoided in elderly patients with delirium, dementia, or cognitive impairment. In general, ER formulations of urinary antispasmodics are associated with lower incidences of AEs with similar efficacy as compared to IR products. Pharmacologic treatment should be based on AEs, tolerability, convenience, and cost *(American Geriatric Society 2019, American Urological Association 2019, Burkhard et al 2018, Lightner et al 2019, Qaseem et al 2014*).

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Publication Date: March 10, 2020

Therapeutic Class Overview
Anti-gout agents

INTRODUCTION

- Gout is a form of inflammatory arthritis characterized by acute intermittent episodes of synovitis with joint swelling and pain; the episodes are referred to as acute gouty arthritis flares or attacks *(Newberry 2016).* The inflammation is induced by the deposition of monosodium urate (MSU) crystals in synovial fluid and other tissues. MSU crystal formation and deposition can occur during a state of hyperuricemia, which is typically defined as a serum uric acid (sUA) level > 6.8 mg/dL *(Neogi 2011).*
- Hyperuricemia can be caused by impaired renal excretion or overproduction of serum urate and/or overconsumption of purine-rich foods that are metabolized to urate. Humans lack the enzyme uricase and therefore cannot convert urate to the soluble allantoin (excreted in the urine) as the end product of purine metabolism. Hyperuricemia is a necessary but not sufficient precondition for the development of urate crystal deposition disease and should be distinguished from gout, the clinical syndrome. Most hyperuricemic individuals never experience a clinical event resulting from urate deposition *(Becker 2018).*
- Long-term success in achieving and maintaining sub-saturating sUA levels is associated with clinical benefits that include cessation of acute gout flares, resolution of tophi, and improvement in patient physical function and health-related quality of life (QOL) *(Becker 2018).*
- Lowering sUA levels can be achieved by decreasing uric acid production via xanthine oxidase inhibitors (XOIs) or by increasing excretion via uricosuric agents *(Becker 2018).*
  - The 2 XOIs available are Zyloprim (allopurinol) and Uloric (febuxostat). While both agents function as XOIs, they differ in their mechanism of action. Allopurinol acts as a purine analogue, while febuxostat occupies a channel in the xanthine oxidase (XO) dimer, impairing access to purine base substrates.
  - Probenecid is a uricosuric and renal tubular blocking agent. It inhibits the tubular reabsorption of urate, thus increasing the urinary excretion of uric acid.
  - Zurampic (lesinurad) is a uricosuric which inhibits uric acid transporter 1 (URAT1) and organic anion transporter 4 (OAT4), and is used in combination with an XOI for the treatment of hyperuricemia associated with gout.
  - Colchicine is the agent of choice for acute gout attacks, but it can also be used prophylactically. The exact mechanism of action of colchicine in gout is not completely known, however, it is effective for pain associated with an acute gout attack.
  - Pegloticase is a pegylated uricase, which stimulates the breakdown of uric acid. It is reserved for refractory cases of gout and is administered via intravenous (IV) infusion every 2 weeks.
- Combination products such as Duzallo (lesinurad/allopurinol) and probenecid/colchicine are also available and are included in this class review.
- Non-steroidal anti-inflammatory drugs (NSAIDs) are utilized as an alternative to colchicine for prophylaxis during the initiation of urate-lowering therapies *(Becker 2018)*. However, NSAIDs will not be included as part of this class review.
- Medispan class: Antigout Agent; Uric Acid Transporter 1 (URAT1) Inhibitor; Uricosuric agent; Xanthine Oxidase Inhibitor; Enzyme; Enzyme, Urate-Oxidase

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Colcrys (colchicine)†	✔
Duzallo (lesinurad/allopurinol)	-
Krystexxa (pegloticase)	-
Mitigare (colchicine)†	✔
probenecid	✔
probenecid/colchicine	✔
Uloric (febuxostat)	-

Drug	Generic Availability
Zurampic (lesinurad)	-
Zyloprim (allopurinol)	✔

†Colcrys and Mitigare are both branded colchicine products; both have authorized generics available.

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Colcrys (colchicine)	Duzallo (lesinurad/ allopurinol)	Krystexxa (pegloticase)	Mitigare (colchicine)	probenecid	probenecid/ colchicine	Uloric (febuxostat)	Zurampic (lesinurad)	Zyloprim (allopurinol)
Treatment and prophylaxis of gout flares in adults	✔			✔ ¥					
Chronic management of hyperuricemia in patients with gout							✔		
Treatment of chronic gout in adult patients refractory to conventional therapy			✔						
Treatment of hyperuricemia associated with gout		✔ *			✔			✔ **	
Management of patients with signs and symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy)									✔
Treatment of gouty arthritis when complicated by frequent, recurrent acute attacks of gout						✔			

*Duzallo is recommended for patients who have not achieved target sUA levels with a medically appropriate dose of allopurinol alone.
**Zurampic is recommended for patients who have not achieved target sUA levels with a XOI alone.
¥Mitigare is indicated for prophylaxis of gout flares only (not FDA-approved for the treatment of gout flares).

(*Prescribing information: Colcrys 2015, Duzallo 2017, Krystexxa 2016, Mitigare 2014, probenecid 2016, probenecid/colchicine 2016, Uloric 2018, Zurampic 2016, Zyloprim 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 EFFICACY SUMMARY

- Probenecid has been available since the 1950s and allopurinol and colchicine/probenecid have been available since the 1960s. Studies for these agents are therefore mainly limited to trials from the 1960s that were observational in nature. It should also be noted that there is limited literature evaluating the use of colchicine/probenecid.
- Colchicine was in use prior to the creation of the Food and Drug Administration (FDA), and therefore was "grandfathered" without receiving FDA approval. In 2006, however, colchicine was formally studied and officially approved under the brand name Colcrys. Mitigare, another brand of colchicine, was FDA-approved a few years later.

- A meta-analysis of 11 randomized controlled trials (RCTs) (n = 1258) was conducted in 2014 to assess the safety and efficacy of allopurinol (*Seth et al 2014*).
  - Moderate-quality evidence from 1 trial (n = 57) indicated that allopurinol 300 mg daily probably does not reduce the rate of gout attacks, but increases the proportion of participants achieving target sUA over 30 days.
  - In 2 studies (n = 453), there was no significant increase in withdrawals due to adverse effects (AEs) or serious AEs.
  - Low-quality evidence from 3 trials (n = 1136) indicated there may be no difference in the incidence of acute gout attacks with allopurinol up to 300 mg daily vs febuxostat 80 mg daily over 8 to 24 weeks (21% with allopurinol vs 23% with febuxostat, relative risk [RR] 0.89, 95% confidence interval [CI], 0.71 to 1.1); however more participants may achieve target sUA levels with febuxostat 80 mg daily vs allopurinol 300 mg daily (38% with allopurinol vs 70% with febuxostat, RR 0.56, 95% CI, 0.48 to 0.65).
- Colchicine's benefits and risks were examined in a meta-analysis conducted in 2014 (n = 124) (*Van Echteld et al 2014*).
  - Based upon pooled data from 2 trials, there was low-quality evidence that a greater proportion of patients receiving high-dose colchicine experienced a ≥ 50% decrease in pain from baseline up to 32 to 36 hours compared with placebo.
  - Only 1 trial included reduction of inflammation as part of a composite measure comprising pain, tenderness, swelling and erythema, each graded on a 4-point scale (none 0 to severe 3) to derive a maximum score for any 1 joint of 12. They reported the proportion of patients who achieved a 50% reduction in this composite score. Based upon 1 trial (n = 43), there was low-quality evidence that more patients in the high-dose colchicine group had a 50% or greater decrease in composite score from baseline up to 32 to 36 hours than patients in the placebo group.
- In a meta-analysis conducted in 2012, 6 febuxostat studies (n = 3978), were examined to determine the benefits and risks of febuxostat at multiple doses (*Tayar et al 2012*).
  - Patients taking febuxostat 120 mg and 240 mg reported more frequent gout flares vs placebo at 4 to 28 weeks (RR 1.7; 95% CI, 1.3 to 2.3, and RR 2.6; 95% CI, 1.8 to 3.7, respectively). No statistically significant differences were observed at febuxostat 40 mg and 80 mg. Compared to placebo, patients on febuxostat 40 mg were 40.1 times more likely to achieve sUA levels < 6.0 mg/dL at 4 weeks (95% CI, 2.5 to 639), with an absolute treatment benefit of 56% (95% CI, 37% to 71%). For febuxostat 80 mg and 120 mg, patients were 68.9 and 80.7 times more likely to achieve sUA levels < 6.0 mg/dL at their final visit compared to placebo (95% CI, 13.8 to 343.9; 95% CI, 16.0 to 405.5, respectively).
  - When comparing allopurinol to febuxostat at 24 to 52 weeks, the number of gout flares was not significantly different between the 2 groups, except for febuxostat 240 mg (RR 2.3; 95% CI, 1.7 to 3.0). Patients on febuxostat 40 mg showed no statistically significant differences in benefits or AEs. Patients on febuxostat 80 mg and 120 mg were 1.8 and 2.2 times more likely to achieve sUA levels < 6.0 mg/dL at their final visit, respectively, at 24 to 52 weeks.
- The combination of lesinurad with XOIs has been demonstrated to result in additive sUA lowering beyond that of XOIs alone. The Combining Lesinurad with Allopurinol in Inadequate Responders trials (CLEAR 1 and CLEAR 2) were replicate phase 3, 12-month, multicenter (MC), placebo-controlled (PC), double-blind (DB), RCTs (n = 603 and n = 610, respectively) assessing the efficacy and safety of lesinurad 200 mg and 400 mg once daily in combination with a patient's current stable dose of allopurinol (≥ 300 mg daily or ≥ 200 mg daily for those with moderate renal impairment) compared to placebo plus allopurinol. The primary endpoint was the proportion of patients achieving an sUA level < 6.0 mg/dL at month 6 (*Bardin et al 2016, Saag et al 2017).*
  - Results for CLEAR 1 showed that 54.2% and 59.2% of the lesinurad 200 mg and 400 mg daily plus allopurinol-treated groups, respectively, achieved the target sUA level compared to 27.9% of the placebo plus allopurinol-treated group at month 6 (both $p < 0.0001$ vs placebo + allopurinol).
  - Results for CLEAR 2 similarly showed that 55.4% and 66.5% of the lesinurad 200 mg and 400 mg daily plus allopurinol-treated groups, respectively, achieved the target sUA level compared to 23.3% of the placebo plus allopurinol-treated group at month 6 (both $p < 0.0001$ vs placebo + allopurinol).
  - The majority of gout patients inadequately responding to allopurinol alone who were treated with lesinurad plus allopurinol achieved a target sUA level by month 1 and this was maintained throughout both 12-month studies.
  - Key secondary endpoints [frequency of gout flares requiring treatment during months 6 to 12 and complete resolution of ≥ 1 target tophi by month 12 (in patients with target tophi at baseline)] were not met, possibly due to the low gout flare rates and a low number of patients with target tophi at baseline.
  - An increase in serum creatinine (sCr) (1.5 x baseline) was more prevalent in the lesinurad 400 mg group. These sCr increases were transient and reversible.

- The Combination Treatment Study in Subjects with Tophaceous Gout with Lesinurad and Febuxostat (CRYSTAL) was a third pivotal phase 3, 12-month, MC, PC, DB, RCT (n = 324) evaluating the efficacy and safety of lesinurad 200 mg and 400 mg once daily in combination with febuxostat 80 mg compared to placebo plus febuxostat in treatment-naïve and treatment-experienced patients with tophaceous gout and elevated sUA levels (*Dalbeth et al 2017*).
  - Lesinurad 200 mg or 400 mg once daily in combination with febuxostat significantly increased the proportion of patients achieving sUA target (< 5.0 mg/dL) at all monthly visits from months 1 to 12, except for the lesinurad 200 mg + febuxostat group at month 6, compared to febuxostat alone in patients with tophaceous gout.
  - Although treatment with lesinurad + febuxostat resulted in a greater area of tophus resolution compared to febuxostat alone and an increase in the proportion of patients with complete resolution of ≥ 1 target tophi, these endpoints were not statistically significant.
- The FDA approval of pegloticase was based on two 6-month, replicate, MC, DB, PC, RCTs. Adult patients with chronic gout refractory to conventional therapy who were randomized to receive pegloticase 8 mg IV every 2 weeks, every 4 weeks, or placebo. The primary endpoint in both trials was the proportion of patients who achieved sUA < 6 mg/dL for at least 80% of the time during month 3 and month 6 (*Sundy et al 2011)*.
  - sUA normalized within 24 hours of the first infusion in all patients receiving pegloticase, but afterward, some patients lost the urate-lowering response, whereas others maintained sUA < 6.0 mg/dL throughout the trial. Data showed that a greater proportion of patients treated with pegloticase every 2 weeks achieved urate lowering to below 6 mg/dL than patients receiving placebo. In trial 1, when pegloticase was dosed at 8 mg every 2 weeks, 47% of patients responded with sUA in the target range. When pegloticase was dosed at 8 mg every 4 weeks, 20% responded vs none in the placebo group. In trial 2, when pegloticase was dosed at 8 mg every 2 weeks, 38% of patients responded. With pegloticase 8 mg every 4 weeks, 49% of patients responded, while none of the placebo patients responded.
  - Forty percent of patients in the biweekly pegloticase group and 21% in the monthly group had a complete response for ≥ 1 tophi by the final visit compared with 7% of patients receiving placebo (p = 0.002 and p = 0.20, respectively). Both pegloticase dosing groups reported significant improvements in physical function and QOL compared with placebo.

CLINICAL GUIDELINES

- The American College of Physicians (ACP) published guidelines in 2016 for the management of acute and recurrent gout (*Qaseem et al 2017*).
  - Corticosteroids, NSAIDs, or colchicine (low-dose preferred) are recommended to treat patients with acute gout.
  - ACP recommends against initiating long-term urate-lowering therapy in most patients after a first gout attack or in patients with infrequent attacks.
  - Febuxostat (40 mg/day) and allopurinol (300 mg/day) are equally effective at decreasing sUA levels.
  - Data on the most appropriate duration of urate-lowering therapy are insufficient. However, moderate to high quality evidence suggests that urate-lowering therapy reduces the risk for acute gout attacks after 1 year, but not within the first 6 months of treatment.
- In 2012, the American College of Rheumatology (ACR) published guidelines for the management of gout. Some key points include:
  - An XOI, ie, allopurinol or febuxostat, is recommended as the first-line pharmacologic urate-lowering therapy.
  - Probenecid is recommended as an alternative first-line pharmacologic urate-lowering therapy option in the setting of contraindication or intolerance to at least 1 XOI agent.
  - sUA level should be lowered sufficiently to durably improve signs and symptoms of gout, with a target of < 6 mg/dL at a minimum, and often < 5 mg/dL.
  - Combination oral urate-lowering with 1 XOI and 1 uricosuric agent is appropriate when the sUA target has not been met by therapeutically-appropriate doses of an XOI monotherapy.
  - If sUA target is not achieved, a uricosuric agent (titrated to maximum appropriate dose) can be added.
  - If sUA target still has not been achieved, then pegloticase can be considered. Pegloticase is appropriate for patients with severe gout disease burden and refractoriness to, or intolerance of, appropriately dosed oral urate-lowering options.
- A 2016 update to the European League Against Rheumatism (EULAR) 2006 guidelines for the management of gout makes the following key recommendations (*Richette et al 2016*):
  - Recommended first-line options for acute flares are colchicine (within 12 hours of flare onset) at a loading dose of 1 mg followed 1 hour later by 0.5 mg on day 1 and/or an NSAID (plus proton pump inhibitor if appropriate), oral

corticosteroid, or articular aspiration and injectable corticosteroids. Colchicine and NSAIDs should be avoided in patients with severe renal impairment.
- In patients with normal renal function, allopurinol is recommended for first-line urate-lowering therapy, starting at a low dose (100 mg/day) and increasing by 100 mg increments every 2 to 4 weeks if required, to reach the sUA target. If the sUA target cannot be reached by an appropriate dose of allopurinol, allopurinol should be switched to febuxostat or a uricosuric or combined with a uricosuric. Febuxostat or a uricosuric are also indicated if allopurinol cannot be tolerated.
- In patients with crystal-proven, severe debilitating chronic tophaceous gout and poor QOL, in whom the sUA target cannot be reached with any other available drug at the maximal dosage (including combinations), pegloticase is indicated.

SAFETY SUMMARY

- **Contraindications**
  - Colchicine is contraindicated in patients with renal or hepatic impairment who are taking a P-glycoprotein or strong cytochrome P450 (CYP) 3A4 inhibitor, due to the potential for life-threatening and fatal colchicine toxicity.
  - Febuxostat is contraindicated in patients being treated with azathioprine or mercaptopurine.
  - Lesinurad is contraindicated in patients with severe renal impairment (creatinine clearance [Clcr] < 30 mL/min), end-stage renal disease, kidney transplant recipients, or patients on dialysis. Lesinurad should also be avoided in patients with tumor lysis syndrome or Lesch-Nyhan syndrome.
  - Pegloticase is contraindicated in patients with G6PD deficiency, due to risk of hemolysis and methemoglobinemia.
  - Probenecid is contraindicated in patients with known blood dyscrasias or uric acid kidney stones.
- **Boxed Warnings**
  - Lesinurad-containing products
    - Acute renal failure has occurred with lesinurad, especially when lesinurad was given alone.
    - Lesinurad should be used in combination with an XOI.
  - Pegloticase
    - Anaphylaxis may occur with any infusion, and generally manifests within 2 hours of the infusion. However, delayed-type hypersensitivity reactions have also been reported. Patients should be pre-medicated with anti-histamines and corticosteroids.
- **Warnings**
  - With the majority of these agents (except for colchicine), gout prophylaxis should be continued at the initiation of therapy, due to risk of gout flares.
  - The febuxostat product information carries a warning about cardiovascular events based on pre-approval clinical trials that showed a higher rate of cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes compared to allopurinol *(FDA 2017).*
    - The FDA issued a drug safety communication alerting the public that the preliminary results from a required safety clinical trial show an increased risk of cardiac-related death with febuxostat compared to allopurinol.
      - The preliminary results show that overall, febuxostat did not increase the risk of cardiac-related death compared to allopurinol. However, when the outcomes were evaluated separately, febuxostat showed an increased risk of cardiac-related deaths and death from all causes.
  - The FDA approved a new warning for skin reactions that was added to the febuxostat product information in February 2018. Post marketing reports of serious skin and hypersensitivity reactions, including Stevens-Johnson Syndrome, drug reaction with eosinophilia and systemic symptoms, and toxic epidermal necrolysis have been reported in patients taking febuxostat. Anaphylaxis and severe allergic reactions have been reported with allopurinol (especially in patients with renal failure), pegloticase (boxed warning), and probenecid.
  - Caution should be used in patients with hepatic impairment when taking allopurinol or febuxostat.
  - Caution should also be used when administering allopurinol and lesinurad in patients with renal insufficiency.
  - Bone marrow suppression has been reported after allopurinol initiation, and blood dyscrasias have been reported at therapeutic doses of colchicine.
- **Adverse Effects**
  - Liver function abnormalities may be seen with allopurinol, febuxostat, and probenecid.
  - Rash has been noted with allopurinol and febuxostat.
  - Nausea, vomiting, gout flares, and headache are AEs that have been observed with most of the agents in this review.
- **Drug Interactions**

- Allopurinol and febuxostat inhibit XO, which can cause an increase in azathioprine and mercaptopurine levels when given concomitantly. The dose of azathioprine or mercaptopurine will require reduction when used concomitantly with allopurinol. Concomitant use of either of these agents with febuxostat is contraindicated.
- Increased colchicine levels can be seen when used with strong CYP 3A4 inhibitors.
- When administered with probenecid, an increase in methotrexate and NSAID levels may be seen.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Colcrys (colchicine)	Tablets	Oral	Prophylaxis: Once or twice daily Treatment: 2 tablets at first sign of gout flare, followed by 1 tablet 1 hour later	Dosage adjustment of prophylactic dose recommended in patients with severe renal or hepatic failure
Duzallo (lesinurad/allopurinol)	Tablets	Oral	Once daily	Should be taken with food and water; should not be initiated or continued in patients with a CLcr < 45 mL/min; not recommended in patients with severe hepatic impairment
Krystexxa (pegloticase)	Injection	IV	Every 2 weeks	Should not be administered via IV push or bolus; premedication is recommended
Mitigare (colchicine)	Capsules	Oral	Once or twice daily	Dose adjustments should be considered in patients with severe renal and/or hepatic impairment
probenecid	Tablets	Oral	Twice daily	Should not be started until acute gouty attack has subsided; dose adjustments may be necessary in patients with renal impairment
probenecid/colchicine	Tablets	Oral	Once daily for 1 week, then twice daily	Should not be started until acute gouty attack has subsided; dose adjustments may be necessary in patients with renal impairment
Uloric (febuxostat)	Tablets	Oral	Once daily	Dose should be limited in patients with severe renal impairment
Zurampic (lesinurad)	Tablets	Oral	Once daily	Should be taken in combination with an XOI; should not be initiated or continued in patients with a CLcr < 45 mL/min; not recommended in patients with severe hepatic impairment
Zyloprim (allopurinol)	Tablets	Oral	In divided doses for doses > 300 mg	Dose should be adjusted in patients with renal failure; better tolerated when taken following meals

See the current prescribing information for full details

CONCLUSION

- Gout is a form of inflammatory arthritis characterized by acute intermittent episodes of synovitis presenting with joint swelling and pain; the episodes are referred to as acute gouty arthritis flares or attacks *(Newberry 2016).* The inflammation is induced by the deposition of MSU crystals in synovial fluid and other tissues. MSU crystal formation and deposition can occur during a state of hyperuricemia, which is typically defined as an sUA level > 6.8 mg/dL *(Neogi 2011).*
- Lowering sUA levels can be achieved by decreasing uric acid production via XOIs (ie, allopurinol or febuxostat) or by increasing excretion with agents such as probenecid and lesinurad *(Becker 2018).*
- XOIs are the preferred treatment for lowering sUA, while colchicine is the preferred treatment for acute gout attacks.
- With the majority of these agents, gout prophylaxis should be continued at the initiation of therapy, due to risk of gout flares.
- The FDA recently issued a drug safety communication alerting the public that preliminary results from a required safety clinical trial show an increased risk of cardiac-related death with febuxostat compared to allopurinol. Overall, febuxostat did not increase the risk of cardiac-related death compared to allopurinol. However, when the outcomes were evaluated separately, febuxostat showed an increased risk of cardiac-related deaths and death from all causes (*FDA 2017).*
- Lesinurad and pegloticase carry boxed warnings for acute renal failure and anaphylaxis, respectively.
- Caution should be used when prescribing anti-gout medications, as several agents in this class have a number of potential drug-drug interactions.
- Pegloticase, the only IV anti-gout agent, should be utilized only in advanced, tophaceous, and symptomatic gout cases that are refractory to other anti-gout medications (*Becker 2018).*

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Publication Date: May 2, 2018

Therapeutic Class Overview
Ophthalmics, Antibiotics, and Combinations

INTRODUCTION

- Blepharitis is a chronic inflammatory condition of the eyelids, often presenting with symptoms of eye irritation and redness. Overgrowth of normal bacterial flora plays a role in the pathophysiology of blepharitis, with the most common causative organisms being *Staphylococcus* species. The mainstay of the treatment of blepharitis is patient education regarding eyelid hygiene as well as the use of ophthalmic antibiotics. Of note, blepharitis is a chronic condition without definitive cure; therefore, satisfactory results require a long-term commitment to treatment and appropriate expectations. Ophthalmic corticosteroids may also be used acutely to treat exacerbations (*American Academy of Ophthalmology [AAO] 2018b*).
- Bacterial conjunctivitis rarely causes permanent visual loss or structural damage, as mild cases may be self-limited, and will resolve without treatment in immunocompetent individuals. The most common causative pathogens seen with bacterial conjunctivitis include *Staphylococcus (S.) aureus, Streptococcus pneumoniae, Haemophilus influenzae,* and *Moraxella catarrhalis*. Use of ophthalmic antibiotics is associated with earlier clinical and microbiological remission when compared to placebo. The selection of an ophthalmic antibiotic is typically empirical, and the most convenient or least expensive ophthalmic antibiotic is typically effective for most cases of conjunctivitis (*AAO 2018c; American Optometric Association [AOA] 2007*).
- Severe bacterial conjunctivitis is characterized by purulent discharge, pain, and marked eye inflammation. In these cases, cultures and slides for gram staining should be obtained, and the results of these laboratory tests should guide the choice of the antibiotic. Methicillin-resistant *S. aureus* has been isolated in patients with bacterial conjunctivitis with increasing frequency and may be resistant to many available ophthalmic antibiotics. In patients with conjunctivitis caused by *Neisseria (N.) gonorrhoeae* and *Chlamydia (C.) trachomatis*, systemic antibiotic therapy is necessary, and while not necessary, ophthalmic antibiotics are also typically used (*AAO 2018c; AOA 2007*).
- Bacterial keratitis is characterized by an inflammation of the cornea and rarely occurs in the normal eye due to the cornea's natural resistance to infection. However, several predisposing factors such as contact lens wear, trauma, corneal surgery, ocular surface disease, systemic disease, and immunosuppression may alter the defense mechanisms of the ocular surface and allow for infection of the cornea. Due to corneal scarring or topographic irregularity, many forms of this infection result in visual loss. Untreated or severe bacterial keratitis can result in corneal perforation and may develop into endophthalmitis and result in the loss of the eye. The most common causative organisms of bacterial keratitis include *Staphylococci* and gram-negative rods, of which the most frequent organisms identified are *Pseudomonas* species. Ophthalmic antibiotics are the preferred method of treatment in many cases, and antibiotic ointments may be useful at bedtime in less severe cases or as adjunctive therapy. In severe cases, patients should be followed daily until stabilization or clinical improvement is documented (*AAO 2018a*).
- Though not Food and Drug Administration (FDA)-approved for this indication, ophthalmic antibiotics are routinely used to prevent postoperative infections after eye surgeries such as refractive surgeries and cataract removal, while ophthalmic corticosteroids may also be used to reduce inflammation associated with surgeries (*AAO 2016; AAO 2017; AOA 2004*).
- Ophthalmic antibiotic and steroid combinations are included in this review.
- Medispan class: Ophthalmic Antibiotics, Ophthalmic Anti-infective Combinations, Ophthalmic Sulfonamides, and Ophthalmic Steroid Combinations.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Aminoglycosides	
Gentak (gentamicin)* ointment & solution	✔
Tobrex (tobramycin) ointment & solution	✔ †
Macrolides	
Azasite (azithromycin) solution	-
erythromycin ointment	✔
Other	
Bacitracin ointment	✔
Bleph-10 (sulfacetamide sodium)§ ointment & solution	✔
Quinolones	
Besivance (besifloxacin) suspension	-
Ciloxan (ciprofloxacin) ointment & solution	✔ †
levofloxacin solution	✔
Moxeza, Vigamox (moxifloxacin) solution	✔ ‖
Ocuflox (ofloxacin) solution	✔
Zymaxid (gatifloxacin) solution	✔
Combinations	
Neo-Polycin (bacitracin/neomycin/polymyxin) ointment	✔
Neo-Polycin HC (bacitracin/neomycin/polymyxin/hydrocortisone) ointment	✔
AK-Poly-Bac, Polycin (bacitracin/polymyxin) ointment	✔
Blephamide (sulfacetamide/prednisolone 10-0.2%) ointment & suspension	-
sulfacetamide/prednisolone 10-0.23% (0.25%) solution	✔
Maxitrol (neomycin/polymyxin/dexamethasone) ointment & suspension	✔
neomycin/polymyxin/hydrocortisone suspension	✔
gramicidin/neomycin/polymyxin solution	✔
Pred-G (gentamicin/prednisolone) ointment & suspension	-
Polytrim (polymyxin/trimethoprim) solution	✔
Tobradex (tobramycin/dexamethasone 0.3-0.1%) ointment & suspension	✔ **
Tobradex ST (tobramycin/dexamethasone 0.3-0.05%) suspension	-
Zylet (tobramycin/loteprednol) suspension	-

*Gentak is a branded generic of gentamicin ophthalmic ointment.
†Solution only
§Brand name Bleph-10 is available in solution only; generics are available for solution and ointment.
‖Multiple generic versions of Vigamox are available; a single generic version of Moxeza is available.
**Suspension only

(*Drugs@FDA, 2020; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2020; Drug Facts and Comparisons, 2020; Clinical Pharmacology, 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Agents within this review that contain ocular corticosteroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea, and anterior segment of the globe where the inherent risk of corticosteroid use in certain infective conjunctivitis is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation or thermal burns; or penetration of foreign bodies.

Indication	Aminoglycosides		Macrolides		Other		Quinolones							Combinations										
	gentamicin	tobramycin	Azasite	erythromycin	bacitracin	sulfacetamide	ciprofloxacin	levofloxacin	ofloxacin	Besivance	Moxeza	Vigamox	Zymaxid	bacitracin/neomycin/polymyxin	bacitratin/neomycin/polymyxin/hydrocortisone	bacitracin/polymyxin	Blephamide	Maxitrol	neomycin/polymyxin/hydrocortisone	gramicidin/neomycin/polymyxin	Pred-G	polymyxin/trimethoprim	Tobradex; Tobradex ST	Zylet
Treatment of bacterial conjunctivitis			✔				✔	✔	✔	✔	✔	✔	✔											
Treatment of corneal ulcers							✔ †		✔															
Treatment of external infections of the eye and its adnexa caused by susceptible bacteria		✔												✔		✔ *				✔				
Treatment of superficial ocular infections involving the conjunctiva and/or cornea				✔	✔											✔ ‖								
Prophylaxis of ophthalmia neonatorum due to *N. gonorrhoeae* or *C. trachomatis*				✔ §																				
Treatment of ocular bacterial infections including conjunctivitis, keratitis, keratoconjunctivitis, corneal ulcers, blepharitis, blepharoconjunctivitis, acute meibomianitis, and dacryocystitis	✔																							

Indication	Aminoglycosides		Macrolides		Other		Quinolones							Combinations									
	gentamicin	tobramycin	Azasite	erythromycin	bacitracin	sulfacetamide	ciprofloxacin	levofloxacin	ofloxacin	Besivance	Moxeza	Vigamox	Zymaxid	bacitracin/neomycin/polymyxin	bacitratin/neomycin/polymyxin/hydrocortisone	bacitracin/polymyxin	Blephamide	Maxitrol	neomycin/polymyxin/hydrocortisone	gramicidin/neomycin/polymyxin	Pred-G	polymyxin/trimethoprim	Tobradex; Tobradex ST	Zylet
Treatment of surface ocular infections, including acute bacterial conjunctivitis and blepharoconjunctivitis																						✔		
Treatment of conjunctivitis and other superficial ocular infections						✔																		
Adjunctive treatment with systemic treatment for trachoma						✔ †																		
Steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where bacterial ocular infection or a risk of bacterial ocular infection exists															✔		✔	✔	✔		✔		✔	✔

†solution only
§ The effectiveness of erythromycin in the prevention of ophthalmia caused by penicillinase-producing *N. gonorrhoeae* is not established.
*Polycin brand only
‖generic and AK-Poly-Bac brand only

(*Prescribing information: AK-Poly-Bac 2018; Azasite, 2017; bacitracin, 2019; bacitracin/neomycin/polymyxin, 2016; bacitracin/neomycin/polymyxin/hydrocortisone, 2016; bacitracin/polymyxin, 2020; Besivance, 2020; Bleph-10, 2017; Blephamide ointment, 2018; Blephamide suspension, 2017; Ciloxan ointment, 2019; Ciloxan solution, 2019; erythromycin, 2018; Gentak, 2017; gentamicin, 2017; levofloxacin, 2017; Maxitrol suspension, 2019; Maxitrol ointment, 2019; Moxeza, 2019; Neo-Polycin 2018; Neo-Polycin HC 2018; neomycin/polymyxin/gramicidin 2016; neomycin/polymyxin/hydrocortisone, 2019; Ocuflox, 2017; Polycin 2018; polymyxin/trimethoprim, 2020; Polytrim, 2019; Pred-G ointment, 2018; Pred-G suspension, 2018; sulfacetamide ointment, 2018; sulfacetamide solution, 2016; sulfacetamide/prednisolone solution, 2016; Tobradex ointment, 2020; Tobradex suspension, 2020; Tobradex ST, 2019; tobramycin 2020; Tobrex ointment, 2020; Tobrex solution, 2020; Vigamox, 2019; Zylet, 2019; Zymaxid, 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

Antibiotics

- Clinical trials have demonstrated that ophthalmic antibiotics are effective in treating and providing relief of bacterial conjunctivitis in pediatric and adult patients (*Abelson et al 2007; Abelson et al 2008; Bremond-Gignac et al 2014; Cochereau et al 2007; DeLeon et al 2012; Gross et al 1997; Hwang et al 2003; Karpecki et al 2009; Kernt et al 2005; McDonald et al, 2009; Schwab et al 2003; Sheikh et al 2012; Silver et al 2005; Silverstein et al 2011; Silverstein et al, 2012; Tauber et al 2011; Tepedino et al 2009; Williams et al 2013*). Several studies comparing ophthalmic antibiotics such as azithromycin, besifloxacin, levofloxacin, and moxifloxacin to placebo have concluded that these medications resulted in significantly higher clinical resolution rates at days 1 through 5 (*Abelson et al 2008; DeLeon et al 2012; Hwang et al 2003; Karpecki et al 2009; Silverstein et al 2011; Tauber et al 2011; Tepedino et al 2009*).
  - One clinical trial demonstrated that there was no difference in clinical cure rate between treatment with ophthalmic polymyxin B/trimethoprim and ophthalmic moxifloxacin in treating conjunctivitis in children (p = 0.59) (*Williams et al 2013*). In a 5-day trial, a higher percentage of patients receiving levofloxacin had microbial eradication at the final visit compared to patients receiving ofloxacin for the treatment of bacterial conjunctivitis (p = 0.034); however, clinical cure rates were similar between the 2 treatments (p value not reported) (*Schwab 2003*).
  - Most other studies have shown no significant difference between ophthalmic antibiotic treatments with regard to bacterial eradication, clinical resolution, clinical response, efficacy, microbial eradication, physician's judgment of resolution, severity rating, or symptom improvement (*Ableson et al 2007; Cochereau et al 2007, Gross et al 1997; McDonald et al 2009; Sanfilippo et al 2017; Silver et al 2005*). While no difference was found between ophthalmic formulations of azithromycin and tobramycin with regard to clinical resolution and bacterial eradication, ophthalmic azithromycin produced the same clinical outcome with 65% fewer drops (*Abelson et al 2007*). In all studies, most adverse events were mild with no significant difference seen with regard to the rate of adverse events. Common adverse events included burning, ocular discomfort, stinging, and tearing (*Abelson et al 2007; Cochereau et al 2007; Gross et al 1997; McDonald et al 2009; Schwab et al 2003; Silver et al 2005; Williams et al 2013*).
  - A number of studies consisted of patients with multiple diagnoses such as blepharitis, blepharoconjunctivitis, bacterial conjunctivitis, keratoconjunctivitis, or symptoms of surface ocular infections. These studies found that the ophthalmic formulations of gentamicin, levofloxacin, ofloxacin, and tobramycin solution were efficacious in resolving or curing multiple ocular infections (*Gwon 1992 Sep; Gwon 1992 Dec; Kanda et al 2012*). No significant differences were observed in any study with regard to cure rates, decline in bacterial counts, bacterial eradication or reduction of bacteria, microbial improvement, or overall improvement. In one study, ophthalmic ofloxacin was shown to significantly decrease the cumulative summary score on days 3 through 5 in patients with conjunctival hyperemia, eyelid crusting or discharge, and positive bacterial culture when compared to ophthalmic tobramycin ($p < 0.05$); however, by day 11, there were no significant differences between the 2 treatments with regard to clinical, microbial, and overall improvement rates (*Gwon 1992 Sep*). In studies of patients with multiple diagnoses, the most commonly reported adverse events were similar between treatment groups. The most common adverse events included burning, mild discomfort, and stinging on instillation.
  - In one study evaluating the treatment of ophthalmia neonatorum, conjunctivitis in newborn babies principally caused by *N. gonorrhoeae*, prophylaxis with ophthalmic erythromycin ointment was found to be most effective prior to the infant's second week of life. The efficacy of ophthalmic erythromycin prophylaxis from days 0 to 14 was statistically significant when compared to no prophylaxis; however, the efficacy was not significant from days 15 to 60 (14 vs 9%; p = 0.05 and 7 vs 8%; p = 0.92, respectively) (*Bell et al 1993*). In another study, ophthalmic erythromycin prophylaxis resulted in significantly fewer reports of conjunctival redness and tearing or serious or purulent discharge during the first 24 hours to 2 weeks of life when compared to no prophylaxis (18.4 vs 22.4%; p = 0.03) (*Ali et al 2007*).

Antibiotic-steroid combinations

- Clinical trials have demonstrated that ophthalmic antibiotic-steroid combination products are effective in treating patients with external ocular infections, including bacterial blepharitis, conjunctivitis, and blepharokeratoconjunctivitis (*Rhee et al 2007; Shulman et al 1996; White et al 2008*).
  - In one study involving patients with moderate blepharokeratoconjunctivitis, reductions in blepharitis and conjunctivitis symptom scores were greater with ophthalmic tobramycin/dexamethasone therapy compared to ophthalmic tobramycin/loteprednol therapy, while the reductions in keratitis symptom scores were similar between the 2 treatment groups (*Rhee et al 2007*).

- In another study, the reduction in composite symptom scores in patients with blepharokeratoconjunctivitis was similar between the tobramycin/dexamethasone and tobramycin/loteprednol groups; however, the increase in intraocular pressure was significantly greater with tobramycin/dexamethasone than tobramycin/loteprednol (White et al 2008). Another pooled analysis of data from 2 trials in patients with blepharokeratoconjunctivitis who were randomized to either tobramycin/dexamethasone or tobramycin/loteprednol found similar effects on blepharitis severity; however, tobramycin/loteprednol demonstrated a better safety profile with respect to intraocular pressure (Comstock 2017).
- Another study involving patients with moderate to severe acute blepharitis/blepharoconjunctivitis showed initial therapy with the combination of tobramycin/dexamethasone ST provides faster inflammation relief than ophthalmic azithromycin based on a statistically significant lower mean global score ($p = 0.0002$) (Torkildsen et al 2011).
- One study showed that when compared to dexamethasone alone, neomycin/polymyxin B/dexamethasone resulted in significantly greater bacterial eradication and decrease in bacterial count in patients with bacterial blepharitis or conjunctivitis; however, the reduction in signs and symptoms of ocular infection was similar between the 2 treatment groups (Shulman et al 1996).
- In a study involving patients undergoing cataract extraction by either manual extraction or phacoemulsification with intraocular lens implantation, ophthalmic tobramycin/dexamethasone was non-inferior to ophthalmic neomycin/polymyxin B/dexamethasone concerning inflammation scores at days 3, 8, 14, and 21. Inflammation scores in the ophthalmic tobramycin/dexamethasone group were significantly lower than scores seen in the ophthalmic neomycin/polymyxin B/gramicidin group at days 8, 14, and 21 ($p < 0.05$ for all), and scores in the ophthalmic neomycin/polymyxin B/dexamethasone group were significantly lower than those seen in the ophthalmic neomycin/polymyxin B/gramicidin group at day 8 ($p < 0.05$) (Notivol et al 2004).
- In patients undergoing cataract and posterior chamber lens implant surgery, treatment with ophthalmic gentamicin resulted in lower bacterial colony count compared to ophthalmic neomycin/polymyxin B/dexamethasone at days 6 and 8 ($p = 0.033$); however, there was no significant difference between the 2 groups with regard to the degree of intraocular inflammation or the global assessment of the success of therapy and local tolerance (p value not reported) (Van Endt et al 1997). In a separate study involving patients undergoing cataract extraction by either manual extraction or phacoemulsification with intraocular lens implantation, ophthalmic tobramycin/dexamethasone was non-inferior to ophthalmic neomycin/polymyxin B/dexamethasone concerning inflammation scores at days 3, 8, 14, and 21. Inflammation scores in the ophthalmic tobramycin/dexamethasone group were significantly lower than scores seen in the ophthalmic neomycin/polymyxin B/gramicidin group at days 8, 14, and 21 ($p < 0.05$ for all), and scores in the ophthalmic neomycin/polymyxin B/dexamethasone group were significantly lower than those seen in the ophthalmic neomycin/polymyxin B/gramicidin group at day 8 ($p < 0.05$) (Notivol et al 2004).

CLINICAL GUIDELINES

- The AAO preferred practice pattern (PPP) states that bacterial keratitis should be treated with an ophthalmic antibiotic that may be selected based on the isolated organism; if no organism is identified, treatment with cefazolin or vancomycin plus either gentamicin or tobramycin or an ophthalmic fluoroquinolone alone is recommended. The AAO guideline also notes that fewer gram-positive cocci are resistant to ophthalmic gatifloxacin, moxifloxacin, and besifloxacin than other fluoroquinolones. Topical antibiotic eye drops are capable of achieving high tissue levels and are the preferred method of treatment in most cases. Ocular ointments may be useful at bedtime in less severe cases and may be useful for adjunctive therapy. Ointments lack solubility and are not able to penetrate into the cornea significantly for optimum therapeutic benefit (*AAO 2018a*).
- The AAO PPP recommends that initial treatment of blepharitis is to use warm compresses on the eyelids and incorporate eyelid cleansing, with or without hypochlorous acid based cleansers, and eyelid massage. The AAO PPP also states that topical ophthalmic antibiotics such as bacitracin or erythromycin ointments may reduce symptoms of blepharitis; the guideline also notes that tobramycin/dexamethasone ophthalmic suspension and ophthalmic azithromycin have been shown to reduce some signs and symptoms of blepharitis. To prevent resistance, topical antibiotics with different mechanisms of action can be used intermittently if needed (*AAO 2018b*).
- For the treatment of bacterial conjunctivitis, the AAO PPP states that indiscriminate use of topical antibiotics or corticosteroids should be avoided, because antibiotics can induce toxicity and corticosteroids can potentially prolong or worsen some infections. If treatment is warranted, it is recommended that the least expensive or most convenient broad-spectrum topical antibiotic be selected for a 5- to 7-day course of treatment. Systemic antibiotic therapy is necessary to treat conjunctivitis due to *N. gonorrhoeae* and *C. trachomatis*, and topical therapy may be used concomitantly (*AAO 2018c; AOA 2007*).

- Short-term use of ophthalmic corticosteroids is recommended to reduce inflammation in the treatment of blepharitis, conjunctivitis, and keratitis, and can be considered in postoperative prophylaxis (*AAO 2016; AAO 2018a; AAO 2018b; AAO 2018c*).
- The AAO cataract in the adult eye PPP states that postoperative regimens of topically applied antibiotics, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and oral analgesic agents vary among practitioners. There are no controlled investigations that establish optimal regimens for the use of topical agents. Therefore, it is the decision of the operating surgeon to use any or all of these products singly or in combination (*AAO 2016*).
- The United States Preventative Services Task Force (USPSTF) recommends ophthalmia neonatorum prophylaxis with erythromycin ophthalmic ointment for all newborns (*USPSTF 2019*).

SAFETY SUMMARY

- Products are contraindicated if there is a hypersensitivity to any component.
- Warnings/precautions of anti-infective agents include the following: 1) do not wear contact lenses while infected; 2) prolonged use may result in overgrowth of non-susceptible organisms, including fungi; and 3) cutaneous sensitization may occur with products containing neomycin.
  - The most frequent adverse effects were burning, stinging, and irritation upon instillation, redness, blurred vision, itching, swelling, tearing, eye pain, and photophobia. Non-ocular reactions can occur and include headache, pharyngitis, dizziness, and allergic reactions.
- Prolonged use of corticosteroids may result in the following: development of glaucoma, corneal or scleral thinning which can lead to perforation, suppression of host response causing secondary infection, and/or purulent infections of the eye may be masked or activity enhanced.
  - If using these products for longer than 10 days, IOP should be monitored. Use after cataract surgery may delay healing.
  - Blephamide (sulfacetamide/prednisolone) may cause acute anterior uveitis in susceptible individuals. The p-aminobenzoic acid present in purulent exudates competes with sulfonamides and can reduce their effectiveness.
- Reactions occurring most often from the presence of the anti-infective ingredient are allergic sensitization reactions including itching, swelling, and conjunctival erythema. The reactions due to the corticosteroid component are elevation of IOP with possible development of glaucoma, and infrequent optic nerve damage; posterior subcapsular cataract formation; and delayed wound healing.
- These agents are minimally absorbed; therefore, drug interactions are not likely to occur.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Usual Recommended Frequency	Comments
Azasite (azithromycin)	Ophthalmic solution: 1%	Twice daily, 8 to 12 hours apart for the first 2 days, then once daily for the next 5 days	Safety and efficacy have not been established in children < 1 year of age.
Bacitracin	Ophthalmic ointment: 500 units/gram	Apply directly into the conjunctival sac 1 to 3 times daily	No data in pediatric patients.
Besivance (besifloxacin)	Ophthalmic suspension: 0.6%	Three times daily, 4 to 12 hours apart for 7 days	Safety and efficacy have not been established in children < 1 year.
Bleph-10 (sulfacetamide sodium)	Ophthalmic ointment: 10% Ophthalmic solution: 10%	**Ointment**: every 3 to 4 hours and at bedtime for 7 to 10 days **Solution**: every 2 to 3 hours for 7 to 10 days *Trachoma*: every 2 hours; must also use systemic administration	Safety and efficacy have not been established in infants < 2 months of age.
Ciloxan (ciprofloxacin)	Ophthalmic ointment: 0.3% Ophthalmic solution: 0.3%	**Corneal ulcers**: *Solution*: every 15 minutes for the first 6 hours, every 30 minutes for the remainder of the first day. Second day: every hour	**Ointment**: Safety and efficacy have not been established in children < 2 years of age. **Solution**: Safety and efficacy have been established in all

Drug	Available Formulations	Usual Recommended Frequency	Comments
		Third through 14th day: every 4 hours **Conjunctivitis**: *Ointment*: 3 times daily for first 2 days, then twice daily for the next 5 days *Solution*: every 2 hours while awake for 2 days, then every 4 hours while awake for next 5 days	ages.
Erythromycin	Ophthalmic ointment: 0.5%	**Superficial infections**: Apply directly to the infected structure up to 6 times daily, depending on the severity of the infection. **Prophylaxis of neonatal gonococcal or chlamydial conjunctivitis:** apply into each lower conjunctival sac.	For neonates: The ointment should not be flushed from the eye following instillation.
Gentak (gentamicin)	Ophthalmic ointment: 0.3% Ophthalmic solution: 0.3%	**Ointment**: 2 or 3 times a day **Solution**: every 4 hours *Severe infections:* dosage may be increased to as much as every hour.	Safety and efficacy in neonates have not been established.
Levofloxacin	Ophthalmic solution: 0.5%*	Every 2 hours while awake, up to 8 times per day on days 1 and 2, then every 4 hours while awake, up to 4 times per day for days 3 to 7	Safety and efficacy have not been established in children < 6 year of age.
Moxeza, Vigamox (moxifloxacin)	Ophthalmic solution: 0.5% (Moxeza - twice daily formulation), 0.5% (Vigamox - 3 times daily formulation)	**Moxeza**: twice daily for 7 days **Vigamox**: 3 times daily for 7 days	**Moxeza**: Safety and efficacy have not been established in infants < 4 months of age. **Vigamox**: Safety and efficacy have been established in all ages.
Ocuflox (ofloxacin)	Ophthalmic solution: 0.3%	**Conjunctivitis**: every 2 to 4 hours days 1 and 2, then 4 times daily for days 3 through 7 **Corneal ulcers:** *Days 1 and 2*: every 30 minutes, while awake *Days 3 through 7 to 9*: hourly, while awake *Days 7 to 9 through treatment completion*: 4 times daily	Safety and efficacy have not been established in children < 1 year of age.
Tobrex (tobramycin)	Ophthalmic ointment: 0.3% Ophthalmic solution: 0.3%	**Ointment**: *Mild to moderate disease*: 2 or 3 times a day *Severe infections*: every 3 to 4 hours until improvement, following which treatment should be reduced prior to discontinuation. **Solution**: *Mild to moderate disease*: every 4 hours *Severe infections*: hourly until improvement, following which	Safety and efficacy have not been established in infants < 2 months of age.

Drug	Available Formulations	Usual Recommended Frequency	Comments
		treatment should be reduced prior to discontinuation	
Zymaxid (gatifloxacin)	Ophthalmic solution: 0.5%	Every 2 hours while awake up to 8 times on day 1, then 2 to 4 times per day while awake on days 2 through 7	Safety and efficacy have not been established in children < 1 year of age.
Combinations			
bacitracin/ neomycin/ polymyxin	Ophthalmic ointment: bacitracin zinc 400 units, neomycin 3.5 mg, polymyxin B sulfate 10,000 units per gram	Every 3 or 4 hours for 7 to 10 days, depending on the severity of the infection	Safety and efficacy have not been established in pediatric patients.
bacitracin/ neomycin/ polymyxin/ hydrocortisone	Ophthalmic ointment: bacitracin zinc 400 units/neomycin sulfate 3.5 mg/polymyxin B sulfate 10,000 units/hydrocortisone 10 mg per gram	Every 3 or 4 hours depending on the severity of the condition	Not more than 8 grams should be prescribed initially.
Blephamide (sulfacetamide/ prednisolone)	Ophthalmic ointment: sulfacetamide 10%/ prednisolone 0.2% Ophthalmic suspension: sulfacetamide 10%/ prednisolone 0.2%	**Ointment** Apply 3 or 4 times daily and once or twice at night to the conjunctival sac(s) **Suspension** Every 4 hours during the day and at bedtime into the conjunctival sac(s)	Ointment: Not more than 8 grams should be prescribed initially. Suspension: Not more than 20 mL should be prescribed initially; shake well before using.
gramicidin/ neomycin/ polymyxin	Ophthalmic solution: neomycin sulfate 1.75 mg, polymyxin B sulfate 10,000 units, gramicidin 0.025 mg per mL	Every 4 hours for 7 to 10 days *Severe infections*: may increase to every hour	Safety and efficacy have not been established in pediatric patients.
Maxitrol (neomycin/ polymyxin/ dexamethasone)	Ophthalmic ointment: neomycin 3.5 mg/ polymyxin B sulfate 10,000 units/dexamethasone 0.1% per gram Ophthalmic suspension: neomycin 3.5 mg/polymyxin B sulfate 10,000 units/ dexamethasone 0.1% per mL	**Ointment** Up to 3 or 4 times daily into the conjunctival sac(s) **Suspension** *Mild disease:* Up to 4 to 6 times daily in the conjunctival sac(s) *Severe disease*: Drops may be used hourly, being tapered to discontinuation as the inflammation subsides.	Ointment: Not more than 8 grams should be prescribed initially. Suspension: Not more than 20 mL should be prescribed initially.
neomycin/ polymyxin/ hydrocortisone	Ophthalmic suspension: neomycin sulfate 3.5 mg/polymyxin B sulfate 10,000 units/hydrocortisone10 mg per mL	Every 3 to 4 hours into the affected eye(s) depending on the severity of the infection	Not more than 20 mL should be prescribed initially.
Polysporin (bacitracin/ polymyxin)	Ophthalmic ointment: bacitracin zinc 500 units, polymyxin B sulfate 10,000 units per gram	Every 3 or 4 hours for 7 to 10 days, depending on the severity of the infection	No data in pediatric patients.

Drug	Available Formulations	Usual Recommended Frequency	Comments
Polytrim (polymyxin/ trimethoprim)	Ophthalmic solution: polymyxin B sulfate 10,000 units, trimethoprim 1 mg per mL	*Mild to moderate infections*: Every 3 hours (maximum of 6 doses per day) for a period of 7 to 10 days	Safety and efficacy have not been established in infants < 2 months of age.
Pred-G (gentamicin/ prednisolone)	Ophthalmic ointment: gentamicin 0.3%/ prednisolone acetate 0.6% Ophthalmic suspension: gentamicin 0.3%/ prednisolone acetate 1%	**Ointment** Apply 1 to 3 times daily in the conjunctival sac(s) **Suspension** Instill 2 to 4 times daily into the conjunctival sac(s). During the initial 24 to 48 hours, the dosing may be increased up to every hour.	Ointment: Not more than 8 grams should be prescribed initially. Suspension: Not more than 20 mL should be prescribed initially.
Tobradex, Tobradex ST (tobramycin/ dexamethasone)	Ophthalmic ointment: tobramycin 0.3%/ dexamethasone 0.1% Ophthalmic suspension: tobramycin 0.3%/ dexamethasone 0.1% Ophthalmic ST suspension: tobramycin 0.3%/ dexamethasone 0.05%	**Ointment** Up to 3 or 4 times daily into the conjunctival sac(s) **Suspension** Every 4 to 6 hours into the conjunctival sac(s); during the initial 24 to 48 hours, the dosage may be increased to every 2 hours **ST Suspension** Every 4 to 6 hours into the conjunctival sac(s); during the initial 24 to 48 hours, the dosage may be increased to every 2 hours	Ointment: Not more than 8 grams should be prescribed initially. Suspension, ST Suspension: Not more than 20 mL should be prescribed initially. Shake well before using.
Zylet (tobramycin/ loteprednol)	Ophthalmic suspension: tobramycin 0.3%/ loteprednol etabonate 0.5%	Every 4 to 6 hours into the conjunctival sac(s); during the initial 24 to 48 hours, the dosing may be increased to every 1 to 2 hours	Not more than 20 mL should be prescribed initially. Shake vigorously before using.

*A generic levofloxacin 1.5% ophthalmic solution was approved in February 2019 by the FDA; however, it is not available at this time. The branded 1.5% solution has been discontinued, and no other generics of this strength are currently approved.

See the current prescribing information for full details

CONCLUSION

- Ophthalmic antibiotics are used to treat ophthalmic infections, including blepharitis, conjunctivitis, and keratitis as well as several others. Classes of ophthalmic antibiotics include aminoglycosides, macrolides, quinolones, and other miscellaneous and combination products. For all FDA-approved indications, but not all products, a generic ophthalmic antibiotic is available.
- Ophthalmic antibiotic-steroid combination products are indicated for the treatment of steroid-responsive ocular inflammatory conditions where the presence or risk of a superficial bacterial ocular infection exists. At least 1 generic is available in each formulation: ointment, solution, and suspension.
- In comparative clinical trials, no one ophthalmic antibiotic has been shown to be more effective than another in bacterial eradication, clinical resolution, clinical response, or symptom improvement and no one ophthalmic antibiotic-steroid combination product has been shown to be more effective than another with regard to symptom improvement or reduction of postoperative inflammation.
- In clinical studies, adverse events were mild with no significant difference seen with regard to the rate of adverse events. Common adverse events reported include burning, ocular discomfort, stinging, and tearing.
- Ophthalmic antibiotics and combinations are not intended to be used for prolonged periods of time in order to avoid overgrowth of non-susceptible organisms and reduce the risk of resistance. Should super-infection occur, the ophthalmic antibiotic should be discontinued, and an alternative therapy should be initiated. Steroid-containing ophthalmic products

may also increase the risk of IOP elevation, cataract formation, and delayed healing after cataract surgeries, and should be used with caution.

- Guidelines published by the AAO recommend that topical ophthalmic antibiotics such as bacitracin or erythromycin ointments may be used to reduce symptoms of blepharitis; the guideline also notes that tobramycin/dexamethasone ophthalmic suspension and ophthalmic azithromycin have been shown to reduce some signs and symptoms of blepharitis. To prevent resistance, topical antibiotics with different mechanisms of action can be used intermittently if needed (*AAO 2018b*).
- Guidelines state that keratitis should be treated with an ophthalmic antibiotic that may be selected based on the isolated organism, and if no organism is identified, treatment with cefazolin or vancomycin plus either gentamicin or tobramycin or an ophthalmic fluoroquinolone alone is recommended. The AAO guideline also notes that fewer gram-positive cocci are resistant to ophthalmic gatifloxacin, moxifloxacin, and besifloxacin than other fluoroquinolones (*AAO 2018a*).
- For the treatment of bacterial conjunctivitis, indiscriminate use of topical antibiotics or corticosteroids should be avoided, because antibiotics can induce toxicity and corticosteroids can potentially prolong or worsen some infections. If treatment is warranted, it is recommended that the least expensive or most convenient broad-spectrum antibiotic be selected for a 5- to 7-day course of treatment, if needed. Systemic antibiotic therapy is necessary to treat conjunctivitis due to *N.gonorrhoeae* and *C. trachomatis*, and topical therapy may be used concomitantly (*AAO 2018c; AOA 2007*).
- Short-term use of ophthalmic corticosteroids is recommended by treatment guidelines to reduce inflammation in the treatment of blepharitis, conjunctivitis, and keratitis and can be considered in postoperative prophylaxis (*AAO 2016; AAO 2018a; AAO 2018b; AAO 2018c*).
- The AAO cataract practice pattern states that postoperative regimens of topically applied antibiotics, corticosteroids, NSAIDs, and oral analgesic agents vary among practitioners. There are no controlled investigations that establish optimal regimens for the use of topical agents (*AAO 2016*).

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Publication Date: May 28, 2020

Annual Review – Established Drug Classes

Therapeutic Class Overview
Antihistamines, Second-generation

INTRODUCTION

- Oral antihistamines have been a mainstay in the treatment of allergic rhinitis and chronic idiopathic urticaria (CIU) since their development in the first half of the 20th century *(Janssen 1993)*.
- Although first-generation antihistamines are effective at ameliorating symptoms associated with allergic rhinitis, acute urticaria, and CIU, use in practice is limited by their lack of selectivity for the histamine 1 (H_1)-receptor and their ability to cross the blood-brain barrier, both resulting in adverse effects. Second-generation antihistamines were developed to maintain the efficacy of the first-generation agents, while reducing associated adverse effects. Due to a more complex chemical structure, the movement of second-generation antihistamines across the blood-brain barrier is reduced. In addition to a safer adverse event profile, second-generation agents have a longer duration of action, which allows for once- or twice-daily dosing for most products *(Lehman et al 2006)*.
- Despite the efficacy of second-generation antihistamines for the treatment of allergic rhinitis, they are not effective in the treatment of nasal congestion *(Lehman et al 2006, Seidman et al 2015)*. Because of this, they are often combined with a decongestant. Second-generation antihistamines combined with pseudoephedrine have been shown to improve symptoms and quality of life in patients with allergic rhinitis and nasal congestion compared to antihistamines alone *(Seidman et al 2015)*.
- This review focuses on the use of the second-generation antihistamines for the treatment of CIU, acute urticaria, perennial allergic rhinitis (PAR), and seasonal allergic rhinitis (SAR).
- Several products formerly available by prescription (Rx) are now available over-the-counter (OTC). This review includes Rx products and those that are sold both by Rx and OTC. Products sold solely OTC are identified as such but are not the focus of this review. The clinical efficacy section retains some information on OTC products that were formerly available by Rx for informational purposes.
- Medispan Class: Antihistamines – Non-Sedating and Cough/Cold/Allergy Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Cetirizine*	
cetirizine oral solution/syrup (Rx/OTC)	✓
Quzyttir (cetirizine) injection (Rx only)	-
OTC-only products include tablets, chewable tablets, liquid-filled capsules, and orally disintegrating tablets (ODT)	
Desloratadine	
Clarinex (desloratadine) tablet (Rx only)	✓
Clarinex (desloratadine) ODT (Rx only) ‡	✓
Fexofenadine*	
OTC-only products include tablets, oral suspension, and ODT	
Levocetirizine*	
levocetirizine tablet (Rx/OTC)	✓
levocetirizine oral solution (Rx/OTC)	✓
Loratadine*	
OTC-only products include tablets, capsules, chewable tablets, solution/syrup, and ODT	
Antihistamine – decongestant combinations*	
Clarinex-D 12 Hour (desloratadine/pseudoephedrine extended release tablet) (Rx only)	-
Clarinex-D 24 Hour (desloratadine/pseudoephedrine extended release tablet) (Rx only)‡	-†

Data as of May 17, 2020 KM-U/HJI-U/KAL

Drug	Generic Availability
Semprex-D (acrivastine/pseudoephedrine capsule) (Rx only)	-
OTC-only combinations include fexofenadine/pseudoephedrine, loratadine/pseudoephedrine, and cetirizine/ pseudoephedrine extended release tablets	

*Medication or combination is available OTC in at least 1 dosage form or strength. OTC products are available in various brand and private label names.
‡Clarinex oral solution/syrup, Clarinex ODT, and Clarinex-D 24 Hour brands are no longer marketed. A generic Clarinex oral solution/syrup was approved by the FDA in 2015 but is not currently marketed.

(*Clinical Pharmacology 2020, Drugs@FDA 2020, Facts and Comparisons 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2a. FDA-Approved Indications – Single Entity and Combination Prescription Agents

Indication	Cetirizine	Desloratadine*	Levocetirizine	Acrivastine/ Pseudoephedrine	Desloratadine/ Pseudoephedrine
CIU	✓† (age 6 months to 5 years)	✓ (age 6 months and older)	✓ (age 6 months and older)		
Acute urticaria	✓‡§ (age 6 months and older)				
PAR	✓† (age 6 to 23 months)	✓ (age 6 months and older)	✓ (age 6 months to 2 years)		
SAR		✓ (age 2 years and older)			
Relief of symptoms of SAR, including nasal congestion				✓ (12 years and older)	✓ (12 years and older)

*The ODT formulation is not recommended for use in patients ≤ 6 years of age because the oral solution (which is not currently marketed) is better suited for these patients.
†Oral solution indications
‡Intravenous solution indications
§Limitations of use: Not recommended in pediatric patients less than 6 years of age with impaired renal or hepatic function

(*Clinical Pharmacology 2020, Facts and Comparisons 2020, Prescribing information: Cetirizine 2020, Clarinex 2020, Clarinex-D [12 hour] 2019, Quzyttir 2020, Semprex-D 2019, Xyzal 2019*)

Table 2b. OTC Indications – Single Entity OTC Agents

Indication	Cetirizine	Fexofenadine	Levocetirizine	Loratadine
Temporary relief of runny nose; sneezing; itchy, watery eyes; or itching of the nose and throat due to hay fever or other upper respiratory allergies	✓ (age 2 to 64 years)	✓ (age 2 to 64 years)	✓ (age 2 to 64 years)	✓ (age 2 years and older)

(*OTC label: Allegra Allergy 2020, Children's Allegra Allergy 2019, Claritin 2020, Children Claritin Allergy 2020, Xyzal 2017, Children's Xyzal Allergy 2019, Zyrtec 2020, Children's Zyrtec Allergy 2018*)

Table 2c. OTC Indications – Combination OTC Agents*

Indication	Cetirizine/ Pseudoephedrine	Fexofenadine/ Pseudoephedrine	Loratadine/ Pseudoephedrine
Temporary relief of runny nose; sneezing; itchy, watery eyes; or itching of the nose and throat due to hay fever or other upper respiratory allergies	✓ (age 12 to 64 years)	✓ (age 12 to 64 years)	✓ (age 12 years and older)
Temporary relief of nasal congestion due to the common cold, hay fever or other upper respiratory allergies		✓ (age 12 to 64 years)	✓ (age 12 years and older)
Reduction of swelling of nasal passages	✓ (age 12 to 64 years)	✓ (age 12 to 64 years)	✓ (age 12 years and older)
Temporary relief of sinus congestion and pressure	✓ (age 12 to 64 years)	✓ (age 12 to 64 years)	✓ (age 12 years and older)
Temporary restoration of freer breathing through the nose	✓ (age 12 to 64 years)	✓ (age 12 to 64 years)	✓ (age 12 years and older)

*Although these agents do not require a prescription, they are available behind the pharmacy counter and do have some restriction (based on federal and/or state law) on total quantity purchased per month

(*OTC label: Allegra-D 2020, Claritin-D 12 hour 2019, Claritin-D 24 hour 2019, Zyrtec-D 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

- Clinical trials have demonstrated that second-generation antihistamines are more effective in treating and providing symptomatic relief of CIU, PAR, and SAR compared to placebo *(Kaplan et al 2005, Kapp et al 2006, Kim et al 2006, Monroe et al 2003, Nathan et al 2006, Nayak et al 2017, Nettis et al 2006, Potter et al 2003, Potter et al 2005, Okubo et al 2005, Ring et al 2001, Simons et al 2003)*.
- Within-class comparisons have not consistently demonstrated superior efficacy with any one agent over another *(Anuradha et al 2010, Boyle et al 2005, Ciprandi et al 2005, Day et al 1998, Day et al 2001, Day et al 2004, Garg et al 2007, Handa et al 2004, Lee et al 2009, Meltzer et al 1996, Nayak et al 2017, Potter et al 2009, Prenner et al 2000, Purohit et al 2004, Van Cauwenberge et al 2000)*.
- The efficacy of intravenous cetirizine was demonstrated in a randomized, controlled, single-dose study of adults with acute urticaria randomized to intravenous cetirizine 10 mg or diphenhydramine 50 mg. The primary efficacy endpoint, change from baseline in patient-rated pruritis score at 2 hours, demonstrated noninferiority of intravenous cetirizine (adjusted mean difference, 0.06; 95% confidence interval [CI], -0.28 to 0.4). Intravenous cetirizine was also associated with a lower rate of return to the emergency department (6% vs 14%) and time between treatment and discharge (1.7 vs 2.1 hours). The efficacy of intravenous cetirizine in pediatric patients 6 months and older is based on extrapolation of data in adults *(Berger et al 2019, Ernst 2019)*.
- In a systematic review by Benninger et al, second-generation antihistamines were associated with a 23.5% reduction from baseline in total nasal symptom scores for SAR, and a 51.4% reduction in symptoms of PAR. Although intranasal corticosteroids were more effective for SAR (40.7% reduction), they were not as effective as long-term oral antihistamines in patients with PAR (37.3% reduction) (*Benninger et al 2010*).
- In a comparative effectiveness review by the Agency for Healthcare Research and Quality (AHRQ), oral selective antihistamines were equivalent to montelukast for nasal and eye symptoms in patients with SAR. Based on evidence of safety, in order to avoid insomnia, an oral selective antihistamine was preferred over the combination of an oral selective antihistamine with a decongestant or monotherapy with a decongestant *(Glacy et al 2013)*.

- In a systematic review of 73 randomized controlled trials in CIU, at standard treatment doses, the second-generation antihistamines were effective when compared with placebo. Cetirizine 10 mg once daily in the short term and in the intermediate term was effective in completely suppressing urticaria. Evidence was limited for desloratadine given at 5 mg once daily in the intermediate term and at 20 mg in the short term. Levocetirizine at 5 mg was effective for complete suppression in the intermediate term but not in the short term. No single agent was demonstrated to be more effective than another, and there is a lack of available head-to-head trials *(Sharma et al 2014)*.

CLINICAL GUIDELINES

- According to current clinical guidelines for the management of allergic rhinitis, intranasal corticosteroids should be considered first-line therapy in the majority of patients with moderate to severe allergic rhinitis and may also be effective in some forms of nonallergic rhinitis. Although intranasal corticosteroids are the most effective drugs for treating allergic rhinitis, second-generation antihistamines may be used in patients with mild-to-moderate disease, especially those with a preference for oral therapy and with complaints of sneezing and itching. Considering their safety profile, second-generation antihistamines should be considered as first-line symptomatic treatment for acute and chronic urticaria *(Bernstein et al 2014, Brozek et al 2017, Dykewicz et al 2017, Grattan et al 2007, Seidman et al 2015, Wallace et al 2008, Zuberbier et al 2018)*.

SAFETY SUMMARY

- Levocetirizine is contraindicated in patients with severe renal impairment and in pediatric patients 6 months to 11 years of age with impaired renal function.
- Due to the pseudoephedrine component, the combination agents are contraindicated in patients with narrow angle glaucoma, severe hypertension or coronary artery disease, or urinary retention. The combination agents should not be used when there has been treatment with a monoamine oxidase inhibitor within the last 14 days.
- The most common adverse effects are associated with sedation and fatigue or dry mouth. The most common adverse effect with cetirizine oral solution was headache.

DOSING AND ADMINISTRATION

- For the combination agents, at least 14 days must elapse after discontinuation of a monoamine oxidase inhibitor before starting treatment.
- Extended-release products should be swallowed whole; tablets should not be broken, chewed, or crushed.

Table 3. Dosing and Administration of the Single Entity and Combination Prescription Agents

Drug	Dosage Form(s)	Usual Recommended Frequency	Comments
Single Entity Agents			
Cetirizine	Oral solution	Once or twice daily	Dosage adjustment in renal and hepatic impairment is required.
Cetirizine	Solution for intravenous injection	Once daily as needed	Dosage adjustments in children 6 months to 11 years of age are required. Not recommended in patients < 6 years of age with impaired renal or hepatic function.
Desloratadine	Tablet, ODT	Once daily	Dosage adjustment in renal and hepatic impairment is required.
Levocetirizine	Tablet, oral solution	Once daily in the evening	Dosage adjustment in renal impairment is required.
Combination Agents			
Acrivastine/ pseudoephedrine	Capsule	Four times per day	Avoid use in patients with creatinine clearance ≤ 48 mL/minute.

Drug	Dosage Form(s)	Usual Recommended Frequency	Comments
Desloratadine/ pseudoephedrine	Extended-release tablet	Once or twice daily (the once-daily product is not currently marketed)	Avoid use in patients with renal and hepatic impairment (combination product was not studied in these populations).

See the current prescribing information for full details.

CONCLUSION

- Second-generation antihistamines have been shown to significantly improve the symptoms of allergic rhinitis and CIU, without the unwanted adverse effects associated with the first-generation agents *(Sur et al 2010)*.
- Currently, all of the single entity second-generation antihistamines are available as generics and/or OTC in at least 1 dosage form. Cetirizine, fexofenadine, levocetirizine, and loratadine can be purchased OTC, and several different dosage forms are available for the OTC products. Cetirizine is also available as an intravenous formulation approved for acute urticaria. *(Clinical Pharmacology 2020, Facts and Comparisons 2020, Micromedex 2020)*.
- Current evidence supports the use of second-generation antihistamines in the treatment of seasonal and perennial allergic rhinitis as well as CIU. In a systematic review by Benninger et al, second-generation antihistamines were associated with a 23.5% reduction from baseline in total nasal symptom scores for SAR, and a 51.4% reduction in symptoms of PAR *(Benninger et al 2010)*.
- Overall, clinical trials have not consistently demonstrated one single-entity second-generation antihistamine agent to be more efficacious or safe than the others. Furthermore, there is a lack of head-to-head trials comparing the combination second-generation antihistamine products, rendering a comparison of the agents difficult.
- Current consensus guidelines are consistent among organizations that antihistamines are somewhat less effective than intranasal corticosteroids, but may be used on a daily or as-needed basis. Second-generation antihistamines are recommended as they are less sedating and cause less central nervous system impairment compared to first-generation agents. Oral decongestants can be a useful addition to antihistamines in the treatment of nasal congestion *(Brozek et al 2017, Dykewicz et al 2017, Seidman et al 2015)*.
- Considering their efficacy and safety profile, second-generation antihistamines should be considered as first-line symptomatic treatment of urticaria. Additionally, patients should be offered the choice of at least 2 nonsedating antihistamines as response varies among individuals *(Bernstein et al 2014, Grattan et al 2007, Zuberbier et al 2018)*.

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Publication Date: July 2, 2020

INTRODUCTION

- Cardiovascular disease (CVD) accounts for nearly 1 in 3 deaths in the United States (U.S.). The core health behaviors including smoking, physical activity, diet and weight; and health factors including cholesterol, blood pressure (BP), and glucose control contribute to cardiovascular (CV) health. Based on data from 2013 to 2016, among adults ≥ 20 years of age, the mean total cholesterol (TC) in the U.S. was 190.8 mg/dL, and the mean low-density lipoprotein cholesterol (LDL-C) was 112.1 mg/dL (*Virani et al 2020*).
- Evidence that serum cholesterol contributes to atherosclerotic CVD (ASCVD) comes from multiple sources, including animal studies, epidemiological studies, and randomized controlled trials (RCTs). U.S. population studies suggest that optimal TC levels are around 150 mg/dL, which corresponds to an LDL-C level of approximately 100 mg/dL. Adult populations with cholesterol concentrations in this range generally have low rates of ASCVD. RCTs of cholesterol-lowering drugs in high risk patients confirm that lowering LDL-C reduces ASCVD, confirming the general principle that "lower is better" for LDL-C levels *(Grundy et al 2019)*.
  - In addition to healthy lifestyle interventions, statins are the cornerstone of lipid-lowering therapy on the basis of morbidity and mortality outcome trials *(Grundy et al 2019, Jellinger et al 2017)*. Based on National Health and Nutrition Examination Survey (NHANES) data from 2007 to 2014, an estimated 38.9 million people in the U.S. are prescribed statins (*Fan et al 2019*).
- There are several classes of medications used to alter lipids, including the hydroxymethylglutaryl (HMG) coenzyme A reductase inhibitors (statins), fibric acid derivatives, bile acid sequestrants, omega-3 fatty acids, nicotinic acid (niacin), cholesterol absorption inhibitors, proprotein convertase subtilisin/kexin 9 (PCSK9) inhibitors, and the newest class, ATP-Citrate Lyase (ACL) inhibitors. Each medication class differs with respect to the mechanism of as well as the degree of lipid-lowering; therefore, Food and Drug Administration (FDA)-approved indications for a particular medication class are influenced by the underlying lipid abnormality.
- This review will focus on the cholesterol absorption inhibitors and ACL inhibitors.
  - The cholesterol absorption inhibitor, Zetia (ezetimibe), is also effective in the management of hypercholesterolemia and has a unique mechanism of action compared to the other available treatments. Specifically, this agent works to reduce blood cholesterol by inhibiting the absorption of both dietary and biliary cholesterol, which results in a decrease in hepatic cholesterol stores, an increase in hepatic cholesterol sequestering from the circulation, and ultimately, lower systemic cholesterol levels. Ezetimibe is the only cholesterol absorption inhibitor available.
  - The ACL inhibitor, bempedoic acid, inhibits an earlier or upstream step in the cholesterol biosynthesis pathway from the statins, resulting in an increase in LDL receptors in the liver and increased clearance of LDL-C from the blood. The guidelines have not been updated to include bempedoic acid and its place in therapy.
- Therapeutic lifestyle changes, including diet, exercise and smoking cessation, remain essential modalities in the management of patients with hypercholesterolemia (*Arnett et al 2019, Jellinger et al 2017, Grundy et al 2019, Mach et al 2020*). In general, the statins are considered first-line therapy for decreasing LDL-C levels (*Grundy et al 2019*). Under certain circumstances, nonstatin medications (ezetimibe, bile acid sequestrants, and PCSK9 inhibitors) may be useful in combination with statin therapy (*Grundy et al 2019*).
- Medispan Class: Intestinal Cholesterol Absorption Inhibitors; Antihyperlipidemics, Adenosine Triphosphate-Citrate Lyase Inhibitors

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Nexletol (bempedoic acid)	-
Nexlizet (bempedoic acid/ezetimibe)	-
Zetia (ezetimibe)	✔

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Nexletol (bempedoic acid)	Nexlizet (bempedoic acid/ ezetimibe)	Ezetimibe
Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or established ASCVD who require additional lowering of LDL-C	✓	✓	
Adjunct to diet to reduce elevated total cholesterol (TC), LDL-C, apolipoprotein B (apoB), and non-high-density lipoprotein cholesterol (non-HDL-C) in patients with primary hyperlipidemia, alone or in combination with a statin			✓
Adjunct to diet to reduce elevated TC, LDL-C, apoB, and non-HDL-C in patients with mixed hyperlipidemia in combination with fenofibrate			✓
Adjunct to diet to reduce elevated TC and LDL-C in patients with homozygous familial hypercholesterolemia (HoFH), in combination with atorvastatin or simvastatin			✓
Adjunct to diet to reduce elevated sitosterol and campesterol in patients with homozygous sitosterolemia (phytosterolemia)			✓

(*Prescribing information: Nexletol 2020, Nexlizet 2020, Zetia 2013)*

- 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.

- In December 2015, the FDA's Endocrinologic and Metabolic Advisory Committee met to discuss Merck's application for a label update to be applied to all ezetimibe-containing products. Based on results from the IMPROVE-IT trial, the proposed indication was ezetimibe in combination with a statin is indicated to reduce the risk of CV events in patients with coronary heart disease (CHD). The FDA advisory panel voted 10-5 against expanding the use of ezetimibe plus statin therapy for the reduction of CV events in patients with CHD. A few of those reasons cited in the FDA transcript included:
  - Many panel members were not convinced that the IMPROVE-IT trial results were clinically robust. Effect was small even before considering the issues regarding missing observation time.
  - Those high-risk subgroups which demonstrated improved benefit, including diabetics and patients aged ≥ 75 years, were promising, but some members felt these results were currently at the point of hypothesis.
  - Some felt "CHD" was too broad for the population studied within the IMPROVE-IT trial.
  - Overall safety was generally favorable and not concerning, but some panelists expressed concerns over the small but troubling risk for hemorrhagic stroke in the ezetimibe group.
- The FDA issued a complete response letter rejecting Merck's application for a secondary-prevention indication for ezetimibe-containing products *(FDA Zetia/Vytorin transcript 2015, Merck Press Release 2016).*

CLINICAL EFFICACY SUMMARY

Ezetimibe

- In clinical trials, ezetimibe consistently demonstrated superiority over placebo in the management of hypercholesterolemic conditions. Ezetimibe significantly lowered TC, LDL-C, apoB, non-HDL-C, and triglycerides (TG), and increased HDL-C compared to placebo in clinical studies ranging in length from 8 to 26 weeks *(Dujovne et al 2002, Gonzalez-Ortiz et al 2006, Kalogirou et al 2007, Knopp et al 2003, Musliner et al 2008, Salen et al 2004, Wierzbicki et al 2005).*
- Numerous studies have demonstrated that the addition of ezetimibe to a statin has the potential to produce further reductions in LDL-C levels compared to monotherapy with either of the agents alone *(Ballantyne et al 2003, Bays et al*

2004, Chenot et al 2007, Constance et al 2007, Feldman et al 2004, Feldman et al 2006, Goldberg et al 2004, Goldberg et al 2006, Hing Ling et al 2012, Hong et al 2018, Kerzner et al 2003, Okada et al 2011, Ose et al 2007, Pearson et al 2007, Sakamoto et al 2017, Shaya et al 2019, Stein et al 2004, Stojakovic et al 2010).

- In addition, when ezetimibe was combined with fenofibrate, significant reductions in LDL-C, TG, and TC were observed as compared to either therapy alone *(Ansquer et al 2009, Farnier et al 2005, McKenney et al 2006)*.
- Ezetimibe with PCSK9 inhibitors:
  - The ODYSSEY Mono trial compared ezetimibe to the PCSK9 inhibitor Praluent (alirocumab). It was a 24-week, Phase 3, randomized, double-blind (DB), active-controlled (AC), double-dummy trial of male and female patients aged ≥ 18 years with a 10-year risk of fatal CV events of ≥ 1% and < 5%, based on the European Systematic Coronary Risk Estimation. Patients were not receiving statin or any other lipid-lowering therapy for at least 4 weeks prior to screening and were randomized (permuted-block design) in a 1:1 ratio to receive either ezetimibe 10 mg/day orally plus subcutaneous (SC) placebo every 2 weeks (n = 51) or alirocumab 75 mg SC every 2 weeks plus oral placebo daily (n = 52). The primary endpoint was the percent change from baseline in calculated LDL-C at 24 weeks. Mean baseline LDL-C levels were 141.1 mg/dL in the alirocumab arm and 138.3 mg/dL in the ezetimibe arm. For the primary efficacy analysis, least-squares (LS) mean (standard error [SE]) percent reductions in LDL-C from baseline to week 24 were 47 (3)% in the alirocumab group vs 16 (3)% in the ezetimibe group, with a statistically significant LS mean (SE) difference between groups of 32 (4)% (p < 0.0001). Alirocumab demonstrated tolerability and safety comparable with ezetimibe. Alirocumab demonstrated superior efficacy in monotherapy compared with ezetimibe over 24 weeks of treatment *(ClinicalTrials.gov [NCT01644474]; Roth et al 2014*). A pooled analysis of 8 ODYSSEY clinical trials of up to 104 weeks in high-risk patients receiving background statin therapy found that alirocumab reduced LDL-C levels to a significantly greater degree than both ezetimibe and placebo in various pooled analyses, with results sustained up to week 104 *(Farnier et al 2016).* Another pooled analysis of 10 ODYSSEY trials found that alirocumab reduced non-HDL-C and apoB levels to a significantly greater degree than placebo or ezetimibe at 24 weeks; this effect was maintained for up to 78 weeks (*Bays et al 2017)*.
  - The GAUSS-3 trial compared the PCSK9 inhibitor Repatha (evolocumab) to ezetimibe in a 24-week, Phase 3, randomized, DB, AC, double-dummy trial of patients who had a history of intolerance to ≥ 2 statins. At baseline, patients had a mean age of 61 years, 34.6% had CHD, and a mean LDL-C level of 212.3 mg/dL. Patients were administered atorvastatin 20 mg/day and placebo in a 24-week crossover period, in which 42.6% developed muscle symptoms while taking atorvastatin but not while taking placebo. A total of 218 patients were randomized (1:2) to ezetimibe 10 mg/day (n = 73) or evolocumab 420 mg/month (n = 145). Evolocumab significantly outperformed ezetimibe for the co-primary end points of mean percent change in LDL-C level from baseline to the mean of weeks 22 and 24 levels (between group mean percent change difference, -37.8%) and from baseline to week 24 levels (ezetimibe, -16.7%; 95% confidence interval [CI], -20.5% to -12.9% vs evolocumab, -54.5%; 95% CI, 57.2% to 51.8%; p < 0.001). At 24 weeks, there were no differences between groups in muscle symptoms (ezetimibe, 28.8% vs evolocumab, 20.7%; p = 0.17). Evolocumab was associated with reduced TC and apoB levels and increased HDL-C levels (p < 0.005 for each), but no significant differences in TG or very low-density lipoprotein cholesterol (VLDL-C) levels (*Nissen et al 2016).*
  - A meta-analysis that compared PCSK9 inhibitors to ezetimibe (2 RCTs) and ezetimibe and statins (5 RCTs) found an LDL-C reduction of 30.2% (95% CI, 34.18 to 26.23) with PCSK9 inhibitors compared to ezetimibe alone and a reduction of 39.2% (95% CI, 56.15 to 22.26) compared to ezetimibe plus statins. The risk difference (RD) for risk of CVD events (3 RCTs) was 1.06% (odds ratio [OR] 0.45; 95% CI, 0.27 to 0.75) with PCSK9 inhibitors compared to ezetimibe plus statins; however, the data were of very low quality so the finding was considered to have considerable uncertainty. Risk of adverse events (AEs) (4 RCTs) were increased with PCSK9 inhibitors compared to ezetimibe plus statins (RD, 3.7%; OR, 1.18; 95% CI, 1.05 to 1.34) *(Schmidt et al 2017).*
  - A network meta-analysis of 15 trials compared different doses of PCSK9 inhibitors to one another and to ezetimibe. Patients in this analysis were on background, maximally tolerated statin therapy. Compared to ezetimibe, the percent LDL-C reductions with evolocumab 140 mg every 2 weeks, alirocumab 75 mg every 2 weeks, and alirocumab 150 mg every 2 weeks were 46.1% (95% CI, 53.28 to 39.06), 26.1% (95% CI, 31.19 to 20.81), and 32.5% (95% CI, 40.77 to 23.87), respectively. The percent LDL-C reductions with evolocumab 420 mg monthly and alirocumab 300 mg monthly compared to ezetimibe were 47.5% (95% CI, 55.22 to 39.89) and 28.3% (95% CI, 38.38 to 17.97), respectively (*Toth et al 2017*).
- CV outcomes
  - The IMPROVE-IT trial was a multi-center (MC), DB, placebo-controlled (PC), RCT in 18,144 patients designed to assess CV outcomes through the addition of ezetimibe 10 mg to simvastatin 40 mg compared to simvastatin 40 mg

alone in patients hospitalized with acute coronary syndromes. After a median of 6 years, patients randomized to ezetimibe/simvastatin had a 6.4% relative risk reduction (or approximately a 2% absolute reduction) of CV events (defined as a composite of CV death, nonfatal myocardial infarction (MI), unstable angina requiring re-hospitalization, coronary revascularization, or nonfatal stroke) compared with those who received simvastatin alone (hazard ratio [HR], 0.94; 95% CI, 0.89 to 0.99; p = 0.016). There were no significant differences in AEs *(Cannon et al 2015).*

- A Bayesian network meta-analysis of 39 RCTs found that PCSK9 inhibitors had the highest probability of having the lowest risk of major adverse CV events (Surface Under Cumulative Ranking Curve [SUCRA] 85%), followed by statins (SUCRA 75%) and ezetimibe plus statins (SUCRA 51%). PCSK9 inhibitors also had the highest probability of having the lowest rate of MI and stroke (SUCRA 84% and 80%, respectively), followed by ezetimibe plus statins (SUCRA 80% and 75%) and statins (SUCRA 42% and 56%). Statins had the highest probability of having the lowest rates of all-cause mortality and CV mortality (SUCRA 82% and 84%, respectively), followed by PCSK9 inhibitors (SUCRA 81% and 78%) and ezetimibe plus statins (SUCRA 44% and 50%) (*Khan et al 2018*).
- A systematic review of 26 RCTs (N = 23,499) evaluated ezetimibe vs placebo or ezetimibe plus other lipid-modifying drugs vs other lipid-modifying drugs alone in adults, with or without CVD, with at least 12 months of follow-up for the prevention of CVD and all-cause mortality. Ezetimibe plus statins probably reduces the risk of MACE compared to statins alone (risk ratio, 0.94; 95% CI, 0.90 to 0.98; a decrease from 284/1000 to 267/1000, 95% CI, 256 to 278; 10 RCTs, N = 21,727; moderate-quality evidence). The IMPROVE-IT study carried 88.8% of the weight. All-cause mortality was not different in analyses of ezetimibe plus statins or fenofibrate (risk ratio, 0.98; 95% CI, 0.91 to 1.05; 8 studies; N = 21,222; high quality evidence). Ezetimibe plus statin reduced the risk of non-fatal MI (risk ratio, 0.88; 95% CI, 0.81 to 0.95; 6 studies; N = 21,145; moderate quality evidence) compared to statin monotherapy. The IMPROVE-IT study carried 97.8% of the weight and also provided the data on any MI and fatal MI. Ezetimibe plus statin reduced the risk of non-fatal stroke (risk ratio, 0.83; 95% CI, 0.71 to 0.97; 6 studies; N = 21,105; moderate quality evidence) compared to statin monotherapy (*Zhan et al 2018*).
- The PRECISE-IVUS trial evaluated ezetimibe with atorvastatin compared with atorvastatin monotherapy in patients who had undergone a percutaneous coronary intervention. Combination therapy resulted in significantly better coronary plaque regression and significantly lower LDL-C levels than monotherapy *(Tsujita et al 2015).* Similar results were seen in the ZIPANGU trial, which also compared atorvastatin monotherapy with a combination of ezetimibe and atorvastatin (*Ueda et al 2017*). In a study of Chinese patients who had undergone percutaneous coronary intervention, combination therapy with ezetimibe and a moderate-intensity statin produced greater reductions in non-HDL-C, TC, and LDL-C when compared to moderate-intensity statin monotherapy and intensive statin monotherapy (*Dai et al, 2017*). In a study of statin-naive patients who had undergone a percutaneous coronary intervention in Japan, combination therapy with ezetimibe and pitavastatin demonstrated a significant reduction in LDL-C vs the statin alone; however, combination therapy did not result in a significant change in coronary plaque regression or tissue component compared with statin monotherapy (*Hibi et al 2017*).

- One study evaluated the safety and efficacy of ezetimibe in children aged 6 to 10 years with HeFH (ezetimibe is approved for children aged 10 to 17 years) for 12 weeks. TC, non-HDL-C, and apoB were all significantly reduced with ezetimibe compared to placebo, and safety was similar to that seen in other studies with older children and adults *(Kusters et al 2015).* One systematic review in children and adolescents with HeFH included evidence as it related to treatment with ezetimibe. In 1 trial of 248 patients, ezetimibe with simvastatin resulted in greater LDL-C reductions compared with simvastatin monotherapy after 33 weeks (mean, -54% vs -38.1% [standard deviation, 1.4% for each group]). One trial of ezetimibe monotherapy (n = 138) demonstrated mean LDL-C reductions of 28% (95% CI, -31% to -25%) from baseline and a negligible change with placebo after 12 weeks (*Lozano et al 2016).*

Bempedoic acid

- The effects of bempedoic acid on the lipid parameters were studied in the Cholesterol Lowering via bempedoic acid, an ACL-Inhibiting Regimen (CLEAR) study series, which included 2 trials in patients with ASCVD or HeFH (CLEAR WISDOM and CLEAR HARMONY) and 2 trials in patients with statin intolerance (CLEAR SERENITY and CLEAR TRANQUILITY).
  - CLEAR WISDOM (N = 779) and CLEAR HARMONY (N = 2230) were both 52-week, Phase 3, DB, MC, PC RCTs that evaluated bempedoic acid 180 mg daily in high-risk patients or patients with ASCVD or HeFH on maximally tolerated statins (*Goldberg et al 2019, Ray et al 2019*).
    - In the ASCVD/HeFH or high-risk population on maximally tolerated statins, bempedoic acid significantly reduced the mean LDL-C level by 17.4% in the CLEAR WISDOM trial to 18.1% in the CLEAR HARMONY trial at week 12 vs placebo. In CLEAR WISDOM, significant reductions were also observed for non-HDL-C, TC, and apolipoprotein

B (apoB). Significant reductions in high-sensitivity C-reactive protein (hs-CRP), a marker of inflammation, were also observed at week 12 in the bempedoic acid group compared to placebo.
    - In the CLEAR HARMONY trial, rates of AEs (primary endpoint) were similar overall in the bempedoic acid and placebo group. The rate of discontinuation due to AEs was higher in the bempedoic acid group (10.9% vs 7.1%; p = 0.005). Gout occurred more frequently in the bempedoic acid group (1.2% vs 0.3%; p = 0.03). The incidence of new-onset or worsening of diabetes mellitus (DM) was lower in the bempedoic acid group compared to placebo (3.3% vs 5.4%, respectively; p = 0.02). As a secondary endpoint, the difference from placebo in the mean LDL-C change from baseline for LDL-C was 18.1% (95% CI, -20.0 to -16.1%; p < 0.001).
  - The 24-week CLEAR SERENITY (N = 345) and the 12-week CLEAR TRANQUILITY (N = 269) trials were Phase 3, DB, MC, PC, RCTs that evaluated the mean percent change from baseline in LDL-C at week 12 in patients with statin intolerance on bempedoic acid 180 mg daily or placebo (*Ballantyne et al 2018, Laufs et al 2019*).
    - In the CLEAR SERENITY trial, statin intolerance was defined as the inability to tolerate ≥ 2 statins, with 1 trial of a low-dose statin. Approximately one-third of patients were on ezetimibe or omega-3 fatty acids, and 8.4% of patients were on very low dose statin therapy.
    - In the CLEAR TRANQUILITY trial, all patients were maintained on open-label (OL) ezetimibe 10 mg daily, and despite being statin intolerant (intolerance to ≥ 1 statin), approximately one-third of the study population was on at least some background statin therapy with 11.6% of patients on atorvastatin 10 mg daily.
    - In the statin intolerant population, bempedoic acid significantly reduced LDL-C by a range of 21.4% to 28.5%.
      - In both trials, bempedoic acid significantly reduced all secondary endpoints at week 12 including non-HDL-C, TC, apoB, and hs-CRP (all p < 0.001).
- The fixed-dose combination of simvastatin/ezetimibe 180 mg/10 mg was evaluated in 301 patients on maximally tolerated statins with high risk for CVD (*Ballantyne et al 2019*). Patients were randomized to the fixed dose combination of bempedoic acid/ezetimibe, bempedoic acid 180 mg daily, ezetimibe 10 mg daily, or placebo. The mean LDL-C baseline level was 149.7 mg/dL. At week 12, bempedoic acid/ezetimibe reduced LDL-C by 38.0% compared to placebo (95% CI, -46.5 to -29.6; p < 0.001), by 19.0% compared to bempedoic acid monotherapy (95% CI, -26.1 to -11.9; p < 0.001) and by 13.1% compared to ezetimibe monotherapy (95% CI, -19.7 to -6.5; p < 0.001).
- CLEAR OUTCOMES is an ongoing, event-driven, DB, MC, PC RCT that will evaluate bempedoic acid for the occurrence of major adverse cardiovascular events (MACE), defined as CV death, nonfatal MI, nonfatal stroke, or coronary revascularization, in approximately 12,600 patients who are statin intolerant with LDL-C ≥ 100 mg/dL, at high risk for, or have established CVD (*ClinicalTrials.gov [NCT02993406]*). Statin intolerance is defined as the inability to tolerate ≥ 2 statins, with 1 at low dose. The CLEAR OUTCOMES trial is anticipated to be completed in 2022.

CLINICAL GUIDELINES

- In general, statins are recommended first-line for the reduction of LDL-C; if the target goal is not achieved, the addition of ezetimibe, or bile acid sequestrants in select patients, should be considered. If further LDL-C reduction is needed to achieve target LDL-C goals in select patients, PCSK9 inhibitors may be considered (*American Diabetes Association [ADA] 2020, Cosentino et al 2020, Grundy et al 2019, Knuuti et al 2020, Mach et al 2020, Rosenzweig et al 2019*).
  - Statin intolerance: In patients with mild statin-associated AEs, rechallenge with a statin should be considered to achieve a maximal LDL-C lowering by modified dosing regimen, an alternate statin, or in combination with nonstatin therapy. In patients at increased ASCVD risk with severe statin-associated muscle symptoms or recurrent statin-associated muscle symptoms despite appropriate statin rechallenge, it is reasonable to use RCT proven nonstatin therapy that is likely to provide net clinical benefit.
- The American Association of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE) guideline recommends LDL-C treatment goals based on ASCVD risk categories. Target LDL-C levels range from < 130 mg/dL for patients at low CV risk with zero ASCVD risk factors, to < 55 mg/dL for patients considered at extreme risk with progressive ASCVD. Statin therapy is recommended as the primary therapy to achieve target LDL-C goals on the basis of morbidity and mortality outcome trials. In statin intolerant patients, an alternate statin, lower statin dose or frequency, or addition of a nonstatin LDL-C therapy such as ezetimibe should be considered. Ezetimibe can be used in combination with statins to further reduce both LDL-C and ASCVD risk (*Garber et al 2020, Jellinger et al 2017*).
- The objective of the Synopsis of the Kidney Disease: Improving Global Outcomes (KDIGO) 2013 Clinical Practice Guideline on Lipid Management in Chronic Kidney Disease (CKD) is to offer guidance on the management of dyslipidemia and use of cholesterol lowering medications in all adults and children with known CKD (defined by reduced estimated glomerular filtration rate [eGFR] or markers of kidney damage, such as abnormal albuminuria). A key element

was the recommendation for statin or combination statin/ezetimibe treatment of adults aged 50 years or older with eGFR rates < 60 mL/min/1.73 m^2 but not treated with chronic dialysis or kidney transplantation (*Tonelli et al 2014).*

SAFETY SUMMARY

Ezetimibe

- Ezetimibe, administered alone or with statin, is generally well tolerated. For ezetimibe monotherapy, AEs that were reported at a frequency ≥ 2% and exceeding placebo included diarrhea, fatigue, upper respiratory tract infection, sinusitis, influenza, arthralgia, and pain in extremity.
- Ezetimibe is contraindicated for use in combination with a statin in patients with active liver disease or unexplained persistent elevations in liver enzymes.
- Cyclosporine may significantly increase ezetimibe serum concentrations. In addition, ezetimibe can increase cyclosporine serum concentrations.
- Ezetimibe serum concentrations may be decreased by the concomitant administration of the bile acid sequestrants.
- The use of ezetimibe with a specific statin or fenofibrate should be in accordance with the prescribing information of that product. When administered with a statin, assessment of liver function should be performed at baseline and according to the statin prescribing information.
- Ezetimibe is Pregnancy Risk Factor C. AEs were observed in some animal reproduction studies. Use is contraindicated in pregnant women who require combination therapy with a statin.

Bempedoic acid

- Warnings for the bempedoic acid products include the risk for hyperuricemia and tendon rupture. Bempedoic acid/ezetimibe has additional warnings for liver enzyme elevations, myopathy and/or rhabdomyolysis, and hepatic impairment.
- Concomitant use of bempedoic acid with pravastatin or simvastatin causes an increase in statin concentration and may increase the risk of statin-related myopathy. Bempedoic acid combinations with simvastatin doses of > 20 mg or pravastatin doses > 40 mg should be avoided.
- Bempedoic acid may be used in patients with moderate hepatic impairment (Child-Pugh B) without dosage adjustment; however, bempedoic acid has not been studied in patients with severe hepatic impairment (Child-Pugh C).
- No data are available on bempedoic acid use in pregnant women to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Because bempedoic acid decreases cholesterol synthesis and possibly other biologically active substances derived from cholesterol, bempedoic acid may cause fetal harm when administered to pregnant women based on the mechanism of action.
- The most common AEs with bempedoic acid and bempedoic acid/ezetimibe (incidence ≥ 2% and greater than placebo) were upper respiratory tract infection, muscle spasms, hyperuricemia, back pain, abdominal pain or discomfort, bronchitis, pain in extremity, anemia, and elevated liver enzymes. Additional AEs with bempedoic acid/ezetimibe were diarrhea, arthralgia, sinusitis, fatigue, and influenza.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Nexletol (bempedoic acid)	Tablets	Oral	Daily	
Nexlizet (bempedoic acid/ ezetimibe)	Tablets	Oral	Daily	• Tablets should be swallowed whole.
Zetia (ezetimibe)	Tablets	Oral	Daily	• Based on available data, there are no pharmacokinetic differences between adolescents and adults. Pharmacokinetic data in the

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				pediatric population < 10 years of age are not available.

See the current prescribing information for full details

CONCLUSION

- Ezetimibe is the only cholesterol absorption inhibitor available and is FDA-approved for the treatment of primary hyperlipidemia, HoFH, and homozygous sitosterolemia. Ezetimibe has a unique mechanism of action and reduces blood cholesterol by inhibiting the absorption of cholesterol by the small intestine.
  - The results from clinical trials consistently demonstrate that ezetimibe is safe and effective for the management of lipid disorders, whether as monotherapy or in combination with a statin or fenofibrate. Efficacy in reducing CV events with simvastatin plus ezetimibe has been demonstrated in the IMPROVE-IT trial; after a median of 6 years, patients randomized to ezetimibe/simvastatin had a 6.4% relative risk reduction (~2% absolute reduction) of CV events (defined as a composite of CV death, nonfatal MI, unstable angina requiring re-hospitalization, coronary revascularization, or nonfatal stroke) compared with those who received simvastatin alone (*Cannon et al 2015*).
- Bempedoic acid is a new lipid lowering agent that reduces LDL-C through ACL inhibition, an upstream step in the cholesterol biosynthesis pathway from the enzyme that statins inhibit, HMG-CoA reductase. The result is decreased cholesterol synthesis in the liver and upregulation of low-density lipoprotein receptors which lower LDL-C in the blood. Bempedoic acid/ezetimibe is a fixed dose combination which lowers LDL-C by ACL inhibition and intestinal cholesterol absorption inhibition.
  - Bempedoic acid has been shown to reduce LDL-C by 17% to 18% over 12 weeks in patients on maximally tolerated statins. In statin intolerant patients, bempedoic acid reduced LDL-C by 21%. Bempedoic acid/ezetimibe in patients on maximally tolerated statins reduced LDL-C by 38% compared to placebo. The effect of bempedoic acid on CV outcomes are pending completion of an ongoing trial.
- The 2018 ACC/AHA cholesterol guidelines emphasize adherence to lifestyle modifications and to statin therapy before considering the addition of a nonstatin drug. The addition of ezetimibe may be considered in very high-risk patients with ASCVD or those with severe primary hypercholesterolemia who have not met their LDL-C target while on statin therapy (*Grundy et al 2019*). Ezetimibe may be helpful for avoiding high doses of statins in patients who are unable to achieve their lipid goals on low- to moderate-dose statin therapy. The cholesterol management guidelines have not yet addressed the place in therapy for bempedoic acid.

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Publication Date: May 14, 2020

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 [ER] tablet), Flolipid (simvastatin oral suspension), Zypitamag (pitavastatin tablet), and Ezallor Sprinkle (rosuvastatin capsule) (*Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*).
- 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 Web site 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	Generic Availability
Altoprev (lovastatin ER)	-
Crestor, Ezallor Sprinkle (rosuvastatin)	✔ -
Flolipid (simvastatin oral suspension)	-
Lescol (fluvastatin)*	✔
Lescol XL (fluvastatin ER)	✔
Lipitor (atorvastatin)	✔
Livalo, Zypitamag (pitavastatin)€	✔ -
Mevacor (lovastatin)*	✔
Pravachol (pravastatin)	✔
Zocor (simvastatin)	✔
Caduet (amlodipine/atorvastatin)	✔
Liptruzet† (ezetimibe/atorvastatin)	✔
Vytorin	✔

Drug	Generic Availability
(ezetimibe/simvastatin)	

Abbreviation: ER = extended-release.
*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 approved by the FDA; however, current market availability is unknown.

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

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 TC, LDL-C, 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 HeFH (Livalo, no further conditions for use) 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 CVD or ≥ 2 other cardiovascular risk factors are present in the pediatric patient	✔ ¶	✔ #	✔ ** (IR)	✔ ¥	✔ ††	✔ ††	✔ **	✔ (atorvastatin)		
Reduce elevated TG and VLDL-C in patients with primary dysbetalipoproteinemia							✔			
Reduce TC and LDL-C in patients with 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 MI and stroke in patients with type 2 diabetes, and without clinically evident 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			✔γ							
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 ≥ 1 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)		

Abbreviations: ApoB = apolipoprotein B, CAD = coronary artery disease, CHD = coronary heart disease, CVD = cardiovascular disease, ER = extended-release, HDL-C = high-density lipoprotein cholesterol, HeFH = heterozygous familial hypercholesterolemia, HoFH = homozygous familial hypercholesterolemia, IR = immediate-release, HTN = hypertension, LDL-C = low-density lipoprotein cholesterol, MI = myocardial infarction, TC = total cholesterol, TG = triglycerides, VLDL-C = very low-density lipoprotein cholesterol.

§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 ≥ 1 year post-menarche, 10 to 16 years of age.

**In adolescent boys and girls who are ≥ 1 year post-menarche, 10 to 17 years of age.

††In children and adolescent patients 8 to 17 years of age

ǂIn children and adolescents ages 7 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

¥For pediatric patients ≥ 8 years of age (Livalo only)

δApproved indications for rosuvastatin capsules (Ezallor Sprinkle)

(*Prescribing information: Altoprev 2018, Caduet 2019, Crestor 2018, Ezallor Sprinkle 2020, Flolipid 2017, Fluvastatin 2017, Lescol XL 2017, Lipitor 2019, Livalo 2019, Lovastatin 2019, Pravachol 2017, Vytorin 2019, Zocor 2019, Zypitamag 2020*)
Clinical Pharmacology 2020

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, 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 al1994, 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 2019, 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 al1996, 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 reduction of 31% 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 major adverse cardiovascular events (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 = 6605) 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 3 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 = 8888) 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 3 to 6 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 = 3086), 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 percutaneous coronary intervention (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%; HR, 0.88; 95% CI, 0.69 to 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 to 0.98; p = 0.029) and ischemic stroke (HR, 0.76; 95% CI, 0.63 to 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 = 4162) 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 2 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 2 treatments (p = 0.11) (*Cannon et al 2004*).
- A meta-analysis which assessed the efficacy of high dose atorvastatin in patients who underwent PCI (N = 2850) found that atorvastatin significantly reduced the risk of MI in patients with PCI compared to placebo (relative risk [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 were no differences in 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 2019*). A more recent systematic review and meta-analysis involving 1191 children and adolescents with familial hypercholesterolemia (aged 13.3 ± 2.5 years) concluded similarly that statin therapy is effective in reducing TC, LDL-C, TG, and apo-B, and increasing HDL-C concentrations, with no major safety issues (*Anagnostis et al 2020*).
- 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.
- A recent review concluded that statin-induced hepatotoxicity occurs rarely and that concern that hepatic damage may occur should not be a reason to avoid statin therapy in patients with appropriate clinical indications for use (*Meurer et al*

2020). The authors recommended liver function testing at statin initiation and as clinically indicated while on therapy; however, ongoing routine monitoring was not recommended. Additionally, statins should be avoided in patients with liver failure, acute liver injury, and decompensated cirrhosis.

- In December 2018, the American Heart Association (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 2019*).
- 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 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 (eg, 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	After initiation and/or upon titration, lipid levels should be analyzed within 2 to 4 weeks and dosage adjusted accordingly. Dosage adjustments may be necessary in	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
		HeFH in pediatric patients 10 to 17 years old: Tablet: initial dose 10 mg/day, maximum dose 20 mg/day	patients taking cyclosporine, clarithromycin, itraconazole, or certain protease inhibitors.	
Fluvastatin	Capsule: 20 mg 40 mg ER 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. ER tablet: 80 mg once daily HeFH in pediatric patients: Capsule: 20 mg daily, maximum dose 40 mg twice daily ER tablet: 80 mg once daily	After initiation and/or upon titration, lipid levels should be analyzed after 4 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 2 divided doses (IR capsule). May be administered with or without food. Tablets may be taken at any time during the day (ER tablet). Tablets should be swallowed whole. (ER tablet).
Lovastatin	ER tablet: 20 mg 40 mg 60 mg Tablet: 10 mg 20 mg 40 mg	Hyperlipidemia: ER 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 2 divided doses; maximum, 80 mg/day Prevention of CVD: ER 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 2 divided doses; maximum, 80 mg/day	Prior to initiation and periodically during therapy, lipid levels should be analyzed and dosage adjusted accordingly.	ER tablet should be taken at bedtime. ER tablets should be swallowed whole. IR tablet should be taken with an evening meal.
Pitavastatin	Tablet: 1 mg 2 mg	Hyperlipidemia:	After initiation and/or upon titration, lipid	May be administered with or without food.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	4 mg	Tablet: initial 2 mg once daily; maintenance, 1 to 4 mg/day; maximum, 4 mg/day <u>Reduce TC, LDL-C and apo B in patients with HoFH (ages 8 years and older):</u> Tablet: initial 2 mg once daily; maximum, 4 mg/day	levels should be analyzed after 4 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.	Tablets may be taken at any time during the day.
Pravastatin	Tablet: 10 mg* 20 mg 40 mg 80 mg	<u>Hyperlipidemia:</u> Tablet: initial 40 mg once daily; maintenance, 40 to 80 mg once daily <u>Prevention of CVD:</u> Tablet: initial 40 mg once daily; maintenance, 40 to 80 mg once daily <u>Pediatric patients</u>: Ages 8 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 4 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.
Rosuvastatin	Tablet: 5 mg 10 mg 20 mg	<u>Tablets:</u> <u>Hyperlipidemia:</u> Initial 10 to 20 mg once daily; maintenance, 5 to 40 mg/day	After initiation and/or upon titration, lipid levels should be	May be administered with or without food.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	40 mg Capsule: 5 mg 10 mg 20 mg 40 mg	<u>Reduce TC, LDL-C and apo B in patients with HoFH:</u> Initial 20 mg once daily; Ages 7 to 17 years: 20 mg once daily <u>Reduce TC, LDL-C and apo B in pediatric patients with HeFH:</u> Aged 8 to less than 10 years: maintenance, 5 to 10 mg/day Aged 10 to 17 years: maintenance, 5 to 20 mg/day <u>Capsules:</u> Initial 10 to 20 mg once daily; usual starting dose in HoFH is 20 mg once daily Maximum dose: 40 mg once daily	analyzed within 2 to 4 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 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	<u>Hyperlipidemia:</u> initial 10 or 20 mg once daily; maintenance, 5 to 40 mg/day <u>Reduce TC and LDL-C in patients with HoFH as an adjunct to other lipid lowering treatments or if such treatments are unavailable:</u> 40 mg once daily <u>Prevention of CVD:</u> initial 10 or 20 mg once daily; maintenance, 5 to 40 mg/day <u>Reduce TC, LDL-C and apo B in pediatric patients with HeFH:</u> Aged 10 to 17 years: 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 4 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. for 12 months or more) without evidence of muscle toxicity)	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 have been taking the 80 mg dose chronically without

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			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. Use caution in patients receiving ≥ 1 gram daily of	evidence of muscle toxicity.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			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 HTN/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 2 to 4 weeks and dosage adjusted accordingly. Dosage should be adjusted to achieve blood pressure goals. In general wait 7 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 ≥ 2 weeks. For patients taking clarithromycin, itraconazole, saquinavir + ritonavir, darunavir + ritonavir, or fosamprenair alone or with	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: 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: 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 ≥ 2 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 verapamil, diltiazem, or dronedarone. Max dose is 10/20 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
			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.	

Abbreviations: ER = extended-release, IR = immediate-release.
*Pravachol 10 mg is no longer available; however, generic pravastatin 10 mg remains available.

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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 efficacy observed between elderly and younger adult patients.	Approved for use in children 9 to 16 years of age for the treatment of HeFH. Safety and efficacy in children for other approved indications have	No dosage adjustment required in mild to moderate renal dysfunction. Use with caution in	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Unclassified† Contraindicated in women who are pregnant or may become pregnant. Potential excretion into

		not been established.	severe renal dysfunction; doses above 40 mg per day have not been studied.		breast milk; contraindicated during breastfeeding
Lovastatin	No dosage adjustment required in the elderly. The initial starting dose of lovastatin ER 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.	Approved for use in children 8 years of age and older for the treatment of HeFH (Livalo). Safety and efficacy in children have not been established (Zypitamag).	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	Approved for use in children 8 to 18 years of age for the treatment of HeFH. Safety and efficacy in children	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

	and younger adult patients.	< 8 years of age have not been established.			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 Sprinkle 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 monitoring is recommended.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Pregnancy Category X Unknown whether excreted in breast milk; contraindicated during breastfeeding.
Combination Products					
amlodipine/ atorvastatin	Safety and efficacy in elderly patients have not been established.	Safety and efficacy in children have not been established.	No dosage adjustment required.	Contraindicated in active liver disease.	Unclassified† Contraindicated for use during pregnancy and in women who may

	Elderly patients have decreased clearance of amlodipine; lower initial doses of amlodipine may be required.	Safety and efficacy of atorvastatin in children < 10 years and amlodipine in children < 6 years of age have not been established			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.

Abbreviation: ER=extended-release.

* 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.

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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 ER), Flolipid (simvastatin oral suspension), Zypitamag (pitavastatin), and Ezallor Sprinkle (rosuvastatin capsule) (*Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*).
- 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, American College of Cardiology (ACC)/AHA and a variety of other organizations released a new guideline on the management of blood cholesterol (*Grundy et al 2019*). 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 proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor.
- The 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease incorporates the 2018 management of blood cholesterol guideline recommendations into their guidance (*Arnett et al 2019*). The guideline also discusses the importance of having patient-clinician risk discussions prior to initiating pharmacologic treatment for reducing ASCVD risk. Statins remain first-line treatment for primary prevention of ASCVD for those with LDL-C elevations ≥ 190 mg/dL, those with diabetes mellitus, and those who have determined to be at sufficient risk for ASCVD after a patient-clinician discussion.
- The 2013 ACC/AHA Guidelines on Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults focus on primary and secondary ASCVD risk reduction in adults (*Stone et al 2014*).
  - These guidelines established 4 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 to 189 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 recommends aggressive pharmacological treatment for patients with HeFH beginning at age 8 to 10 years. Pharmacological treatment may also be considered in younger patients (less than 8 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 3 months, then ezetimibe may be added. If LDL-C continues to be above goal after 3 months of 2-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 2019 AHA Scientific Statement on Cardiovascular Risk Reduction in High-Risk Pediatric Patients recommends initiating both lifestyle interventions and statin therapy for those at high risk, which includes patients with HoFH (*de Ferranti et al 2019*). For patients at moderate risk, including those with HeFH, statin therapy should be initiated if LDL-C goals are not met after 3 months of lifestyle interventions. Respective LDL-C goals for high risk and moderate risk pediatric patients are < 100 mg/dL and < 130 mg/dL. Lastly, the statement also notes that patients with HoFH will also require nonstatin therapies such as LDL apheresis or a PCSK9 inhibitor.
- 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 years (2) they have one or more CVD risk factor such as dyslipidemia, diabetes, HTN, 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 ≥ 1 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 PCSK9 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 basis 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 1% to 2% 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. A recent review concluded that statin-induced hepatotoxicity occurs rarely and that concern that hepatic damage may occur should not be a reason to avoid statin therapy in patients with appropriate clinical indications for use (*Meurer et al 2020*).
- 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 2019*).
- Pravastatin is the only statin that does not undergo 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.

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Publication Date: July 1, 2020

Therapeutic Class Overview
Acne Agents

INTRODUCTION

- Acne vulgaris is a chronic inflammatory dermatosis characterized by open and/or closed comedones (blackheads and whiteheads) and inflammatory lesions including papules, pustules, or nodules (*Zaenglein et al 2016*). Four primary pathogenic factors interact in a complex manner to produce the different acne lesions. The four factors include sebum production by the sebaceous gland, Propionibacterium acnes (*P. acnes*) follicular colonization, alteration in the keratinization process, and the release of inflammatory mediators to the skin (*Thiboutot et al 2009*).
- Several options exist for the treatment of acne vulgaris including topical agents, systemic antibacterial agents, hormonal agents, isotretinoin, laser and light therapies, miscellaneous therapies, complementary and alternative therapies, and dietary restrictions. Topical therapy of acne vulgaris includes agents that are available over the counter or by prescription, and choice of therapy can be influenced by various factors including patient age, site of involvement, extent and severity of disease, and patient preference. Topical agents include antibiotics, benzoyl peroxide, retinoids, azelaic acid, dapsone, and salicylic acid (*Gollnick et al 2016, Zaenglein et al 2016*).
- Traditionally, the treatment of acne vulgaris has been directed toward controlling *P. acnes* and centered on the use of antibiotics. Current treatment modalities are directed toward as many pathogenic factors as possible. Combination treatment has the ability to target multiple pathogenic factors, including inflammatory and noninflammatory lesions (*Eichenfield et al 2013, Thiboutot et al 2009*). Data have shown that combination therapy results in faster and more complete clearing of acne vulgaris lesions compared with monotherapy (*Eichenfield et al 2013, Nast et al 2016, Thiboutot et al 2009*). Combination therapy should be used in the majority of patients with acne (*Gollnick et al 2016, Zaenglein et al 2016*). Additionally, antibiotics and benzoyl peroxide both target *P. acnes*; however, unlike antibiotics, benzoyl peroxide has not been associated with the development of bacterial resistance (*Zaenglein et al 2016*).
- Topical retinoids are recommended as monotherapy in primarily mild, comedonal acne, or in combination with topical or oral antibiotics in patients with mixed or primarily inflammatory moderate acne vulgaris (*Gollnick et al 2016, Zaenglein et al 2016*). The comedolytic and anti-comedogenic properties associated with topical retinoids result in a reduction in the formation of microcomedones and comedones (*Zaenglein et al 2016*). For severe acne, oral antibiotics with topical therapy or oral isotretinoin is recommended for first-line treatment (*Zaenglein et al 2016*, *Zaenglein et al 2018*). Oral isotretinoin is one of several alternatives for treatment-resistant moderate acne.
- The focus of this review will be the use of the topical agents and oral isotretinoin for the treatment of acne. Agents prescribed solely for rosacea and products combining hyaluronate, niacinamide, or resorcinol will not be included in this review. The following table may not be all inclusive as products enter and leave the market frequently in this class.
- Medispan Class: Acne Products

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Antibiotics	
Aczone (dapsone) gel 5%	✔
Aczone (dapsone) gel 7.5%	-
Clindagel (clindamycin) gel 1%	✔
Cleocin T (clindamycin) gel, lotion, solution 1%	✔
Clindacin-P, Clindacin ETZ (clindamycin) swab 1%	✔
Clindacin Pac, Clindacin ETZ (clindamycin and cleanser kit) swab 1%	✔
NuCaraClinPAK (clindamycin and moisturizer kit) gel 1%	✔
Evoclin (clindamycin) foam 1%	✔
Erygel (erythromycin) gel 2%	✔
Ery (erythromycin) pads, solution 2%	✔
Amzeeq (minocycline) topical foam 4%	-

Drug	Generic Availability
Benzoyl Peroxide and Combinations	
benzoyl peroxide bar 10%; cream 2.5%, 10%; cleanser 3.5%; cleanser ER 4.4%; external liquid 2.5%, 4%, 5%, 5.5%, 6%, 6.9%, 7%, 10%; foam 5.3%, 9.8%, 10%; gel 2.5%, 2.75%, 4%, 5%, 5.25%, 8%, 10%; foaming cloths 6%; lotion 5%, 8%, 10%; wash/lotion kits 2.5/3.7%, 2.5/10%	✔ †
Enzoclear (benzoyl peroxide) foam 9.8%	-
Riax (benzoyl peroxide) foam 5.5%, 9.5%	-
BenzePrO, BPO (benzoyl peroxide) foam 5.2%, 9.7%; external liquid 6.8%; foaming cloths 5.8%	-
Zaclir (benzoyl peroxide) lotion 8%	-
Benziq LS (benzoyl peroxide) external liquid 5.25%	-
Vanoxide-HC (benzoyl peroxide/hydrocortisone) lotion 5/0.5%, 7.5/1%	✔
Benzoyl Peroxide – Antibiotic Combinations	
Acanya (benzoyl peroxide/clindamycin) gel 2.5/1.2%	✔
Benzaclin (benzoyl peroxide/clindamycin) gel 5/1%	✔
Duac, Neuac (benzoyl peroxide/clindamycin) gel, kit 5/1.2%	✔
Neuac, NuCaraRxPAK (benzoyl peroxide/clindamycin) gel, kit 2.5/1%	✔
Onexton (benzoyl peroxide/clindamycin) gel 3.75/1.2%	-
Benzamycin (benzoyl peroxide/erythromycin) gel 5/3%	✔
Topical Retinoids – Single Entity	
adapalene external solution 0.1%	✔
adapalene pad 0.1%	✔
Differin (adapalene) cream 0.1%	✔
Differin (adapalene) gel 0.1%†, 0.3%	✔
Differin (adapalene) lotion 0.1%	-
Arazlo (tazarotene) lotion 0.045%	-
Fabior (tazarotene) foam 0.1%	-
Tazorac (tazarotene) gel and cream 0.05%, gel 0.1%	-
Tazorac (tazarotene) cream 0.1%	✔
Altreno (tretinoin) lotion 0.05%	-
Atralin (tretinoin) gel 0.05%	✔
Avita (tretinoin) cream and gel 0.025%	✔
Retin-A (tretinoin) cream 0.025%, 0.05%, 0.1%; gel 0.01%, 0.025%	✔
Retin-A Micro (tretinoin microsphere) gel 0.04%, 0.1%	✔
Retin-A Micro (tretinoin microsphere) gel 0.06%, 0.08%	-
Aklief (trifarotene) cream 0.005%	-
Topical Retinoids – Combination	
Epiduo (adapalene/benzoyl peroxide) gel 0.1/2.5%	✔
Epiduo Forte (adapalene/benzoyl peroxide) gel 0.3/2.5%	-
adapalene/benzoyl peroxide/clindamycin gel 0.3/2.5/1%	✔
Veltin, Ziana (clindamycin phosphate/tretinoin) gel 1.2/0.025%	✔
Miscellaneous Topical Therapies	
Azelex (azelaic acid) cream 20%	-
Sulfacetamide/Sulfur and Combinations	

Drug	Generic Availability
sodium sulfacetamide cream 10% (Ovace Plus); lotion 9.8% (Ovace Plus), 10% (Klaron); shampoo 10% (Ovace Plus); wash external liquid 10% (Ovace, Ovace Plus); wash external gel 10% (Ovace Plus); foam 9.8% (Ovace Plus)	✔
sulfacetamide with sulfur wash 9/4% (Sumaxin), 9/4.5% (Sumadan); with sulfur cleanser 9.8/4.8% (Plexion), 10/2% (Avar LS); with sulfur emulsion 10/1% (BP 10-1, Sulfamez), 10/5% (Avar); with sulfur in urea emulsion 10/4% (BP Cleansing Wash), 10/5%; with sulfur suspension 8/4% (SulfaCleanse 8/4), 10/5%; with sulfur cream 9.8/4.8% (Plexion), 10/2% (Avar-e LS), 10/5% (Avar-e Emollient, Avar-e Green, SSS 10-5); with sulfur foam 10/5% (SSS 10-5); with sulfur lotion 9.8/4.8% (Plexion), 10/5%; with sulfur pad 10/4% (Sumaxin); with sulfur cloths 9.8/4.8% (Plexion)	✔
Sumadan kit wash 9/4.5%, Sumaxin CP kit pad 10/4%, (sulfacetamide sodium/sulfur/skin cleanser)	✔
Sumadan XLT kit wash 9/4.5% (sulfacetamide sodium/sulfur/sunscreen)	✔
sulfur external bar 3%, 10%; lotion 5%	✔ *
SAStid (sulfur/salicylic acid) external bar 3/5%	✔ *
Oral Retinoids	
Absorica (isotretinoin) oral capsule 10 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg	- ‡
Absorica LD (isotretinoin) oral capsule 8 mg, 16 mg, 24 mg, 32 mg	-
Amnesteem, Claravis, Myorisan, Zenatane (isotretinoin) oral capsule 10 mg, 20 mg, 30 mg, 40 mg	✔ δ

Abbreviation: ER = extended-release
*Over-the-counter (OTC) only product(s)
†Prescription and/or OTC product(s)
‡Absorica 10, 20, 30, and 40 mg products are BX rated according to the Orange Book, considered to be not therapeutically equivalent to other pharmaceutically equivalent products.
δClaravis is the reference standard and other products are branded generics considered bioequivalent to Claravis

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications*

Drug	Acne vulgaris	Inflammatory acne vulgaris	Adjunctive therapy for acne vulgaris, acne rosacea, and seborrheic dermatitis	Treatment and prevention of mild to moderate acne vulgaris	Treatment of severe recalcitrant nodular acne
Antibiotics					
Aczone (dapsone)	✔	-	-	-	-
Clindamycin	✔	-	-	-	-
Erythromycin	✔	-	-	-	-
Amzeeq (minocycline)	✔	-	-	-	-
Benzoyl Peroxide – Single Entity					
Benzoyl peroxide	✔	-	-	✔	
Benzoyl Peroxide – Antibiotic Combinations					
Benzoyl peroxide/clindamycin	✔ (Acanya, Benzaclin, Onexton)	✔ (Duac, Neuac)	-	-	-
Benzoyl peroxide/ erythromycin	✔ (Benzamycin)	-	-	-	-
Benzoyl Peroxide – Other Combinations					

Drug	Acne vulgaris	Inflammatory acne vulgaris	Adjunctive therapy for acne vulgaris, acne rosacea, and seborrheic dermatitis	Treatment and prevention of mild to moderate acne vulgaris	Treatment of severe recalcitrant nodular acne
Vanoxide-HC (benzoyl peroxide/hydrocortisone)	✔	-	-	-	-
Topical Retinoids – Single Entity					
Differin (adapalene)	✔	-	-	-	-
Arazlo, Fabior, Tazorac (tazarotene)†	✔ (0.1% Tazorac strengths only)	-	-	-	-
Tretinoin	✔	-	-	-	-
Aklief (trifarotene)	✔	-	-	-	-
Topical Retinoids – Combination					
Epiduo, Epiduo Forte (adapalene/benzoyl peroxide)	✔	-	-	-	-
Veltin, Ziana (clindamycin/tretinoin)	✔	-	-	-	-
Miscellaneous Topical Therapies					
Azelex (azelaic acid)	-	✔	-	-	-
Sulfacetamide	✔ (gel, lotion)	-	-	-	-
Sulfacetamide/sulfur	-	-	✔	-	-
Oral Retinoids					
Absorica, Absorica LD, Amnesteem, Claravis, Myorisan, Zenatane (isotretinoin)	-	-	-	-	✔

*Approved ages vary by product.
†Tazorac is also approved for the treatment of psoriasis.

(*Prescribing information: Absorica/Absorica LD 2019, Acanya 2016, Aczone 7.5% 2019, Aczone 5% 2018, adapalene topical solution 2019, adalapene swab 2019, adapalene/benzoyl peroxide/clindamycin gel 2019, Aklief 2019, Altreno 2018, Amnesteem 2018, Amzeeq 2019, Arazlo 2019, Atralin 2016, Azelex 2019, Benzaclin 2017, Benzamycin 2019, BPO 4% gel 2018, Claravis 2018, Cleocin T 2019, Clindagel 2017, Differin cream 2011, Differin lotion 2018, Duac 2015, Epiduo 2018, Epiduo Forte 2015, Fabior 2018, Myorisan 2018, Onexton 2018, Retin-A 2019, Retin-A MICRO 2017, Tazorac gel 2018, Tazorac cream 2017,Vanoxide-HC 2018, Veltin 2019, Zenatane 2019, Ziana 2017, Clinical Pharmacology 2020, Lexi-comp 2020, Micromedex 2020*)

- 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

- All agents included in this review are FDA-approved for the treatment of acne vulgaris, and clinical trials have demonstrated their effectiveness compared to a placebo vehicle. In addition, there have been some trials evaluating the comparative efficacy of the agents in the class. This clinical efficacy summary will focus on comparative trials.

Dapsone

- Dapsone was shown to be effective in the management of acne. In a clinical trial comparing dapsone 5% gel to the combination of dapsone plus adapalene, dapsone plus benzoyl peroxide, or dapsone plus moisturizer, all treatment arms showed similar efficacy in reducing inflammatory lesions over 12 weeks (*Fleischer et al 2010*).
- The approval of dapsone 7.5% gel was based on 2 randomized, double-blind (DB), vehicle-controlled, multicenter (MC) studies. A total of 4,340 patients were randomized to receive dapsone 7.5% gel or vehicle once daily for 12 weeks. The primary endpoint was the percentage of patients with none (score of 0) or minimal (score of 1) on the 5-point Global

Acne Assessment Score (GAAS) scale at week 12. The key secondary endpoints were mean absolute change from baseline in both inflammatory and non-inflammatory lesion counts (*Eichenfield et al 2016, Stein et al 2016*).
  - The majority of the subjects had moderate acne vulgaris, ie, 20 to 50 inflammatory and 30 to 100 non-inflammatory lesions at baseline.
  - In both studies, the GAAS success rate was approximately 30% in the dapsone arm and 21% in the vehicle arm.
  - In Study 1, the mean percent reduction in inflammatory lesions was 55.5% in the dapsone group and 49% in the vehicle group. In Study 2, it was 53.8% and 47.3%, respectively.
  - For the mean percent reduction in non-inflammatory lesions, 44.4% was reported in the dapsone group and 38.4% in the vehicle group in Study 1. In Study 2, it was 45.9% in the dapsone group and 40.4% in the vehicle group.

Benzoyl Peroxide

- There is limited evidence that differentiates the various formulations (gels, lotions, solutions, etc.) and strengths of the benzoyl peroxide and antibiotic combination agents. Clinical studies evaluating combination therapy with benzoyl peroxide and either clindamycin or erythromycin have consistently demonstrated that these agents are more effective compared to their respective monotherapies (*Chalker et al 1983, Cunliffe et al 2002, Leyden et al 2001, Lookingbill et al 1997, Thiboutot et al 2008b, Webster et al 2009, Xu et al 2016*).
- In a study by Leyden et al (N = 492), patients with moderate to severe acne vulgaris were randomized to receive benzoyl peroxide/clindamycin, benzoyl peroxide/erythromycin, or benzoyl peroxide alone for 10 weeks. The decrease in the number of inflammatory lesions from baseline, the primary endpoint, was significantly greater for those treated with benzoyl peroxide/clindamycin compared to benzoyl peroxide alone (P = 0.04). The average decrease in the number of inflammatory lesions was similar in patients treated with benzoyl peroxide/clindamycin and benzoyl peroxide/erythromycin (P = 0.4) (*Leyden et al 2001*).
- In a meta-analysis by *Seidler et al,* there was a significantly greater percent reduction in noninflammatory acne lesion count with benzoyl peroxide/clindamycin 2.5%/1.2% (-43.4%; 95% confidence interval [CI] depicted but not reported) compared to benzoyl peroxide/clindamycin 5%/1% (-38.2%; 95% CI depicted but not reported), benzoyl peroxide alone (-34.2%; 95% CI depicted but not reported), clindamycin alone (-27.9%; 95% CI depicted but not reported) and placebo (-14.9%; 95% CI depicted but not reported) over 10 to 12 weeks of treatment (*Seidler et al 2011*).
- Three clinical trials comparing benzoyl peroxide/clindamycin to adapalene monotherapy have reported consistently that the combination of benzoyl peroxide/clindamycin significantly reduces total lesion count over 12 weeks compared to adapalene (*Langner et al 2008, Ko et al 2009*). The combination of benzoyl peroxide/clindamycin in two trials also significantly reduced inflammatory lesion counts compared to baseline at week 12 to a greater extent than adapalene (*Langner et al 2008, Ko et al 2009*). For non-inflammatory lesion count, there were conflicting results among the studies (*Guerra-Tapia et al 2012, Ko et al 2009, Langner et al 2008*).

Topical Retinoids

- Topical retinoids can be used alone or in combination with antibiotics to treat both inflamed and noninflamed acne lesions, or for maintenance treatment of acne (*Medical Letter 2016*). All topical retinoids normalize keratinization and appear to have anti-inflammatory effects.
- Several comparative studies have been conducted evaluating the topical retinoids. Efficacy results are mixed, with trials demonstrating:
  - Equivalent efficacy between tretinoin 0.04% microgel and tretinoin 0.1% microgel (*Berger et al 2007*)
  - Equivalent efficacy between adapalene 0.1% gel and tretinoin 0.025% gel (*Cunliffe et al 1997, Ellis et al 1998, Grosshans et al 1998*)
  - Equivalent efficacy between adapalene 0.1% gel and tretinoin 0.1% microgel (*Nyirady et al 2001*)
  - Equivalent efficacy between adapalene 0.1% gel and tazarotene 0.1% cream (*Pariser et al 2008*)
  - Equivalent efficacy between adapalene 0.3% gel and tazarotene 0.1% gel (*Thiboutot et al 2008a*)
  - Greater efficacy with tazarotene 0.1% plus clindamycin 1% gel over adapalene 0.1% plus clindamycin 1% gel (*Maiti et al 2017*).
  - Greater efficacy with tazarotene 0.1% cream over adapalene 0.3% gel (*Tanghetti et al 2010*)
  - Greater efficacy with tazarotene 0.1% cream over adapalene 0.1% cream (*Shalita et al 2005*)
  - Greater efficacy with tretinoin 0.05% gel over adapalene 0.1% gel (*Pierard-Franchimont et al 1999*)
  - Greater efficacy with adapalene 0.1% gel over tretinoin 0.025% gel (*Cunliffe et al 1997, Shalita et al 1996*)

- Two studies (n = 820 for each study) demonstrated that tretinoin 0.05% lotion was more effective than a vehicle in improving Evaluator's Global Severity Score (EGSS) and reducing the number of inflammatory and non-inflammatory facial lesions at week 12 in patients aged ≥ 9 years (all P < 0.001). Success rates were 9.6% higher in Study 1 and 7.3% higher in Study 2 compared to the vehicle (*Tyring et al 2018*).
- Two studies (n = 1614 total) found that tazarotene 0.045% lotion significantly improved EGSS and the number of inflammatory and non-inflammatory lesions compared to vehicle in patients aged ≥ 9 years with moderate to severe acne. Success rates were 12.3% to 12.5% higher compared to vehicle in Study 1 and 2, respectively (*Arazlo prescribing information 2019*).
- Two randomized studies (n = 2420 total) found that patients aged ≥ 9 years with moderate acne experienced greater improvement in Investigator's Global Assessment (IGA) of the face and the number of inflammatory and non-inflammatory lesions (all P < 0.001) with trifarotene 0.005% cream compared to vehicle (*Tan et al 2019*).
- A meta-analysis of 5 MC, investigator-blinded, randomized controlled trials (RCTs) compared the efficacy of adapalene 0.1% gel to tretinoin 0.025% gel in the treatment of patients with acne vulgaris (N = 900) (*Cunliffe et al 1998*). Overall, adapalene demonstrated equivalent efficacy to tretinoin in terms of reducing inflammatory lesions (P = 0.51), non-inflammatory lesions (P = 0.38), and total lesion count (P = 0.48) at week 12, but demonstrated more rapid efficacy in reducing inflammatory and total lesions at week 1 compared to tretinoin (P < 0.05).
- A systematic review of 54 clinical trials compared the efficacy and safety/tolerability of the topical retinoids for the treatment of acne vulgaris:
  - Of 5 studies that compared use of adapalene to tazarotene, 4 found no difference in the percent change of the total lesion count between the two treatments. One study, which combined both adapalene and tazarotene with clindamycin, found a significant change in lesion count with tazarotene plus clindamycin (17.54 vs 11.03; P = 0.007).
  - In 1 study comparing adapalene 0.3%, 0.1% to tretinoin 0.05%, a significantly greater reduction in total lesion count was found with tretinoin at week 12 (76.7% tretinoin vs 66.4% adapalene 0.3% vs 57.8% adapalene 0.1%; P < 0.001).
  - In a 12-week study of 40 patients, no difference in efficacy was found between tretinoin and tazarotene in the change in IGA, absolute change in inflammatory and noninflammatory lesion count, and total lesion count from baseline to week 12.
  - When comparing safety, 62% of patients receiving tretinoin 0.05% reported adverse effects (AE), compared to 19% and 40% with adapalene 0.1% and 0.3%, respectively. Treatment with tazarotene was associated with significantly more AE than treatment with adapalene (55.4 vs 24.4%; P < 0.0012) (*Kolli et al 2019*).
- A retrospective, investigator-blinded, vehicle-controlled, photographic assessment study was conducted to assess the efficacy of topical retinoids as monotherapy for the treatment of inflammatory acne (*Leyden et al 2005*). Five investigators rated pre- and post-treatment photographs of patients (N = 577) who had participated in 12- or 15-week, DB, RCTs of tazarotene 0.1% gel, adapalene 0.1% gel, tretinoin 0.1% microgel, tretinoin 0.025% gel, and tazarotene 0.1% cream.
  - Tazarotene, adapalene, and tretinoin were all superior to vehicle. Between-retinoid comparisons showed greater incidences of clinically significant improvements in overall acne severity in the tazarotene group compared with the groups receiving adapalene (P ≤ 0.001) or tretinoin (P ≤ 0.01).
- There are several limitations to these studies, including relatively small sample sizes (Range: N = 25 to 323), short duration (typically 12 weeks), enrollment of patients with varying degrees of acne severity, and comparisons between different strengths and formulations of topical retinoids. In addition, most studies that showed greater efficacy data with adapalene were sponsored by Galderma, greater efficacy data with tretinoin were sponsored by Johnson and Johnson (Ortho Dermatologics), and greater efficacy data with tazarotene were sponsored by Allergan. Based on the varying efficacy results and study limitations, it is not clear whether one topical retinoid is more effective than another.
- Tazarotene foam led to greater decreases from baseline for all types of acne lesions compared to vehicle foam; direct comparisons to other forms of tazarotene and other therapies have not been completed (*Fabior prescribing information, 2018, Feldman et al 2013*).
- For the combination products, several studies evaluated the effectiveness of the combination products compared to their individual components. The adapalene/benzoyl peroxide combination showed a statistically superior success rate compared to monotherapy with adapalene or benzoyl peroxide (*Gold et al 2009, Gollnick et al 2009, Pariser et al 2007, Thiboutot et al 2007*). In addition, the clindamycin/tretinoin combination had statistically significant superiority for all comparisons vs monotherapy with clindamycin or tretinoin (*Jarratt et al 2012, Leyden et al 2006, Schlessinger et al 2007*).

Oral retinoids

- A 2018 Cochrane review evaluated 31 RCTs of oral isotretinoin to assess its efficacy and safety for acne vulgaris. Included trials were comparisons to placebo, systemic antibiotics plus topical agents (combination therapy), or isotretinoin in various formulations or dose regimens (*Costa et al 2018*). For the primary outcome of total inflammatory lesion count, oral isotretinoin did not produce a greater reduction in acne lesions compared to combination therapy after 20 to 24 weeks of therapy in patients with moderate to severe acne (risk ratio [RR] 1.01; 95% CI 0.96 to 1.06; n=3 studies; 400 patients). Another primary outcome of serious adverse effect frequency detected 1 serious event of Stevens-Johnson syndrome in the isotretinoin group. The risk of serious adverse effects was higher with oral isotretinoin compared to combination therapy but was not considered statistically significant (RR 3.0; 95% CI 0.12 to 72.98). Less serious adverse effects were significantly higher with isotretinoin compared to combination therapy (RR 1.67; 95% CI 1.42 to 1.98; n=2 studies; 351 patients). Oral isotretinoin compared to oral isotretinoin plus topical agents did not demonstrate a significant difference in outcomes. For dose regimens, continuous low dose and conventional isotretinoin dose demonstrated a greater decrease in inflammatory lesion count compared to intermittent dosing (1 week each month). Due to study design limitations, the authors of the review rated the level of this evidence as low to very low.

Other products

- No pertinent clinical studies were recently identified for the treatment of acne vulgaris with sulfacetamide or azelaic acid as monotherapy. Both are FDA-approved for the treatment of acne vulgaris.

CLINICAL GUIDELINES

- The American Academy of Dermatology (AAD) 2016 guidelines, the 2016 European evidence-based recommendations, and a 2018 consensus from the Global Alliance to Improve Outcomes in Acne generally suggest the use of combinations to treat acne (*Nast et al 2016, Thiboutot et al 2018, Zaenglein et al 2016*). The 2016 AAD Guidelines recommend retinoids as monotherapy in primarily comedonal acne, or in combination with topical or oral antibiotics in patients with mixed or primarily inflammatory acne lesions. Topical antibiotics are noted as effective therapies for acne; however, they are not recommended as monotherapy due to the risk of resistance. Benzoyl peroxide or combinations with antibiotics (erythromycin or clindamycin) are effective treatments as well and are recommended as monotherapy for mild acne, or with a topical retinoid or systemic antibiotic therapy for moderate to severe acne. Oral isotretinoin is one of the recommended treatment options for severe nodular acne and moderate acne that is treatment resistant or that causes scarring or psychosocial distress. Azelaic acid (Azelex) is a useful adjunctive therapy per the AAD and topical dapsone 5% gel can be recommended for inflammatory acne, particularly in adult females (*Zaenglein et al 2016, Thiboutot et al 2018*).
- A 2016 consensus-based guideline for the treatment of acne recommends that patients with predominant comedonal acne should initially be treated with a topical retinoid (preferred), azelaic acid or salicylic acid. For patients with predominant papulopustular acne, fixed combination topicals are recommended, and should be used along with oral antibiotics, oral isotretinoin, oral zinc, or oral anti-androgenic hormonal therapy (women only) for patients with moderate to severe disease. For nodular/conglobate acne, treatment should include monotherapy with oral isotretinoin, or fixed combination topicals plus oral antibiotics for men; for women, these options may be supplemented with oral anti-androgenic hormonal therapy. To prevent the disease from recurring, maintenance therapy with a topical retinoid (preferred) or azelaic acid is recommended once a patient is clear or almost clear of their acne (*Gollnick et al 2016*).
- The 2013 recommendations from the American Academy of Pediatrics (AAP) state that acne management of pediatric patients is similar to acne treatment in older adolescents and adults. For mild acne, AAP recommends benzoyl peroxide, a topical retinoid, or a combination of benzoyl peroxide with an antibiotic or retinoid. For moderate and severe acne, combination topical therapy with the possible addition of oral antibiotics may be considered. Oral isotretinoin may be considered for some patients with severe, refractory, and scarring acne (*Eichenfield et al 2013*).

SAFETY SUMMARY

- Oral isotretinoin carries a black box warning regarding its teratogenicity risk; therefore, its use is contraindicated in female patients who are or may become pregnant. If pregnancy does occur during treatment, the drug should be discontinued and the patient should be referred to a specialist in reproductive toxicity. The drug is available only through a restricted program call the iPLEDGE program which requires enrollment by prescribers, patients, pharmacies, and

distributors. The restricted program has very specific requirements regarding use of contraception if the drug is used in females with reproductive potential.

- Contraindications for the acne agents are primarily hypersensitivity to any component of the product. For clindamycin-containing products, clindamycin is contraindicated in patients with a history of regional enteritis, ulcerative colitis or antibiotic-associated colitis. Tazarotene (Arazlo, Fabior, Tazorac) is contraindicated in pregnant women.
- Warnings for antibiotics include the risk for superinfection and pseudomembranous colitis. Gels contain alcohol and may be flammable; use caution. Benzoyl peroxide-containing products may cause bleaching of fabric or hair; use care when applying. Retinoids and benzoyl peroxide-containing products may cause ultraviolet (UV) sensitivity; avoid exposure or limit exposure with sunscreen. Retinoids may cause local application site reactions such as erythema, scaling, and dryness especially for the first few weeks of use. Azelaic acid products may cause hypopigmentation, and can irritate the eyes and mucous membranes. Dapsone gel can cause methemoglobinemia resulting in hospitalization, particularly in patients with glucose-6 phosphate dehydrogenase deficiency or idiopathic methemoglobinemia.
- Warnings for oral isotretinoin include avoidance of micro-dosed progesterone preparations as contraception, risk of psychiatric disorders (depression, psychosis, suicidal behavior/thoughts), pseudotumor cerebri, Stevens-Johnson syndrome, acute pancreatitis, lipid abnormalities, hearing impairment, hepatotoxicity, inflammatory bowel disease, skeletal abnormalities, ocular abnormalities, and glucose and creatine phosphokinase abnormalities.
- Adverse events for topical acne agents are generally limited to local application site reactions including burning/stinging, erythema, scaling, and dryness.
- Common adverse reactions of oral isotretinoin include dryness in skin, lips, and eyes; arthralgia; headache; dermatitis; musculoskeletal discomfort; reduced visual acuity; and upper respiratory symptoms/infection.
- Avoid concurrent use of clindamycin with erythromycin due to possible antagonistic therapeutic effects based on in vitro data.
- In June 2014, the FDA warned that certain OTC topical acne products can cause rare but serious and potentially life-threatening allergic reactions or severe irritation. The hypersensitivity reactions may occur within minutes to a day or longer after product use.
  - The OTC topical acne products of concern are marketed under various brand names such as Proactiv, Neutrogena, MaxClarity, Oxy, Ambi, Aveeno, Clean & Clear, and as store brands. They are available as gels, lotions, face washes, solutions, cleansing pads, toners, face scrubs, and other products.
  - Based on the information reported to the FDA, it cannot be determined if the serious hypersensitivity reactions were triggered by the acne products' active ingredients, benzoyl peroxide or salicylic acid, the inactive ingredients, or by a combination of both. The FDA is continuing to monitor and evaluate this safety issue, and will work with manufacturers regarding any future label changes that would address the risk of severe hypersensitivity reactions.
  - The hypersensitivity reactions may occur within minutes to a day or longer after product use. These serious hypersensitivity reactions differ from the local skin irritation that may occur at the product application site, such as redness, burning, dryness, itching, peeling, or slight swelling, that are already included in the Drug Facts labels.

(*Clinical Pharmacology 2020, FDA Drug Safety Communication 2014, Micromedex 2020*)

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Antibiotics				
Aczone (dapsone)	Gel	Topical	Apply once (7.5% dose) to twice daily (5% dose).	If no improvement in 12 weeks, treatment should be reassessed. The 7.5% gel is indicated in age ≥ 9 years. The 5% gel is indicated in age ≥ 12 years.
Clindagel, Cleocin T, Clindacin-P, Clindacin ETZ, Clindacin Pac,	Foam, gel, lotion, solution, swab, swab + cleanser kit, gel kit	Topical	Foam and gel (Clindagel): Apply once daily.	If topical antibiotic therapy is longer than a few weeks, the

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Evoclin, NuCaraClinPAK (clindamycin)			Gel (Cleocin T), lotion, solution, or swab: Apply twice daily.	addition of topical benzoyl peroxide is recommended. Indicated in age ≥ 12 years.
Erygel, Emgel, Ery (erythromycin)	Gel, pads, solution	Topical	Apply once to twice daily.	If no improvement after 6 to 8 weeks, or if the condition worsens, discontinue treatment. If topical antibiotic therapy is longer than a few weeks, the addition of topical benzoyl peroxide is recommended.
Amzeeq (minocycline)	Foam	Topical	Apply once daily.	Indicated in age ≥ 9 years.
Benzoyl Peroxide and Combinations				
BenzePrO, BPO, Benziq LS, Enzoclear, Riax, Zaclir (benzoyl peroxide)	Rx and/or OTC products: bar, cream, cleanser, cleanser ER, external liquid, foam, gel, lotion, wash + lotion kits, wash Rx products: Cleansing lotion, external liquid, foam, foaming cloths, gel, lotion, wash	Topical	Cream, foam, gel, solution, lotion: Apply once daily. Foaming cloths, lotion, cleanser, bar, wash, liquid: Apply 1 to 3 times daily.	Improvement is usually noted in 3 to 4 weeks.
Vanoxide-HC (benzoyl peroxide/ hydrocortisone)	Lotion	Topical	Apply 1 to 3 times daily.	Product expires 3 months after dispensed.
Benzoyl Peroxide – Antibiotic Combinations				
Acanya, Benzaclin, Duac, Neuac, NuCaraClinPAK, Onexton (benzoyl peroxide/clindamycin)	Gel, gel kit	Topical	Benzaclin: Apply twice daily. All other products: Apply once daily in the evening.	Indicated in age ≥ 12 years.
Benzamycin (benzoyl peroxide/erythromycin)	Gel	Topical	Apply twice daily.	Indicated in age ≥ 12 years.
Topical Retinoids – Single Entity				
Differin (adapalene)	Rx only: cream, lotion, solution, pad Rx/OTC: gel	Topical	Apply once daily in the evening.	Indicated in age ≥ 12 years.
Arazlo, Fabior, Tazorac (tazarotene)	Foam, gel, cream, lotion	Topical	Apply once daily in the evening.	Efficacy has not been established past 12 weeks. Indicated in age ≥ 12 years. Arazlo is indicated in age ≥ 9 years.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Altreno, Atralin, Avita, Retin-A, Retin-A Micro (tretinoin)	Lotion, gel, cream, microsphere gel	Topical	Apply once daily.	Altreno is indicated in age ≥ 9 years, Atralin is indicated in age ≥ 10 years, and all other products in age ≥ 12 years.
Aklief (trifarotene)	Cream	Topical	Apply once daily in the evening.	Indicated in age ≥ 9 years.
Topical Retinoids - Combination				
Epiduo, Epiduo Forte (adapalene/benzoyl peroxide)	Gel	Topical	Apply once daily.	Epiduo is indicated in age ≥ 9 years and Epiduo Forte in age ≥ 12 years.
adapalene/benzoyl peroxide/clindamycin	Gel	Topical	Apply once daily.	
Veltin, Ziana (clindamycin/tretinoin)	Gel	Topical	Apply once daily in the evening.	Indicated in age ≥ 12 years.
Miscellaneous Topical Therapies				
Azelex (azelaic acid)	Cream	Topical	Apply twice daily.	Indicated in age ≥ 12 years.
Sulfacetamide/Sulfur and Combinations				
Klaron, Ovace, Ovace Plus (sulfacetamide) Avar, Avar LS, Avar-e LS, Avar-e Emollient, Avar-e Green, BP 10-1, BP Cleansing Wash, Plexion, SSS 10-5, SulfaCleanse 8/4, Sulfamez, Sumadan, Sumadan XLT, Sumaxin, Sumaxin CP (sulfacetamide/sulfur)	Monotherapy: Cream, foam, gel, lotion, shampoo, wash external liquid With sulfur: cleanser, cloths, cream, emulsion, foam, gel, lotion, pad, suspension, wash Kits with sulfur: wash + cleanser, pad + cleanser, wash + sunscreen	Topical	Foam, cleanser cream, lotion, gel, bar, wash, kits: Apply 1 to 3 times daily.	Indicated in age ≥ 12 years.
Sulfur SAStid (sulfur/salicylic acid)	OTC only: Bar	Topical	Apply 1 to 3 times daily.	
Oral Retinoids				
Absorica, Absorica LD, Amnesteem, Claravis, Myorisan, Zenatane (isotretinoin)	Capsule	Oral	Amnesteem, Claravis, Myorisan, Zenatane: Twice daily with food. Absorica, Absorica LD: Twice daily with or without food.	Once daily dosing is not recommended. Duration of treatment: 15 to 20 weeks Pregnancy tests should be performed before prescribing, each month during therapy, and 1 month after discontinuation.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Baseline lipids and liver function tests should be performed. Absorica and Absorica LD are indicated in age ≥ 12 years. The other oral isotretinoin products have not been studied in children < 12 years of age.

Abbreviation: ER = extended release, OTC = over-the-counter, Rx = prescription
See the current prescribing information for full details
(*Clinical Pharmacology 2020*, *Lexi-comp 2020*)

CONCLUSION

- Current treatment of acne vulgaris is primarily topical agents. Guidelines suggest the use of combinations to treat acne (*Eichenfield et al 2013, Gollnick et al 2016, Nast et al 2016, Thiboutot et al 2018, Zaenglein et al 2016*).
- Dapsone (Aczone), clindamycin, erythromycin, and minocycline (Amzeeq) are topical antibiotics for the treatment of acne vulgaris. Most agents have formulations available as generics (Aczone 7.5% remains brand only, while the 5% formulation is available as a generic; minocycline is brand-only). Antibiotics have a slow onset of action and are at increased risk for bacterial resistance. Antibiotics should be used in combination therapy if used for more than a few weeks (*Eichenfield et al 2013, Thiboutot et al 2009*).
- Many benzoyl peroxide products are OTC agents. Various dosage formulations and strengths are available. Benzoyl peroxide is used in combination with other topical agents for acne. Excessive drying may occur with benzoyl peroxide use and may be observed as marked peeling, erythema, possible edema, and allergic contact sensitization. Additionally, benzoyl peroxide may bleach hair and/or fabric so care must be used to limit accidental exposure (*Lexi-comp 2020*). In 2014, the FDA warned that certain OTC topical acne products can cause rare but serious and potentially life-threatening allergic reactions or severe irritation. The hypersensitivity reactions may occur within minutes to a day or longer after product use. Based on the information reported to the FDA, it cannot be determined if the serious hypersensitivity reactions were triggered by the acne products' active ingredients, benzoyl peroxide or salicylic acid, the inactive ingredients, or by a combination of both (*FDA Drug Safety Communication 2014*).
- Topical retinoids, including adapalene (Differin), tazarotene (Arazlo, Fabior, Tazorac), tretinoin (Retin-A, Altreno, Atralin, Avita), and Aklief (trifarotene) are effective in the treatment of acne vulgaris. Combinations of topical retinoids include adapalene/benzoyl peroxide (Epiduo, Epiduo Forte) and clindamycin/tretinoin (Veltin, Ziana). In studies comparing the agents, no one agent was consistently more efficacious than another, and combination agents demonstrated greater efficacy when compared to monotherapy with their components. Guidelines do not recommend one retinoid over another (*Eichenfield et al 2013, Gollnick et al 2016, Thiboutot et al 2009, Zaenglein et al 2016*). Most of the adverse reactions associated with retinoids are dermatological and may lessen with continued use. Retinoids cause increased sun sensitivity, and their use should be avoided with other agents that cause excessive drying. Differin gel is now available as an OTC product.
- The topical benzoyl peroxide and antibiotic combination products include benzoyl peroxide/clindamycin (Acanya, Benzaclin, Duac, Neuac, and Onexton) and benzoyl peroxide/erythromycin (Benzamycin). The benzoyl peroxide/clindamycin products primarily differ in their respective strengths. Acanya contains 2.5% benzoyl peroxide and 1.2% clindamycin, Benzaclin contains 5% benzoyl peroxide and 1% clindamycin, Duac and Neuac contain 5% benzoyl peroxide and 1.2% clindamycin, and Onexton contains 3.75% benzoyl peroxide and 1.2% clindamycin. The benzoyl peroxide and antibiotic combination agents are effective for the treatment of acne vulgaris. Combination treatment with benzoyl peroxide and either clindamycin or erythromycin has been shown to be more effective than treatment with each individual agent alone (*Lookingbill et al 1997, Webster et al 2009, Thiboutot et al 2008, Chalker et al 1983, Cunliffe et al 2002, Leyden et al 2001, Xu et al 2016*). Current clinical guidelines support the use of combination treatment in order to limit the development of bacterial resistance (*Eichenfield et al 2013, Gollnick et al 2016, Thiboutot et al 2009, Zaenglein et al 2016*).

- Oral isotretinoin is a recommended treatment option for severe nodular acne and treatment-resistant moderate acne. (*Eichenfield et al 2013, Gollnick et al 2016, Thiboutot et al 2018, Zaenglein et al 2016*). Its efficacy was not found to be better than the combination of a systemic antibiotic with a topical agent (*Costa et al 2018*). It is available only through a restricted distribution program due to its teratogenic effects. If used in female patients, appropriate contraception is required (*Absorica/Absorica LD 2019*). Additionally, the agent is associated with several other adverse events that require monitoring.
- Two other treatment options are sulfacetamide and azelaic acid (Azelex). Sulfacetamide is available in a variety of dosage forms and strengths and in combination with sulfur. Azelaic acid, a branded agent, is another topical treatment option for acne and is recommended by the guidelines for both mild acne as monotherapy and for moderate acne in combination with another class of topical acne agents (*Nast et al 2016, Gollnick et al 2016, Zaenglein et al 2016*).

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Publication Date: April 3, 2020

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, 2020; Hesketh 2019*).
- 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 2020, Hesketh 2019*):
  - 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 2020*).
- 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 [reaffirmed in 2019], Smith et al 2020*).
- Nausea is common in motion sickness and symptoms may also include vomiting and headache. Motion sickness is thought to result from incongruent vestibular, visual, and somatosensory sensory cues *(Priesol 2020)*.
- 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*).
- Dopamine receptor antagonists, such as prochlorperazine (a phenothiazine) and trimethobenzamide (a benzamide), primarily work by blocking D2-dopamine receptors in the postrema area of the midbrain. They also have M1-muscarinic and H1-histamine antagonizing effects *(Longstreth 2020).* Scopolamine, an anticholinergic drug, is an M1-muscarinic receptor antagonist. Antihistamines are used for motion sickness *(Longstreth 2020).*

- 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 2020*).
- Prescription meclizine is FDA-approved for vertigo; however, over-the-counter products are used for n/v and dizziness associated with motion sickness. Transdermal scopolamine is FDA-approved for n/v associated with motion sickness and for PONV. Prochlorperazine is FDA-approved for treatment of severe n/v, promethazine is approved for motion sickness and n/v associated with certain anesthesia and surgery, and trimethobenzamide is approved for PONV and nausea related to gastroenteritis.
- The scope of this review will focus on the agents outlined in Table 1 for their respective FDA-approved indications as related to CINV, PONV, or n/v associated with other conditions such as pregnancy and motion sickness, with a focus on CINV. Other agents including glucocorticoids may also be effective antiemetics; however, they have been excluded from this review. Although certain agents are FDA-approved for other indications, only those related to n/v are included in 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	–
Compro (prochlorperazine) rectal suppository	✔
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‖	✔
meclizine over-the-counter products	✔
ondansetron injection	✔ ‡
Phenergan (promethazine) injection	✔
prochlorperazine injection, tablet	✔
Promethegan (promethazine) rectal suppository	✔
promethazine injection, tablet, syrup, oral solution	✔
Sancuso (granisetron) transdermal patch	–

Drug	Generic Availability
Sustol (granisetron) extended-release subcutaneous injection	–
Syndros (dronabinol) oral solution	–
Tigan (trimethobenzamide) capsule	✔
Tigan (trimethobenzamide) injection	-
Transderm Scop (scopolamine) transdermal film	✔
Varubi (rolapitant) tablet†	–
Zofran (ondansetron) oral solution, tablet	✔ ‡
Zofran (ondansetron) ODT	✔ ‡
Zuplenz (ondansetron) oral soluble film	–

Abbrv: IV=intravenous, ODT=orally disintegrating tablet

*The FDA website shows the dolasetron tablet product as discontinued. The manufacturer of dolasetron tablets reports a long-term backorder for the 100 mg tablets with no release date. The 50 mg tablets are in the manufacturing process with no release date.

‡Generic available in at least 1 dosage form and/or strength.

†The FDA website 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.

§ Nabilone was discontinued as of September 18, 2019.

‖Marinol brand has been discontinued, but generic dronabinol is available.

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

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 as a single dose regimen, in adults					✔ * (IV emulsion)						
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)	
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)						

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 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				✔							
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)						
Prevention of n/v associated with initial and repeat courses of MEC as a 3 day regimen, in adults					✔ * (IV emulsion)						
Prevention of delayed n/v associated with initial and repeat courses of MEC as a single dose regimen, in adults					✔ * (IV emulsion)						
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)		✔ (generic aprepitant only)						

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 and treatment 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)									
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†, oral soluble film)								
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.

Table 2 (cont.) Food and Drug Administration Approved Indications.

Indication	Antihistamine	Phenothiazines		Anticholinergic	Benzamide
	Meclizine	Promethazine	Prochlorperazine	Scopolamine	Trimethobenzamide
PONV					
Treatment of PONV					✔ † (capsules, injection)
Prevention and control of n/v associated with certain types of anesthesia and surgery		✔ ¥ (injection, suppository, solution, syrup, tablet)			
Antiemetic therapy in postoperative patients		✔ ¥ (suppository, solution, syrup, tablet)			
Prevention of PONV associated with recovery from anesthesia and/or opiate analgesia and surgery				✔	
Motion Sickness					
Prevents and treats n/v or dizziness associated with motion sickness	✔ *				
Prevention of n/v associated with motion sickness				✔	
Active treatment of motion sickness		✔ ¥ (injection)			
Active and prophylactic treatment of motion sickness		✔ ¥ (suppository, solution, syrup, tablet)			

Indication	Antihistamine	Phenothiazines		Anticholinergic	Benzamide
	Meclizine	Promethazine	Prochlorperazine	Scopolamine	Trimethobenzamide
Nausea associated with gastroenteritis					
Nausea associated with gastroenteritis					✔ † (capsules, injection)
Severe nausea and vomiting					
Control of severe n/v			✔ ** (tablets, injection, suppository)		

Abbrv: n/v = nausea and vomiting, FDA = Food and Drug Administration; ODT = orally disintegrating tablets, PONV = postoperative nausea and vomiting
*Antivert (meclizine) is FDA-approved for treatment of vertigo; however, over-the-counter meclizine prevents and treats nausea, vomiting or dizziness associated with motion sickness.
†Tigan not recommended to use in pediatric patients due to risk of extrapyramidal signs and symptoms, other CNS effects, and risk of exacerbating underlying disease in patients with Reye's syndrome or other hepatic impairment.
¥Promethazine is also FDA-approved for multiple indications including those related to allergic conditions, surgical analgesia, and sedation.
**Prochlorperazine is also FDA-approved for treatment of schizophrenia and anxiety.

(*Prescribing information: Akynzeo 2018, Aloxi 2018, Antivert 2019, Anzemet tablets 2018, Bonjesta 2018, Cesamet 2015, Cinvanti 2019, Compro 2016, Diclegis tablets 2018, Emend capsules and oral suspension 2019, Emend for injection 2019, granisetron injection 2020, granisetron tablets 2019, Marinol 2017, meclizine chewable tablets 2019, meclizine soluble film 2019, meclizine tablets ODT 2020, ondansetron injection 2019, Promethegan suppository 2014, prochlorperazine injection 2019, prochlorperazine tablets 2018, promethazine injection 2016, promethazine oral solution 2019, promethazine syrup 2018, promethazine tablets 2019, Sancuso 2017, Sustol 2017, Syndros 2018, Tigan capsules 2017, Tigan injection 2016, Transderm Scop 2019, Varubi 2018, Zofran tablets ODT oral solution 2017, Zuplenz 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

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*).
- Trimethobenzamide has limited data supporting its use in CINV *(Hurley and Eshelman 1980).*
- 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

- In a MA on interventions for hyperemesis gravidarum, drowsiness, dizziness, and dystonia were experienced by more women treated with promethazine compared to metoclopramide in a single study. In another study, duration of hospital admission was not different between promethazine and ondansetron, but sedation was more common with promethazine *(Boelig et al 2016).*
- 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*).

Motion Sickness

- In a MA of 14 studies, scopolamine prevented symptoms of motion sickness more effectively than placebo (RR 0.48; 95% CI, 0.32 to 0.73), but conclusions could not be made regarding its efficacy compared to antihistamines and calcium channel blockers *(Spinks and Wasiak 2011).*

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 Gastroenterological Association [AGA] 2001, Herrstedt et al 2017, Hesketh et al 2017, 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*):
  - 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).
  - Dopamine receptor antagonists (eg, prochlorperazine, metoclopramide) are included as agents that may be added on to regimens for patients who experience n/v despite optimal prophylaxis.
- 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 low emetic risk IV chemotherapy: dexamethasone, metoclopramide, prochlorperazine, or a 5-HT3 receptor antagonist started before chemotherapy and continued daily.
  - For high to moderate emetic risk oral chemotherapy: 5-HT3 receptor antagonist started before chemotherapy and continued daily.
  - For low to minimal emetic risk oral chemotherapy: metoclopramide, prochlorperazine, or a 5-HT3 receptor antagonist started before chemotherapy and continued daily.
  - For breakthrough treatment for CINV (add an agent for a different drug class to the current regimen): olanzapine, lorazepam, dronabinol or nabilone, haloperidol, metoclopramide, scopolamine, prochlorperazine or promethazine, 5-HT3 receptor antagonist, or dexamethasone.
- 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 [reaffirmed 2019]*):
  - 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 pyridoxine 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 weak-to-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 in patients 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.
- Meclizine may cause drowsiness and should be used with caution in patients with asthma, glaucoma, or an enlarged prostate due to its anticholinergic effects. Headache, fatigue, and vomiting are other common adverse events.
- Promethazine has a boxed warning that it should not be used in patients < 2 years old because of the risk of fatal respiratory depression. It should be used with caution in pediatric patients 2 years and older. The injection has a boxed warning for severe tissue injury. Promethazine is also contraindicated in comatose states, hypersensitivity, or for treatment of lower respiratory tract symptoms including asthma. Promethazine injection should not be administered by intra-arterial injection or subcutaneously. Warnings related to promethazine include CNS depression, respiratory depression, lower seizure threshold, bone-marrow depression, and neuroleptic malignant syndrome (NMS).
- Prochlorperazine has a boxed warning regarding increased mortality in elderly patients with dementia-related psychosis who are treated with antipsychotic drugs. Contraindications include hypersensitivity, comatose states or in the presence of large amounts of CNS depressants, pediatric surgery, in pediatric patients < 2 years or weighing < 20 pounds, or for use in pediatric conditions that the dose has not been determined. Other warnings include tardive dyskinesia, NMS, and falls. Adverse events include drowsiness, dizziness, amenorrhea, blurred vision, skin reactions, and hypotension.
- Transdermal scopolamine is contraindicated in acute closure glaucoma and hypersensitivity. Warnings and precautions include acute angle closure glaucoma, neuropsychiatric adverse reactions, and eclamptic seizures in pregnant women. Scopolamine may cause reduced gastrointestinal motility, urinary retention, and also blurred vision if it comes into contact with eyes. Additionally, patients may experience withdrawal symptoms, and transdermal scopolamine should be removed prior to magnetic resonance imaging. The most common reactions for motion sickness include dry mouth,

drowsiness, blurred vision, and pupil dilation, and for PONV include dry mouth, dizziness, somnolence, agitation, visual impairment, confusion, mydriasis, and pharyngitis.

- Trimethobenzamide is contraindicated in hypersensitivity. Warnings and precautions include acute dystonic reactions and other extrapyramidal symptoms, other CNS reactions (eg, coma, depression of mood, disorientation, and seizures), hepatotoxicity, and impairment of mental and/or physical activities. Other adverse events include blurred vision, diarrhea, disorientation, dizziness, drowsiness, headache, jaundice, and muscle cramps.
- 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 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 of anesthesia or immediately before reversal of anesthesia. Do not administer SC injection ER more frequently than once a week.	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 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	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.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			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 nausea and/or vomiting occurring shortly after surgery. Administer IM as a single dose.	Depending on indication and formulation, drug may be administered in patients aged ≥ 1 month.
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	IV solution approved for prevention o CINV in pediatric patients aged ≥ 1 month.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			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	
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 Administer IV over 2 minutes or 30 minutes completing the administration approximately 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				
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.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				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.	
Other single-agent products				
Meclizine	Chewable, immediate-release, and ODT	Oral	Take orally 1 hour before travel (may repeat every 24 hours as needed)	Start at the lowest dose for elderly patients due to anticholinergic effects
Promethazine	Tablet, oral syrup, rectal suppository, injectable solution	Oral Rectal IV/IM	Oral administration (motion sickness): Take orally 30 to 60 minutes before departure, then repeated in 8 to 12 hours as needed Oral and rectal administration (PONV): Take orally or rectally every 4 to 6 hours as needed IV and IM (PONV): Administer IV or IM every 4 to 6 hours as needed	Deep IM injection is the preferred parenteral route of administration
Prochlorperazine	Tablet, rectal suppository, injectable solution	Oral Rectal IV/IM	Oral administration: 3 to 4 times per day Rectal administration: Twice daily IV or IM administration: Administer 3 to 4 hours as needed; or administer 1 to 2 hours (IM) or 15 to 30 minutes (IV) before induction of anesthesia and repeat once if necessary	Lower doses are usually sufficient for elderly patients; increase doses gradually
Scopolamine	Transdermal	Trans-dermal	Motion sickness: Apply patch at least 4 hours before antiemetic effects are needed – for use up to 3 days PONV: Apply patch the evening before scheduled surgery; remove 24 hours after surgery.	Apply to hairless area of the skin behind the ear

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Trimethobenzamide	Capsule, IM solution	Oral IM	Oral: Take orally 3 to 4 times daily IM: Administer 3 to 4 times per day as needed	Reduce daily oral dose in elderly and patients with renal impairment
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 ir 10/10 mg tablets DR. Should be taken on an empty stomach with a glass of water.

Abbrv: CINV = chemotherapy-induced nausea and vomiting, DR = delayed release, ECG = electrocardiogram, ER = extended release, HEC = highly emetogenic cancer chemotherapy, IM = intramuscular, IV = intravenous, ODT = orally disintegrating tablet, PONV = post-operative nausea and vomiting, 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, Longstreth 2018, Longstreth 2020, 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*). 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 [reaffirmed 2019]*).
- 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, Kaushal et al 2010, Kovacs et al 2016, Likun et al 2011, Longstreth 2020, 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, Herrington et al 2008, Herrstedt et al 2005, Longstreth 2020, 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, Lane et al 1991, Longstreth 2020, 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 [reaffirmed 2019]*). 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.
- Other agents used for n/v include meclizine, promethazine, prochlorperazine, scopolamine, and trimethobenzamide. Meclizine and scopolamine are generally used for motion sickness. Prochlorperazine may be used in low emetic risk chemotherapy while prochlorperazine, scopolamine, or promethazine may be used for breakthrough treatment *(NCCN 2019).*

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Publication Date: March 12, 2020

Therapeutic Class Overview
Inflammatory Bowel Disease Agents

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 2019[a], Peppercorn 2020[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 2019[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 an inflamed rectum with symptoms of urgency, bleeding, and tenesmus *(Peppercorn 2020[c], Rubin et al 2019).*
- 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 2019[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 estimates 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 19.2 per 100,000 person-years and the incidence of CD varies from 3.1 to 20.2 per 100,000 person-years. As many as 3 million persons in the U.S. suffer from IBD *(Molodecky et al 2012, Shivashankar et al 2017, Centers for Disease Control and Prevention [CDC] 2019).*
- 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 30 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.
  - 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 with risk factors since food antigens are believed to activate an immune response. Although specific pathogenic antigens have not been conclusively identified, intake of animal fat and polyunsaturated fatty acids is associated with an increased risk of developing CD and UC. Vitamin D deficiency is commonly present among patients with IBD.
- Genetic susceptibility to IBD is not completely understood; however, it is estimated that first-degree relatives of patients with IBD are 3 to 20 times more likely to develop IBD compared with the general population (*Snapper et al 2020*).
- The goals of treatment for 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 2020; Bernstein et al 2015).*
  - Choice of therapy is based on several factors, including disease severity, anatomic extent, response to prior therapies, and prognosis *(Rubin et al 2019).*

- The oral 5-ASA derivatives include balsalazide, mesalamine, olsalazine, and sulfasalazine; mesalamine is the only 5-ASA derivative that has rectal formulations *(Hashash et al 2019)*. Mesalamine is available in several formulations and is also the active component of balsalazide and olsalazine (*Prescribing information: Colazal 2019, Dipentum 2019)*. The 5-ASA preparations have comparable efficacy to sulfasalazine for the management of IBD, but a better tolerability profile. Oral 5-ASAs have not shown differences in safety or efficacy. The choice of treatment agent should be based on indication, disease location, expected patient compliance with the treatment regimen, patient preference, and drug availability *(Cheifetz 2019)*.
- 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 and Ortikos) are approved for the treatment and maintenance of remission of CD. (*Prescribing information: Entocort EC 2019, Ortikos 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 2019)*.
- Other injectable biologic response modifiers known as monoclonal antibodies (MABs) are 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 failed, or were intolerant to, treatment with immunomodulators or corticosteroids, but never failed a TNF blocker or in those who 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 2020, Drugs@FDA 2020).* Of note, a FDA drug safety release revealed a potential risk for developing blood clots in the lungs and death with tofacitinib 10 mg twice daily (a dose approved for UC) when used in patients with rheumatoid arthritis; the FDA subsequently added a boxed warning to the label regarding this risk (*FDA drug safety communication 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) ER capsule	✔
Lialda (mesalamine) DR tablet	✔
Ortikos (budesonide) ER capsule*	-
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.
*Ortikos is approved, but no official launch date is known.

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

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; Ortikos)			
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; Ortikos) ***			
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**)

Indication	Balsalazide	Budesonide	Mesalamine	Olsalazine	Sulfasalazine
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 adequate trial of full doses of 1 or more NSAIDs)	-	-	-	-	✔ (Azulfidine EN-tabs)
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 2019, Asacol HD 2018, Azulfidine 2019, Azulfidine EN-Tabs 2019, Canasa 2017, Colazal 2019, Delzicol 2019, Dipentum 2019, Entocort EC 2019, Lialda 2019, Ortikos 2019, Pentasa 2019, 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 endpoint of failure to induce global or clinical remission in mild to moderately active UC, 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).*
- A network meta-analysis of 15 trials compared oral budesonide MMX to oral mesalamine in 4083 patients with mild-to-moderate UC. Budesonide MMX 9 mg/day and mesalamine > 2.4 g/day showed no statistically significant difference for induction of remission, but mesalamine had a better safety profile (*Bonovas et al 2019*).
- A Cochrane review of 14 trials evaluated the efficacy and safety of oral 5-ASA agents to placebo, no treatment, or any other active treatment for maintenance of surgically-induced remission in CD (N = 1867). Patients receiving 5-ASA had lower rates of relapse during a follow-up period of 12 to 72 months compared with placebo (36% vs 43%, respectively; RR 0.83, 95% CI, 0.72 to 0.96; I^2 = 0%; moderate certainty evidence). At 12 months, 17% (17/101) of the 4 g/day mesalamine group relapsed compared to 26% (27/105) of the 2.4 g/day group (RR 0.65, 95% CI 0.38 to 1.13; moderate certainty evidence). During a follow-up period of 18 to 36 months, sulfasalazine and placebo showed no statistically significant difference in the relapse rate. Adverse event rates were similar between 5-ASA and placebo or biologics (*Gjuladin-Hellon et al 2019*).
- Two 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)*.
- A meta-analysis of 74 studies showed that the highest induction of histologic remission rates for UC was with topical 5-ASA (37.2%; 95% CI, 29.0 to 46.3) and 5-ASA suppositories (44.9%; 95% CI, 28.9 to 62.3). Compared with placebo, 5-ASA enemas (RR 4.14; 95% CI, 2.35 to 7.31), 5-ASA suppositories (RR 3.94; 95% CI, 1.26 to 12.32), and budesonide MMX (RR 3.94; 95% CI, 1.26 to 12.32) had higher histologic remission rates (*Battat et al 2019*).

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 2019 UC guideline in adults from the American College of Gastroenterology (ACG) provides recommendations for the management of UC. Most recommendation statements list specific doses for 5-ASA formulations (ie, at least 2 g/day for oral 5-ASA and at least 1 g/day for rectal 5-ASA) *(Rubin et al 2019)*:
  - For the management of mildly active UC, the guideline recommends rectal 5-ASA therapies for induction and maintenance of remission (strong recommendation, high and moderate quality of evidence, respectively). Oral systemic corticosteroids are used if patients fail to respond to 5-ASA therapy (strong recommendation, low quality of evidence). A rectal 5-ASA enema, in combination with oral 5-ASA therapy, is suggested over oral 5-ASA therapy alone for induction of remission in patients with mildly active left-sided UC (conditional recommendation, low quality of evidence). If patients are intolerant to, or do not respond to this therapy, oral budesonide MMX is the next recommended option (strong recommendation, moderate quality of evidence). Oral 5-ASA should be used for induction of remission in patients with mildly active extensive colitis (strong recommendation, moderate quality of evidence). Oral 5-ASA therapy should be used to maintain remission in patients with mildly active left-sided or extensive UC (strong recommendation, moderate quality of evidence).
  - The addition of budesonide MMX is warranted for remission induction in patients with mildly to moderately active UC not responding to oral 5-ASA (strong recommendation, moderate quality of evidence).
  - The guideline recommends the use of oral budesonide for induction of remission in patients with moderately active UC and oral systemic corticosteroids in patients with moderately to severely active UC of any extent (strong recommendation, moderate quality of evidence).
  - The guideline recommends against the use of systemic corticosteroids for maintenance of remission in patients with UC (strong recommendation, moderate quality of evidence).
- The 2018 guidelines on the management of CD 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). Use of budesonide beyond 4 months is not recommended (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 and 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 2019 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 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. The brand mesalamine product, Apriso, and its branded generic product manufactured by Bausch Health contain phenylalanine, which may be harmful to patients with phenylketonuria; the generic for Apriso manufactured by Mylan Pharmaceuticals does not contain phenylalanine.
- 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	Extended-release capsule (Entocort EC) 3 mg Extended-release capsule (Ortikos) 6 mg, 9 mg Extended-release tablet (Uceris) 9 mg Rectal foam (Uceris) 2 mg/actuation	Oral, Rectal	Extended-release capsule: once daily Extended-release tablet: once daily Rectal foam: once to twice daily	Extended-release capsules (Entocort EC and Ortikos) are 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	Oral, Rectal	Controlled-release capsule (Pentasa): 4 times daily	Delayed-release capsule (Delzicol): approved for

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
	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		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	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.
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 among the oral 5-ASA formulations have been identified *(Wang et al 2016[a]).*
- 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 2019 ACG guideline on UC in adults, rectal 5-ASA is recommended for induction and maintenance of remission of mildly active UC for most patients. Oral 5-ASA may be used for induction or maintenance of remission in cases of mildly active left-sided or extensive UC. Oral budesonide is recommended for induction of remission in patients with moderately active UC (*Rubin et al 2019*).
- 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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Publication Date: March 27, 2020

INTRODUCTION

- Cardiovascular (CV) disease is the underlying cause of approximately 17.8 million deaths globally on an annual basis according to the American Heart Association (AHA) Heart Disease and Stroke Statistics 2020 update. Stroke also causes significant morbidity and mortality. Stroke is the fifth leading cause of death after heart disease, cancer, unintentional injuries/accidents, and chronic lower respiratory disease. Each year, about 795,000 people experience a new or recurrent stroke (*Virani et al 2020*).
- Platelet inhibitors play a major role in the management of CV, cerebrovascular, and peripheral vascular diseases. These agents are indicated for a variety of Food and Drug Administration (FDA)-approved indications including treatment and/or prevention of acute coronary syndromes (ACS) (myocardial infarction [MI], unstable angina [UA]), stroke/transient ischemic attack [TIA], intermittent claudication, prevention of postoperative thromboembolic complications, thrombocythemia, and valvular heart disease. The use of these agents as both monotherapy or combination therapy by national and international clinical guidelines is based on the specific clinical indication and the patient's risk for thromboembolic events (*Aboyans et al 2018, Amsterdam et al 2014, Anderson et al 2013, Baumgartner et al 2017, Bushnell et al 2014, Culebras et al 2014, Fihn et al 2012, Gerhard-Herman et al 2016, Guyatt et al 2012, Ibanez et al 2018, January et al 2014, January et al 2019, Jauch 2013, Kernan et al 2014, Knuuti et al 2020, Lansberg et al 2012, Levine et al 2011, Levine et al 2016a, Levine et al 2016b, Lip et al 2018, Meschia et al 2014, Nishimura, 2017, O'Gara et al 2013, Powers et al 2015, Powers et al 2018, Powers et al 2019, Roffi et al 2016, Smith et al 2011, Smith et al 2017, Valgimigli et al 2018*).
- The platelet inhibitors exert their pharmacologic effects through several different mechanisms of action and have characteristics that distinguish agents from one another.
  - Aspirin (ASA), a salicylate, causes irreversible inhibition of platelet cyclooxygenase, which prevents the formation of thromboxane A2, a platelet aggregate and potent vasoconstrictor. Its use has been the cornerstone of acute treatment for over 15 years; however, evidence from clinical trials demonstrates that ASA reduces adverse clinical events among a broad group of patients treated for both acute and chronic vascular disease (*Harrington et al 2008*).
    - Omeprazole, a component of Yosprala (ASA delayed-release [DR]/omeprazole), in combination with ASA, is an antisecretory compound, which suppresses gastric acid secretion by inhibiting the $[H^+/K^+]$-ATPase enzyme system of the gastric parietal cells. Omeprazole has been characterized as a gastric acid-pump inhibitor as it blocks the final step of gastric acid production, and inhibits both basal and stimulus-induced acid secretion.
  - Zontivity is unique to the class as a selective antagonist of the protease-activated receptor-1 (PAR-1), a primary thrombin receptor, and should only be used with ASA and/or Plavix (clopidogrel) according to their indication or standards of care.
  - Plavix, Effient, and Brilinta inhibit $P2Y_{12}$, an adenosine phosphate receptor on the surface of platelets. Brilinta is the only reversible inhibitor of $P2Y_{12}$ and unlike Plavix does not require hepatic activation. Plavix has a slower onset of action, incomplete platelet inhibition, and poor response in certain patients including those with CYP2C19 polymorphisms. Compared to Plavix, the benefits of Effient have been seen as early as 3 days. Effient and Zontivity are both contraindicated in patients with a history of TIAs.
  - Agrylin has multiple mechanisms in which it exerts its action and is unique in class as it has the ability to reduce platelet counts without affecting white or red blood cell counts.
  - Cilostazol reversibly inhibits platelet aggregation through cyclic AMP phosphodiesterase inhibition. Cilostazol also has vasodilating activity, which has benefits in treating certain diseases.
  - Dipyridamole is a non-nitrate coronary vasodilator that also inhibits platelet aggregation. The mechanism of action of dipyridamole may involve its ability to vasodilate and to increase concentrations of adenosine, a platelet aggregation inhibitor.
- Products included in this class review include Agrylin (anagrelide), Aggrenox (ASA/extended-release [ER] dipyridamole), Brilinta (ticagrelor), cilostazol, Plavix (clopidogrel), dipyridamole, Durlaza (ASA ER), Effient (prasugrel), Yosprala (ASA DR/omeprazole), and Zontivity (vorapaxar). Other platelet aggregation inhibitors used only in inpatient acute care

settings, such as the glycoprotein IIb/IIIa inhibitors and Kengreal (cangrelor); and convenience kits such as clopidogrel 75 mg/ASA 81 mg are not discussed in this review.

- Medispan Class: Platelet Aggregation Inhibitors – Platelet Aggregation Inhibitors, Platelet Aggregation Inhibitors Combinations, Protease-Activated Receptor-1 (PAR-1) Antagonists, Direct-Acting $P2Y_{12}$ Inhibitors, Dipyridamole, Quinazoline Agents, Thienopyridine Derivatives, and Aspirin (Platelet Aggregation Inhibitor).

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single-Entity Agents	
Agrylin (anagrelide)	✔
Durlaza (aspirin ER)	-
Plavix (clopidogrel)	✔
cilostazol	✔
dipyridamole	✔
Effient (prasugrel)	✔
Brilinta (ticagrelor)	-*
Zontivity (vorapaxar)	-
Combination Products	
Aggrenox (aspirin/dipyridamole ER)	✔
Yosprala (aspirin DR/omeprazole)	✔

* Although generic ticagrelor has been approved by the FDA, the generic product has not been launched.

(*Drugs@FDA.com 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Agrylin (anagrelide)	cilostazol	Plavix (clopidogrel)	dipyridamole	Effient (prasugrel)	Brilinta (ticagrelor)	Zontivity (vorapaxar)	Durlaza (aspirin ER)	Aggrenox (aspirin/ dipyridamole ER)	Yosprala (aspirin DR/ omeprazole)
Treatment of patients with thrombocythemia, secondary to myeloproliferative neoplasms, to reduce the elevated platelet count and the risk of thrombosis and to ameliorate associated symptoms including thrombohemorrhagic events	✔ *									
Reduce the risk of death and MI in patients with chronic coronary artery disease (CAD), such as patients with a history of MI or UA pectoris or with chronic stable angina, and to reduce the risk of death and recurrent stroke in patients who have had an ischemic stroke or TIA								✔ †		
Reduction of symptoms of intermittent claudication, as demonstrated by an increased walking distance		✔								
Recent MI, recent stroke, or established peripheral arterial disease (PAD)			✔ ‡							
Reduce the rate of thrombotic CV events in patients with ACS			✔ ‡§							
Prevention of postoperative thromboembolic complications of cardiac valve replacement				✔ ‖						
Reduce the rate of thrombotic CV events in patients with ACS who are being managed with percutaneous coronary intervention (PCI)					✔ ¶					
Reduce the rate of CV death, MI, and stroke in patients with ACS or a history of MI. Also reduces the rate of stent thrombosis in patients who have been stented for the treatment of ACS						✔ #				
Reduce thrombotic CV events in patients with a history of MI or with PAD							✔ ††			
Reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis									✔	
ASA component: Reduce the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin platelet emboli, reducing the combined risk of death and nonfatal MI in patients with previous MI or UA pectoris, reducing the combined risk of MI and sudden death in patients with chronic stable angina pectoris, and for patients who have undergone coronary artery bypass graft (CABG) or percutaneous transluminal coronary angioplasty (PTCA) when there is a pre-existing condition for which ASA is already indicated. Omeprazole component: Decrease the risk of developing ASA-associated gastric ulcers in at-risk patients due to age (≥55 years) or documented history of gastric ulcers.										✔ †**

* Approved in adult and pediatric patients (studied in patients aged ≥ 7 years).
† Not indicated for use in situations where a rapid onset of action is required (such as acute treatment of MI or before PCI).
‡ Plavix has been shown to reduce the rate of MI and stroke.
§ For patients with non-ST-elevation ACS (UA/non-ST-elevation myocardial infarction [NSTEMI]), including patients who are to be managed medically and those who are to be managed with coronary revascularization, and for patients with ST-elevation myocardial infarction (STEMI). Plavix should be administered in conjunction with ASA.
‖ As an adjunct to coumarin anticoagulants.
¶ Patients who are to be managed with PCI as follows: patients with UA or NSTEMI and patients with STEMI when managed with primary or delayed PCI.
# Administer with a daily maintenance dose of ASA of 75 to 100 mg. For at least the first 12 months following ACS, it is superior to Plavix.

†† Has only been studied as an addition to ASA and/or Plavix. There is limited experience with other antiplatelet drugs or with Zontivity as monotherapy.
** Has not been shown to reduce the risk of gastrointestinal (GI) bleeding due to ASA.

(*Prescribing information: Aggrenox 2019, Agrylin 2018, Brilinta 2019, Cilostazol 2017, Durlaza 2015, Effient 2019, Persantine 2019, Plavix 2019, Yosprala 2018, Zontivity 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

- Antiplatelet therapy plays an important role in the long-term prevention of stroke or TIAs. In a large, meta-analysis (MA) of patients with a previous MI, acute MI, previous TIA/stroke, and acute stroke, as well as patients with an increased risk of atherothrombotic events, it was demonstrated that overall, antiplatelet therapy reduced the odds of the composite outcome of stroke, MI, or vascular death in secondary prevention by approximately 25%. With regard to individual endpoints, antiplatelet therapy reduced the odds of nonfatal MI by 34%, nonfatal stroke by 25% and vascular death by 15% (*Antithrombotic Trialists' Collaboration 2002*).
- There are few head-to-head studies comparing the various antiplatelet agents. In 2013, the Agency for Healthcare Research and Quality (AHRQ) conducted a systematic review (SR) of antiplatelet and anticoagulant treatments. The study authors concluded that Effient reduced rates of CV death, MI or stroke at 30 days in patients undergoing early invasive treatments when compared to Plavix and in UA/NSTEMI patients after 1 year, as did Plavix and Brilinta (*Melloni et al 2013*). Another SR of large, quality trials observing dual antiplatelet therapy (DAPT) of Plavix, Effient, or Brilinta plus ASA when compared to ASA monotherapy found DAPT with Effient or Brilinta and ASA vs DAPT with Plavix and ASA was not associated with a risk reduction of stroke. The authors also noted conflicting results within trials (*Gouya et al 2014*). A double-blind (DB), randomized controlled trial (RCT) compared the efficacy of Brilinta vs Plavix to lower the risk of CV death, MI, or ischemic stroke in 13,885 patients with symptomatic PAD, with a median follow-up of 30 months. The primary efficacy endpoint occurred in 10.8% of patients receiving Brilinta vs 10.6% receiving Plavix (hazard ratio [HR] 1.02; 95% confidence interval [CI], 0.92 to 1.13; p = 0.65). Major bleeding occurred at the same frequency with both treatments (1.6%), and Brilinta was discontinued more often than Plavix, mainly due to dyspnea (4.8 vs 0.8%) (*Hiatt et al 2017*).
- The CAPRIE study demonstrated that patients with a recent ischemic stroke or MI, or those with symptomatic PAD who were treated with Plavix experienced a 5.32% annual risk of ischemic stroke, MI, or vascular death compared to 5.83% of patients treated with ASA (relative risk reduction [RRR], 8.7% in favor of Plavix; 95% CI, 0.3 to 16.3; p = 0.043) (*Antithrombotic Trialists' Collaboration 2002, CAPRIE 1996*). Results from the MATCH study demonstrated that the addition of ASA to Plavix in high-risk patients with a recent ischemic stroke or TIA was associated with a nonsignificant difference in reducing major vascular events. In this trial, DAPT was associated with more life-threatening, major, and minor bleeds (*Diener et al 2004*). In the ESPRIT study, patients within 6 months of a TIA or minor stroke of presumed arterial origin were randomized to receive ASA with or without dipyridamole. The rate of the primary composite outcome, death from all vascular causes, nonfatal stroke, nonfatal MI, or major bleeding complications (whichever occurred first), was 13% with combination therapy vs 16% with ASA (HR, 0.80; 95% CI, 0.66 to 0.98, absolute risk reduction [ARR], 1% per year; 95% CI, 0.1 to 1.8) (*Halkes et al 2006*). One MA compared DAPT (ASA plus Plavix) with ASA alone in patients with acute minor ischemic stroke or TIA and found that starting DAPT within 24 hours of symptom onset reduced the absolute risk of non-fatal recurrent stroke, but had no impact on all-cause mortality (*Hao et al 2018*). There was a 0.2% absolute increase in moderate or severe extracranial bleeding with DAPT vs ASA alone. The results were similar to 2 MAs for secondary stroke prevention in patients with TIA or ischemic stroke (*Kheiri et al 2018, Ye et al 2019*). Another MA in elderly patients (≥ 65 years) with ischemic stroke or TIA found that DAPT was superior to ASA monotherapy (RR, 0.79; 95% CI, 0.69 to 0.91), but similarly effective for stroke prevention as Plavix monotherapy (RR, 1.01; 95% CI, 0.93 to 1.10) (*Ding et al 2018*). DAPT also doubled the risk for bleeding in elderly compared to younger patients (RR, 2.18; 95% CI, 1.02 to 4.69).
- With regard to the treatment of ACS, in the CLARITY-TIMI 28 study, patients who presented within 12 hours of a STEMI were randomized to receive either Plavix or placebo for 30 days. Treatment with Plavix was associated with a reduction of the composite endpoint of occluded infarct-related artery on angiography, death, or recurrent MI before angiography (*Sabatine et al 2005a*). Patients included in the COMMIT study were admitted within 24 hours of a suspected acute MI and received either combination therapy with Plavix and ASA or ASA monotherapy. In this study, there was a significant reduction in the risk of the composite endpoint of death, re-infarction, or stroke (p = 0.002), and in death from any cause (p = 0.03) in patients receiving combination therapy after 15 days (*COMMIT 2005*). In the CURE study, investigators compared long-term (3 to 12 months) combination therapy with Plavix plus ASA to ASA monotherapy in patients with a NSTEMI who presented within 24 hours of symptom onset. The results demonstrated that combination therapy resulted in a 20% RRR in the composite outcome of nonfatal MI, stroke, or vascular death (p < 0.001). The compelling benefit of combination therapy noted in the CURE study was in the reduction of nonfatal MI. Due to the low number of strokes that occurred during the study, the associated reduction was not significant. There was also a weak trend suggesting the possibility of small reductions in death associated with combination therapy that was not significant (*CURE 2001, Harrington et al 2008, Lansberg et al 2012*). MAs of ACS patients or those undergoing PCI to reduce thrombotic events,

have conflicting results. Results reported Plavix was superior to placebo in reducing the risk of CV death and stroke. Effient or Brilinta treatment when compared to Plavix provided additional benefit regarding CV mortality and MI, but no advantage in stroke (*Aradi et al 2013*). A secondary analysis of the TRILOGY ACS trial found intensive antiplatelet therapy with Effient may be beneficial in reducing CV deaths, MIs, or strokes when an angiography is performed prior to treatment and anatomic coronary disease is confirmed (*Roe et al 2012, Wiviott et al 2013*). The CHARISMA study was another long-term trial (median, 28 months) that enrolled and randomized patients with clinically evident CV disease to either combination treatment with Plavix and ASA or to monotherapy with ASA. The rate of the primary composite endpoint of MI, stroke, or death from CV causes was not different between the 2 treatments (6.8 vs 7.3%; relative risk [RR], 0.93; 95% CI, 0.83 to 1.05; p = 0.22) (*Bhatt et al 2006*). There is also limited evidence that Plavix has a greater impact on preventing the composite of CV death, MI, and stroke in smokers compared to non-smokers (*Gagne et al 2013*). A MA evaluated the clinical efficacy and safety of $P2Y_{12}$ inhibitors in patients with STEMI undergoing primary PCI, as defined by composite major adverse CV events (MACE). At 1 month, the analysis suggested that Effient was associated with lower MACE vs Plavix (standard dose odds ratio [OR] 0.59; 95% CI, 0.50 to 0.69) and Brilinta (standard dose OR 0.69; 95% CI, 0.56 to 0.84); lower mortality and MI vs Plavix and standard Brilinta; and lower stroke risk vs standard Plavix and Brilinta. At 1 year, Effient was associated with lower mortality and MACE vs Plavix and Brilinta. In general, Effient and Brilinta were more efficacious vs Plavix in this analysis (*Rafique et al 2016*). However, another network meta-analysis (NMA) evaluated the efficacy of $P2Y_{12}$ inhibitors (Plavix, Effient, Brilinta, and cangrelor) in patients undergoing PCI for any indication (STEMI or non-ST elevated ACS) and did not find any significant differences between any of the agents in terms of all-cause mortality, CV death, MI, probable or definite stent thrombosis, stroke, major bleeding, or MACE (*Westman et al 2017*). When used post fibrinolytic therapy in patients with a STEMI, Brilinta and Plavix demonstrated similar rates of bleeding, MACE, mortality, MI, and stroke in a 2018 MA of 5 RCTs, as well as a 2019 RCT (*Kheiri et al 2019, Berwanger et al 2019*).

- The duration of DAPT has been highly debated and often controversial. Evolving evidence has consistently demonstrated that estimated benefits are accompanied by a certain proportion of risk; therefore, not all patients would benefit from DAPT treatment. To further complicate interpretations, often first-generation stents were studied for DAPT; however, newer stents have improved safety benefits, but studies and analyses often have ≥ 1 methodological limitations. Current evidence includes an analysis of the National Heart, Lung, and Blood Institute (NHLBI) observational registry which followed over 3,000 ACS patients following PCI with a drug-eluting stent (DES); this study found that patients who continued on DAPT (Plavix plus ASA) experienced lower mortality after 1 year, but had a higher risk of repeat PCI within 4 years (*Mulukutala et al 2013*). The PRODIGY trial demonstrated that Plavix plus ASA administered in patients who received a DES or bare metal stent for 24 months was not significantly more effective than a 6-month Plavix regimen in reducing the composite of death due to any cause, MI, or cerebrovascular accident (*Valgimigli et al 2012*). However, the DAPT trial found patients who continued DAPT beyond 1 year after the placement of a DES compared with ASA therapy alone, significantly reduced the risk of stent thrombosis, MACE and cerebrovascular events, including MI; but was associated with an increased risk of bleeding and all-cause mortality (*Mauri et al 2014*). Several MAs/systematic reviews have concluded there is no increased risk of stent thrombosis with shorter duration DAPT, and treatment is associated with a lower risk of bleeding. MAs restricted to predominantly newer generation DES have demonstrated increased trends of increased all-cause mortality associated with prolonged duration of DAPT, although not all analyses reached statistical significance (*Elmariah et al 2015, Navarese et al 2015, Udell et al 2016, Misumida et al 2018*). Another MA determined that long-term DAPT was associated with a significant decrease in risk of death, MI, and stroke, primarily in patients with prior MI or stroke, but not PAD, while long-term DAPT was also associated with increased major bleeding. Of note, the study was not able to evaluate the impact of DES on atherothrombotic events (*Fanari et al 2017*). Another MA assessed the efficacy and safety of duration of DAPT in patients with implantation of predominantly newer-generation DES. The analysis determined treatment with DAPT for 12 months vs 3 to 6 months resulted in no significant differences in incidences of death, major hemorrhage, or MI. DAPT for 18 to 48 months vs 6 to 12 months was also associated with no difference in incidence of all-cause death, but showed decreased MI and stent thrombosis, and increased major hemorrhage. A risk-benefit analysis found 3 fewer stent thromboses and 6 fewer MIs but 5 more major bleeds per 1,000 patients/year treated with prolonged DAPT. Also, treatment with DAPT > 1 year after MI reduced the composite risk of CV death, MI, or stroke but increased major bleeding (*Bittl et al 2016*).
- A MA of 16 RCTs looking at the effects of antiplatelet agents (e.g., ASA, Aggrenox, and ASA plus Plavix) and vitamin K antagonists for the prevention of thrombosis in patients with lower limb atherosclerosis undergoing bypass grafting found therapy with ASA or Aggrenox had an effect on peripheral bypass grafts and prosthetic graft patency, but not venous grafts alone. Treatment with Plavix plus ASA had greater increases of bleeding, but no difference in primary graft patency compared to ASA alone (*Bedenis et al 2015*).

- The major clinical study demonstrating the safety and efficacy of Brilinta for its FDA-approved indication is the PLATO study. PLATO was an international, DB, double-dummy (DD), multicenter (MC), RCT that compared Brilinta to Plavix in adult patients hospitalized with documented ACS, with or without ST-segment elevation within the previous 24 hours (n = 18,624). After 12 months, the risk of the primary composite endpoint of vascular death, MI, or stroke was significantly reduced with Brilinta (9.8 vs 11.7%; HR, 0.84; 95% CI, 0.77 to 0.95; p < 0.001). Brilinta also significantly reduced the risk of the secondary endpoints of the composite of all-cause mortality, MI, or stroke (10.2 vs 12.3%; HR, 0.84; 95% CI, 0.77 to 0.92; p < 0.001); the composite of vascular death, MI, stroke, severe recurrent ischemia, recurrent ischemia, TIA, or other arterial thrombotic event (14.6 vs 16.7%; HR, 0.88; 95% CI, 0.81 to 0.95; p < 0.001); MI (5.8 vs 6.9%; HR, 0.84; 95% CI, 0.75 to 0.95; p = 0.005), and vascular death (4 vs 5.1%; HR, 0.79; 95% CI, 0.69 to 0.91). Furthermore, Brilinta significantly reduced the risk of all-cause mortality (4.5 vs 5.9%; HR, 0.78; 95% CI, 0.69 to 0.89). Rates of major bleeding were not different between the 2 treatments (p = 0.43) (*Wallentin et al 2009*).
- Several subanalyses of the PLATO study have been conducted (*James et al 2011, Cannon et al 2010, Steg et al 2010, James et al 2010a, James et al 2010b, Held et al 2011, Wallentin et al 2010, Mahaffey et al 2011, Storey et al 2011, Becker et al 2011, Banerjee et al 2008, Kohli et al 2013, Husted et al 2014, Varenhorst et al 2014, Velders et al 2016*). One subanalysis found Brilinta was associated with fewer first and recurrent composite CV events based on the entire international study population (*Kohli et al 2013*). In patients with ACS undergoing noninvasive (p = 0.045) or invasive procedures (p = 0.0025), Brilinta remained more efficacious compared to Plavix (*James et al 2011, Cannon et al 2010*). However, in patients with ST-elevation or left bundle branch block (p = 0.07), chronic kidney disease (CKD) (p = 0.13), or diabetes (p-value = not reported), and in those who underwent CABG surgery (p = 0.29), there was no difference between Brilinta and Plavix with regard to the primary composite endpoint (*Steg et al 2010, James et al 2010a, James et al 2010b, Held et al 2011*). In patients with or without ST-elevated ACS, gender was not a risk factor for outcomes, but some signals alluded to men benefiting most. The number of primary events that occurred in men was double that of women (*Husted et al 2014*). A genetic substudy was also conducted and demonstrated Brilinta to be more efficacious than Plavix, irrespective of cytochrome P450 2C19 and ABCB1 polymorphisms (p = 0.0380) (*Wallentin et al 2010*). In the original PLATO study, a significantly higher rate of dyspnea was observed with Brilinta; however, data from a substudy revealed Brilinta had no effect on pulmonary function (*Wallentin et al 2009, Storey et al 2011*). In terms of causes of death, Brilinta appeared to have a greater effect on sudden death over Plavix within the study population (*Varenhorst et al 2014*). Another post-hoc subgroup analysis of patients with STEMI treated with primary PCI demonstrated treatment with Brilinta resulted in a reduction of the primary end point compared with Plavix (7.9 vs 8.6%; p = 0.38) (*Velders et al 2016*).
- Mahaffey et al compared the effects of Brilinta and Plavix among patients enrolled in the PLATO study who were from the United States (U.S.) (N = 1,413). The superior benefits of Brilinta in reducing thrombotic CV events were not observed among this specific patient population. Specifically, there was no difference between Brilinta and Plavix in the rate of the primary composite endpoint (11.9 vs 9.5%; HR, 1.27; 95% CI, 0.92 to 7.75; p = 0.15). The authors discussed that among these patients who were treated with Brilinta, the lowest event rates were observed in patients also receiving low-dose ASA maintenance therapy. In contrast, event rates in those treated with Plavix were similar regardless of concurrent high- or low-dose ASA. Despite the potential role that ASA maintenance dosing may play in explaining the regional differences observed within the PLATO study, the authors noted that the pattern of results are consistent with what might be expected by chance alone in a large, multiregional clinical study with multiple exploratory analyses. A potential mechanism by which high-dose ASA is thought to reduce the effects of Brilinta relates to its ability to inhibit the endothelial release of prostacyclin in a dose-dependent fashion at doses greater than 80 mg/day. Prostacyclin reduces platelet reactivity and may contribute synergistically *in vivo* to the antiplatelet effects of $P2Y_{12}$ inhibitors. Therefore, the therapeutic effects of a higher mean level of $P2Y_{12}$ inhibition achieved with Brilinta in the PLATO study may be attenuated when endogenous prostacyclin production is inhibited (*Mahaffey et al 2011*). Until a prospective clinical study comparing the effects of low- vs high-dose ASA maintenance therapy and its effect on the efficacy of Brilinta is conducted, it remains unclear as to why the diminished effects of Brilinta in the U.S. population were observed. Of note, the FDA-approved dosing of Brilinta recommends that after the initial loading dose of ASA (325 mg), a daily maintenance dose of ASA of 75 to 100 mg should be used.
- The GLOBAL LEADERS RCT compared DAPT (ASA plus Brilinta) for 1 month followed by Brilinta monotherapy for 23 months vs standard DAPT (ASA plus either Plavix or Brilinta) for 12 months followed by ASA monotherapy for 12 months for patients undergoing PCI with a DES for either CAD or ACS (*Vranckx et al 2018*). After 2 years, there was no differences between groups for the primary composite outcome of all-cause mortality, or non-fatal MI (RR, 0.87; 95% CI, 0.75 to 1.01). A pre-specified ancillary analysis (GLASSY) found that Brilinta monotherapy after 1 month of DAPT was

noninferior, but not superior, to standard DAPT in terms of all-cause death, nonfatal MI, nonfatal stroke, or urgent target vessel revascularization (RR, 0.85; 95% CI, 0.72 to 0.99); rates of bleeding were not significantly different between groups (*Franzone et al 2019*).

- The TWILIGHT trial compared DAPT (ASA plus Brilinta) for 3 months followed by Brilinta monotherapy for 12 months vs DAPT (ASA plus Brilinta) for 15 months in patients at high risk for bleeding or ischemic events undergoing PCI with a DES (*Mehran et al 2019*). At 15 months, Brilinta monotherapy was associated with a lower risk of bleeding (HR, 0.56; 95% CI, 0.45 to 0.68) and no increased risk of death, MI, or stroke (HR, 0.99; 95% CI, 0.78 to 1.25).
- The FDA approval of Brilinta for the reduction in the rate of CV death, MI, and stroke in patients with a history of MI was based on results from the PEGASUS TIMI-54 trial. Approximately 21,000 patients who had a MI at least 1 to 3 years prior and had a high-risk factor for another event were randomized to treatment with Brilinta 90 mg twice daily, 60 mg twice daily, or placebo in addition to ASA 75 to 150 mg and followed for a median time of 33 months. The primary composite endpoint of time to first event of CV death, MI, or stroke was significantly reduced by 16% with Brilinta 60 mg twice daily plus ASA with event rates 1.27% lower at 3 years in the Brilinta 60 mg twice daily plus ASA group compared to those patients treated with ASA alone ($p = 0.004$) (*Bonaca et al 2015*). Subgroup analyses have also demonstrated similar outcomes for the primary endpoint of MACE between patients with and without diabetes and between patients with and without prior coronary stenting (*Bhatt et al 2016, Furtado et al 2019*). The primary safety endpoint, TIMI major bleeding, was significantly increased with Brilinta treatment but to a lesser degree with the 60 mg twice daily dose (Brilinta 60 mg twice daily plus ASA, 2.3% vs ASA monotherapy, 1.1%; $p < 0.001$) (*Bonaca et al 2015*). The rates of CV mortality or all-cause mortality alone were not significantly different from ASA monotherapy.
- In a 2018 MA, dual or triple antithrombotic therapy with Brilinta vs Plavix significantly increased the risk of clinically significant bleeding (OR, 1.52; 95% CI, 1.12 to 2.06, and OR, 1.7; 95% CI, 1.24 to 2.33, respectively). Among those on triple therapy, a higher risk of MACE was seen with Brilinta compared to Plavix (OR, 1.88; 95% CI, 1.26 to 2.80); patients who received dual therapy exhibited a similar risk of MACE and stroke (*Andreou et al 2018*).
- A MA comparing Brilinta-based antiplatelet regimens to conventional antiplatelet regimens found that, among patients with CAD, Brilinta demonstrated a lower risk of death (HR, 0.84; 95% CI, 0.77 to 0.91) and MI (HR, 0.87; 95% CI, 0.80 to 0.94) (*Cassese et al 2020*).
- The SOCRATES trial evaluated approximately 13,200 patients with an acute, non-severe ischemic stroke or high-risk TIA who had not received intravenous or intra-arterial thrombolysis, were not considered to have had a cardioembolic stroke, and were treated with either Brilinta or ASA for 90 days. Brilinta was not significantly superior to ASA in reducing stroke, MI, or death at 90 days, the primary endpoint (6.7% of the Brilinta group vs 7.5% of those treated with ASA; $p = 0.07$). Additionally, no secondary endpoints were considered significantly different between treatment groups but generally trended towards favoring Brilinta (with the exception of death and CV death). Exploratory analyses indicated that Brilinta may be more effective at 7 days in reducing ischemic stroke and all stroke. However, more patients discontinued treatment in the Brilinta group (17.5%) vs the ASA group (14.7%), mainly due to dyspnea and any bleeding (*Johnston et al 2016*).
- A subgroup analysis of SOCRATES assessed patients from Asian countries (N = 3,858), as the composite of stroke, MI, or death occurred at an increased rate in patients from Asia compared with patients outside of Asia (10.6 vs 5.7%, nominal $p < 0.01$), with higher incidence of major or minor bleeding events in patients from Asia (2.1 vs 1.2%, respectively). In the patients from Asia, treatment with Brilinta significantly reduced the rate of the composite endpoint compared with ASA treatment (9.6 vs 11.6%; HR, 0.81; 95% CI, 0.67 to 0.99), with no significant differences in the rates of major bleeding between treatment groups (*Wang et al 2017*).
- The TiCAB trial compared Brilinta 90 mg twice daily to 100 mg ASA daily in patients undergoing CABG (*Schunkert et al 2019*). Study enrollment was prematurely halted, with only 1859 of the planned 3850 patients enrolled. No significant differences in major CV events or bleeding were demonstrated between the groups, but the study was underpowered to detect between-group differences.
- The THEMIS trial evaluated DAPT with Brilinta plus ASA versus ASA alone in 19,220 diabetic patients with stable CAD (ie, history of PCI or CABG, or documented angiographic stenosis of > 50% in at least 1 coronary artery) (*Steg et al 2019*). Ischemic CV event rates were slightly lower among patients receiving DAPT (HR, 0.90; 95% CI, 0.81 to 0.99), but major bleeding rates were also higher with DAPT (HR, 2.32; 95% CI, 1.82 to 2.94). Adding Brilinta to ASA was not found to have a favorable risk-benefit profile in the overall trial population. A prespecified analysis of patients in the THEMIS trial who had previously undergone PCI (N = 11,154) found that, although major bleeding was still increased (HR, 2.03; 95% CI, 1.48 to 2.76) in this patient population, there may be a net clinical benefit with DAPT (HR, 0.85; 95% CI, 0.75 to 0.95) (*Bhatt et al 2019*).

- The major clinical trial demonstrating the safety and efficacy of Effient for its FDA-approved indication was the TRITON-TIMI 38 (N = 13,608). Results demonstrated that Effient was significantly more effective than Plavix in reducing ischemic events in patients with ACS who underwent PCI. However, the trial did not demonstrate a decrease in the mortality rate with Effient. In addition, the results from TRITON-TIMI 38 did show a significantly higher rate of major, minor, life-threatening, and fatal bleeding events with Effient. Of note, certain patient subgroups, specifically those who were ≥ 75 years of age, those weighing < 60 kg and those with a past history of stroke or TIA, did not demonstrate a clinical benefit with Effient (*Wiviott et al 2007*). In addition, several subgroup analyses were also conducted based on TRITON-TIMI 38 and 1 patient subgroup in particular, those with diabetes, were found to have a significantly greater reduction in ischemic events with Effient when compared to nondiabetic patients being treated with either Effient or Plavix (*Antman et al 2008, Montalescot et al 2009, Murphy et al 2008, O'Donoghue et al 2009, Pride et al 2009, Wiviott et al 2008a, Wiviott et al 2008b*).
- In a 2018 MA, adverse CV outcomes were significantly lower with the use of Effient in comparison to Plavix following PCI. In an evaluation of bleeding outcomes, both agents yielded similar rates of major and minor bleeding episodes (*Brundhun et al, 2018*).
- One MA compared Brilinta and Effient following PCI, both agents demonstrated similar efficacy in reducing all-cause mortality, MACE, and stroke; however, the risk of major bleeding was higher with Brilinta (OR, 1.57; 95% CI, 1.30 to 1.89) (*Guan et al 2018*). Another MA compared these agents in patients with type 2 diabetes following PCI that failed to find any significant differences between agents for mortality, MACE, MI, stroke, or major bleeding (*Yang et al 2018*).
- The ISAR-REACT 5 trial compared Brilinta and Effient in patients (n = 4018) with ACS for whom invasive evaluation was planned (*Schupke et al 2019*). The incidence of the composite primary endpoint (death, MI, or stroke at 1 year) was significantly higher in the Brilinta group (HR, 1.36; 95% CI, 1.09 to 1.70); major bleeding was not significantly different between groups.
- Another MA compared antiplatelet agents (Brilinta and Effient) to Plavix in patients with CKD and an ACS. The other antiplatelets were associated with a reduced risk of MACE (HR, 0.88; 95% CI, 0.79 to 0.99) and no difference in bleeding vs Plavix (*Bonello et al 2018*).
- As concluded in the TRILOGY ACS study, in patients with UA/NSTEMI who do not undergo revascularization, when added to ASA therapy, Effient did not significantly reduce the frequency of death from CV causes, MI, or stroke, as compared with DAPT with Plavix and ASA, and similar risks of bleeding were observed (*Kohli et al 2014, Roe et al 2012*). However, a secondary analysis of patients who underwent angiography prior to Effient treatment experienced fewer CV deaths, MIs, or strokes than those who were in the Plavix arm (*Roe et al 2012, Wiviott et al 2013*).
- First-in-class PAR-1 antagonist, Zontivity, was FDA-approved based on a post-hoc analysis of patients with a history of MI or PAD who were taking ASA and/or a thienopyridine (mainly Plavix) concomitantly. A safety review terminated the full TRACER trial and patients with stroke in the TRA 2°P-TIMI 50 trial due to significantly increased risks for bleeding, including intracranial hemorrhage (ICH). Both trials were placebo-controlled (PC). In the TRA 2°P-TIMI 50 trial, Zontivity demonstrated effectiveness in the secondary prevention of CV events, mainly MI and the composite endpoint of CV death, MI, or stroke, primarily driven by the reduction in MI. Although TRA 2°P-TIMI 50 was not designed to evaluate the benefits and risks of Zontivity in individual patient subgroups, an analysis of patients who were comprised of post-MI and PAD without a history of stroke or TIA was evaluated by the FDA for approval. Those results showed three-year Kaplan Meier (K-M) event rate for the primary efficacy endpoint of 7.9% in the Zontivity group compared to 9.5% in the placebo group (HR, 0.8; 95% CI, 0.73 to 0.89; p < 0.001). The benefit of Zontivity is tempered by the significant increase of bleeding with Zontivity use compared to placebo. Significantly increased bleeding rates were also observed in the TRA 2°P-TIMI 50 trial for GUSTO moderate or severe bleeding, TIMI clinically significant bleeding, and GI bleeding (NNH = 97, 25, 98, respectively). However, there was no significant difference between placebo and Zontivity for fatal bleeds (*Morrow et al 2012, Tricoci et al 2012, FDA Summary Review [Zontivity] 2014, FDA Advisory Committee Transcript [Zontivity] 2014*). Subgroup analyses have concluded that increased bleeding risks may not be observed in all populations. A pre-specified subgroup analysis of stable patients with a history of previous MI determined that Zontivity reduced the primary endpoint, whether treated concomitantly with a thienopyridine or not, and the risks of GUSTO moderate or severe bleeding were similarly increased irrespective of thienopyridine use (P-interaction = 0.37) (*Bohula et al 2015*). Other subgroup analyses have been published and include a number of the TRA 2°P–TIMI 50 primary study authors. These subgroup analyses found a significant difference in the composite primary endpoint of CV death, MI, or stroke for patients with a prior MI but no statistically significant difference in PAD patients; treatment with Zontivity in patients with a prior MI was also associated with greater reductions in CV death, MI, or stroke in patients with ≥ 1 risk factors for recurrent events, with greatest risk reductions in patients with ≥ 3 risk factors (*Bohula et al 2016, Bonaca et al*

2013, Scirica et al 2013). However, the quality of the sub-group analyses is not superior to that of the primary study and the validity of the results is uncertain as methodological limitations were noted. A MA of 5 RCTs (N = 40,630) demonstrated treatment with Zontivity vs placebo resulted in a statistically non-significant reduction in risk of MI (risk reduction [RR] 0.86; 95% CI, 0.80 to 0.93; p = 0.427) and ischemic stroke (RR, 0.84; 95% CI, 0.72 to 0.97; p = 0.92), with no observed differences in all-cause mortality or TIMI bleeding (*Sharma et al 2017*).

- The FDA approval of Yosprala (ASA DR/omeprazole) was based on 2 identically-designed, 6-month, phase 3, MC, DB, active-control (AC), RCTs conducted in the U.S. The trials compared Yosprala 325/40 mg (n = 524) to enteric-coated (EC) ASA 325 mg (n = 525), each administered orally once daily for secondary CV disease prevention in patients who had been taking ASA 325 mg daily for ≥ 3 months and who were at risk for ASA-associated gastric ulcers. Patients taking non-ASA non-steroidal anti-inflammatory drugs (NSAIDs) at baseline were allowed to continue therapy if use was chronic and expected to continue throughout the study period. The primary endpoint was the cumulative incidence of endoscopically-determined gastric ulceration over 6 months. Yosprala significantly reduced the cumulative incidence of gastric ulcers vs EC ASA 325 mg in the pooled analysis (3.2 vs 8.6%, respectively; p < 0.001). Among NSAID-users at baseline, the cumulative incidence of endoscopic gastric ulcer at month 6 was 4.5% with Yosprala vs 10.2% in the EC ASA group, while rates among patients not taking NSAIDs were 3.1% with Yosprala vs 8.4% in the EC ASA group. Significantly fewer patients treated with Yosprala discontinued therapy due to pre-specified upper GI AEs vs patients treated with EC ASA arm (1.5 vs 8.2%, respectively; p < 0.001) (*Whellan et al 2014*).
- The long-term CV and GI safety of Yosprala were evaluated in a 12-month, phase 3, MC, open-label, single-arm trial among patients who were taking ASA 325 mg daily for ≥ 3 months for secondary CVD prevention and were at risk for ASA-associated upper GI events (n = 379). After 12 months, no new or unexpected safety events were noted with Yosprala, while the most common treatment-emergent GI AEs were diarrhea, dyspepsia, and nausea (each occurred in 4 to 5% of the overall safety population). Gastroesophageal reflux disease (GERD) was reported in 1.8% of the overall population (*Goldstein et al 2016*).
- Durlaza 162.5 mg was the first ASA ER formulation approved by the FDA to reduce the risk of death and MI in patients with chronic CAD, and to reduce the risk of death and recurrent stroke in patients who have had an ischemic stroke or TIA. New efficacy studies were not submitted to the FDA for the approval of Durlaza. While Durlaza 162.5 mg has a similar pharmacodynamic effect as immediate-release ASA 81 mg, the clinical benefits of the ER formulation vs immediate-release formulations of ASA are not yet known (*Drugs@FDA.com 2019*).
- There is no evidence to support the use of dipyridamole in the acute treatment of patients presenting with a non-ST-segment elevation ACS (*Harrington 2008*). In addition, the results of a large MA of 29 RCTs demonstrated that in patients with arterial vascular disease, dipyridamole had no clear effect on the secondary prevention of vascular death. Compared to control (no drug or another antiplatelet inhibitor), dipyridamole appeared to reduce the risk of vascular events; however, the effect was only significant in patients presenting with cerebral ischemia (*De Schryver et al 2007*).
- In patients with stable intermittent claudication, cilostazol therapy has been shown to provide improvement in walking distance and speed as determined by standardized exercise treadmill tests and functional status questionnaires (*Beebe et al 1999, Bedenis et al 2014, Money et al 1998, Reilly 2001*). Results of several randomized, DB, PC studies of 6 to 24 weeks' duration indicate that cilostazol is more effective than placebo in increasing initial (until onset of claudication pain) and absolute (intolerable pain) claudication distances (*Bedenis et al 2014, Beebe et al 1999, Money et al 1998, O'Donnell et al 2009a, O'Donnell et al 2009b, Reilly 2001*). Limited data suggest that cilostazol (100 mg twice daily) also may be more effective than pentoxifylline (400 mg 3 times daily) in improving walking distance in patients with intermittent claudication (*Bedenis et al 2014, Beebe et al 1999, Dawson et al 2000, Hiatt 2001, Reilly 2001*).
- Because of its antiplatelet activity, cilostazol has been used alone or in combination with other antiplatelet agents (eg, ASA, Plavix) to prevent thrombosis and restenosis following coronary angioplasty/stent implantation (*Douglas et al 2005, Guyatt et al 2012, Kunishima et al 1997, Park et al 1999, Park et al 2000, Schömig et al 2005, Take et al 1997, Tsuchikane et al 1999, Xu et al 2016, Yoon et al 1999, Zou et al 2015*). In a randomized, DB, PC study, patients undergoing coronary artery stent implantation with bare-metal stents who received cilostazol (100 mg twice daily for 6 months) in addition to therapy with ASA and Plavix (75 mg daily for 30 days) had a larger minimal coronary artery lumen diameter (primary end point) and a 36% reduction in the risk of restenosis (defined as narrowing of the stented coronary artery lumen by at least 50% as documented by quantitative coronary angiography) (*Douglas et al 2005, Schömig et al 2005*). However, more recent studies, including a RCT and a SR of 10 RCTs, comparing triple antiplatelet therapy (ASA, Plavix, and cilostazol) with DAPT (ASA and Plavix), failed to demonstrate or exclude a beneficial effect of cilostazol on clinical outcomes (eg, reinfarction, major bleeding, mortality, periprocedural MI) when added to Plavix and ASA therapy (*Guyatt et al 2012, Xu et al 2016*). For patients undergoing DES implantation in coronary arteries, a MA of 7 RCTs

evaluated the long-term efficacy and safety of adding cilostazol to conventional DAPT (ASA and Plavix). The analysis demonstrated that the addition of cilostazol was associated with a significant reduction in MACE vs DAPT (RR, 0.66; 95% CI, 0.50 to 0.88), without increasing bleeding, but was associated with significantly higher rates of rash, GI adverse effects, headache, and drug discontinuation (*Zou et al 2015*).

- Agrylin is the only platelet inhibitor to be FDA-approved for the treatment of thrombocythemia associated with myeloproliferative disorders, and the agent has demonstrated safety and efficacy for this indication (*Anagrelide study group 1992, Birgegard et al 2004, Dombi et al 2017, Harrison et al 2005, Penninga et al 2004, Silver 2005, Steurer et al 2004, Wiviott et al 2007*).

CLINICAL GUIDELINES

- Antiplatelet therapy is recommended for a variety of indications. The selection of $P2Y_{12}$ inhibitor therapy for patients with CAD varies greatly by individual patient characteristics and bleeding risks. All guidelines agree and recommend long-term treatment with ASA, or Plavix for those who cannot tolerate ASA in patients with ACS (*Amsterdam et al 2014, Guyatt et al 2012, Ibanez et al 2018, January et al 2014, January et al 2019, Levine et al 2011, Levine et al 2016a, Levine et al 2016b, Lip et al 2018, O'Gara et al 2013, Piepoli et al 2016, Roffi et al 2016*).
- The 2016 American College of Cardiology (ACC)/AHA guidelines for DAPT in patients with CAD have updated duration recommendations for 6 previously published guidelines based on data around newer generation stents. Recommendations range based on the benefit/risk profiles of CAD patients but overall, minimum courses of DAPT therapy are now recommended in certain patients. New key recommendations include: (1) Plavix therapy for a minimum of 6 months for patients treated with DES; (2) any $P2Y_{12}$ inhibitor treatment for 12 months in those with ACS; (3) extended DAPT continuation in patients who have low bleeding risk; and (4) shorter duration of DAPT for patients at lower ischemic risk with high bleeding risk and longer DAPT periods for patients at elevated ischemic risk with lower bleeding risk (*Levine et al 2016a*). In 2017, the European Society of Cardiology (ESC) also published guidelines for DAPT in patients with CAD. Recommendations are largely consistent with the 2016 ACC/AHA guidelines for DAPT with several additions. In patients with CAD treated with coronary stent implantation, Plavix plus ASA is recommended for 6 months, irrespective of stent type. In patients with CAD treated with bioresorbable vascular scaffolds, DAPT should be considered for at least 12 months. Brilinta plus ASA is recommended for patients with ACS who do not have contraindications to the drug. For patients with NSTEMI undergoing PCI who are $P2Y_{12}$ inhibitor-naïve, or those with STEMI initially managed with conservative strategies, but now requiring a PCI, Effient plus ASA is recommended unless contraindications exist (*Valgimigli et al 2018*).
- The 2016 ESC guidelines updated recommendations on CV disease prevention. Key recommendations include: (1) in patients with ACS, DAPT with a $P2Y_{12}$ inhibitor (no agent recommended over another) and ASA for 12 months is recommended, unless there are contraindications (e.g., excessive risk of bleeding); (2) a shorter duration of $P2Y_{12}$ inhibitor administration (ranging from 3 to 6 months) should be considered for patients with higher bleed risks after DES implantation; (3) in non-cardioembolic ischemic stroke or TIA, prevention with ASA only, or Aggrenox or Plavix alone is recommended; and (4) in patients with stable CAD, Effient is not recommended and Brilinta is not recommended in stable CAD without a prior ACS (*Piepoli et al 2016*). Many of these recommendations are echoed in the 2017 ESC guidelines for DAPT (*Valgimigli et al 2018*). Additionally, the 2017 guidelines note that continuation of DAPT with Plavix for 6 to 30 months may be considered for patients with stable CAD who have tolerated therapy without complications but continue to have a high thrombotic risk. One month of DAPT can also be considered for patients with stable CAD in whom a 3-month DAPT poses safety concerns. The 2019 ESC guidelines for chronic coronary syndromes recommend DAPT with Plavix and ASA for 6 months following coronary stenting (assuming a normal risk of bleeding); duration of DAPT may be shortened to 3 months or 1 month, depending on risk of bleeding (*Knuuti et al 2020*). ASA monotherapy is recommended for patients with chronic coronary syndromes and previous MI or revascularization, but Plavix may be used as an alternative, particularly for patients with ASA intolerance or history of PAD or stroke/TIA. Adding another antithrombotic drug (no preferred agent) to ASA for long-term prevention may be considered in patients who have a moderate or high risk of ischemic events and no high bleeding risk.
- Other guidelines come from the American College of Chest Physicians (ACCP), which recommend Plavix plus ASA for 6 to 12 months in patients undergoing PCI and stent placement. Effient should not be used in patients < 60 kg, > 75 years of age or with a prior history of stroke. In patients who are stopping anticoagulant therapy and do not have a contraindication to ASA, it is recommended to administer ASA over no ASA to prevent recurrent venous thromboembolism (*Guyatt et al 2012, Kearon et al 2016*).

- The AHA/ACC, 2015 ESC guidelines for the management of patients with NSTEMI ACS, and 2017 ESC guidelines for DAPT provide more specific $P2Y_{12}$ inhibitor recommendations compared to other reputable society groups. For those patients with moderate to severe risk of ischemic events, DAPT with ASA is recommended; however, Brilinta is specifically recommended over Plavix for up to 12 months of treatment. According to the 2015 ESC guidelines, Zontivity may be added to ASA and Plavix for patients with a history of MI, but efficacy is modest and must be weighed against the risk for bleeds. Effient is not recommended for patients with NSTEMI ACS in whom coronary anatomy is not known. (*Amsterdam et al 2014, January et al 2014, January et al 2019, O'Gara et al 2013, Roffi et al 2016, Valgimigli et al 2018*).
- According to the 2019 AHA/ACC focused update for the management of atrial fibrillation (AF), if triple therapy (oral anticoagulant, ASA, and $P2Y_{12}$ inhibitor) is prescribed in AF patients at increased risk of stroke and have undergone PCI, it is reasonable to choose Plavix over Effient. Double therapy with a $P2Y_{12}$ inhibitor (Plavix or Brilinta) and dose-adjusted warfarin or double therapy with a $P2Y_{12}$ inhibitor (Plavix) and certain oral anticoagulants (eg, low dose rivaroxaban 15 mg once daily or dabigatran 150 mg twice daily) are reasonable to reduce the risk of bleeding compared to triple therapy. The 2018 ACCP guidelines for antithrombotic therapy for patients with AF recommend antiplatelet agents (preferably Plavix) for patients with AF undergoing PCI/stenting; the use and duration of triple therapy (2 antiplatelet agents plus an oral anticoagulant) and dual therapy (single antiplatelet agent plus an oral anticoagulant) is dependent on the risk of bleeding and thrombosis (*January et al 2014, January et al 2019, Lip et al 2018*).
- The 2017 ESC guidelines for the management of patients with a STEMI provide the following recommendations for the periprocedural use of platelet aggregation inhibitors in patients undergoing primary PCI: (1) unless there are contraindications such as excessive risk of bleeding, Effient or Brilinta (or Plavix if these are not available or are contraindicated), is recommended before (or at latest at the time of) PCI and should be continued for 12 months; (2) ASA should be administered as soon as possible for patients without contraindications. For patients undergoing fibrinolytic therapy, Plavix plus ASA is recommended. However, patients who undergo PCI should be switched to Effient or Brilinta 48 hours after fibrinolysis. DAPT (ASA plus a $P2Y_{12}$ inhibitor) is recommended for up to 1 year in patients undergoing fibrinolysis plus PCI (*Ibanez et al 2018*). According to the 2017 ESC guidelines for DAPT, pre-treatment with Plavix may be warranted for patients with stable CAD who have a high probability of PCI (*Valgimigli et al 2018*).
- The 2011 AHA/American College of Cardiology Foundation (ACCF) guidelines for secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease recommends ASA, or Plavix if ASA is not tolerated, in all patients with CAD. A $P2Y_{12}$ inhibitor in combination with ASA is recommended in patients after ACS or PCI with stent placement, while patients receiving a bare-metal stent or DES during PCI for ACS should be given Plavix, Effient, or Brilinta for at least 12 months. Patients undergoing coronary artery bypass grafting should be given ASA for 1 year after surgery (*Smith et al 2011*). According to the 2017 ESC guidelines for DAPT, Brilinta or Effient plus ASA may be considered instead of Plavix in stable CAD patients undergoing PCI, taking into account ischemic and bleeding risks (*Valgimigli et al 2018*). These guidelines also recommend Plavix plus ASA in stable CAD patients undergoing coronary stent implantation and in ACS patients who cannot receive Brilinta or Effient, including those with prior intracranial bleeding or an indication for oral anticoagulation.
- According to the 2017 ESC guidelines for DAPT, a proton pump inhibitor (PPI) in combination with DAPT is recommended to minimize bleeding (*Valgimigli et al 2018).*
- The 2012 ACCP guidelines have included recommendations for ASA monotherapy or Aggrenox twice daily for initial therapy for TIA or ischemic stroke in order to prevent stroke (*Guyatt et al 2012*). The AHA/American Stroke Association (ASA) guidelines for acute ischemic stroke reinforce that the combination of ASA and Plavix might be considered for initiation within 24 hours of a minor ischemic stroke or TIA and for continuation for 90 days (*Kernan et al 2014; Powers et al 2018*). A 2019 update to the AHA/ASA guidelines for early management of acute stroke recommends that ASA be started within 24 to 48 hours after stroke onset; in patients with minor noncardioembolic strokes who did not receive alteplase, dual therapy with ASA and Plavix has been shown to reduce recurrent ischemic stroke if initiated within 24 hours of symptom onset and continued for 21 days (*Powers et al 2019*). Other guidelines state Plavix plus ASA is probably more effective at reducing stroke compared with ASA monotherapy, but is less effective than warfarin (*Culebras et al 2014, Kernan et al 2014*). The 2014 AHA/ASA guidelines for the primary prevention of stroke state that current clinical data reflect risk but no benefit of ASA for the prevention of a first stroke in the general population, and that there is no evidence that antiplatelet medications reduce the risk of stroke in the general population at low risk (*Meschia et al 2014*). A 2017 AHA/ASA statement on the prevention of stroke in patients with silent cerebrovascular disease recommends that it is reasonable to avoid antiplatelet agents when there is no specific CV or cerebrovascular indication, but to otherwise use them according to currently recommended indications (*Smith et al 2017*). The 2011

AHA/ACCF guidelines recommend that patients with extracranial carotid or vertebral atherosclerosis who have had ischemic stroke or TIA should be given ASA alone, Plavix alone, or a combination of Aggrenox (*Smith et al 2011*). The 2018 AHA/ASA guidelines for acute ischemic stroke note that Brilinta is not recommended over ASA in the treatment of minor stroke; this recommendation is echoed in the 2019 update (*Powers et al 2018, Powers et al 2019*).

- For the treatment of PAD, treatment with ASA is recommended for asymptomatic disease, and ASA or Plavix is recommended for secondary prevention of CV events in symptomatic PAD but not as dual therapy (*Alonso-Coello et al 2012, Smith et al 2011*). However, the 2011 ACC/AHA guidelines do state the combination of ASA and Plavix may be considered to reduce the risk of CV events in patients with symptomatic PAD, including those with intermittent claudication or critical limb ischemia, prior lower extremity (*Anderson et al 2013*). The 2016 ACC/AHA guidelines for patients with lower extremity PAD recommend antiplatelet therapy with ASA alone (75 to 325 mg per day) or Plavix alone (75 mg per day) to reduce MI, stroke, and vascular death in patients with symptomatic PAD (*Gerhard-Herman et al 2016*). The 2017 ESC guidelines for patients with PAD also recommend single-agent antiplatelet therapy (Plavix is preferred over ASA) for symptomatic patients, but recommend ASA plus Plavix for at least 1 month after coronary artery stenosis. Other indications for DAPT in the setting of PAD include after infra-inguinal stent implantation for at least 1 month, and in below-the-knee bypass with a prosthetic graft. Antiplatelet therapy is not routinely recommended for patients with isolated asymptomatic lower extremity arterial disease (*Aboyans et al 2018*).
- The 2012 ACCP guidelines recommend the addition of cilostazol to ASA or Plavix therapy in patients with refractory intermittent claudication who do not respond to conservative measures (*Guyatt et al 2012, Alonso-Coello et al 2012*). The 2016 ACC/AHA guidelines for patients with lower extremity PAD recommend cilostazol as an effective therapy to improve symptoms and increase walking distance in patients with claudication (*Gerhard-Herman et al 2016*). The 2017 ESC guidelines for patients with PAD do not specifically recommend cilostazol for patients with intermittent claudication, but do acknowledge that this agent may yield mild-to-moderate improvements in walking distance (*Aboyans et al 2018*).
- The 2017 AHA/ACC guidelines for the management of patients with valvular heart disease recommend antithrombotic therapy with ASA in addition to anticoagulation with a vitamin K antagonist in patients with a mechanical valve prosthesis, and daily ASA in all patients with a bioprosthetic aortic or mitral valve. Compared with oral anticoagulation alone, the addition of DAPT increases bleeding complications by at least 2- to 3-fold. Plavix 75 mg daily may be a reasonable antithrombotic therapy option for the first 6 months after transcatheter aortic valve replacement (TAVR), in addition to life-long ASA 75 mg to 100 mg daily (*Nishimura et al 2017*). The 2017 ESC guidelines for the management of valvular heart disease provide the following recommendations for patients with mechanical prosthesis: (1) triple therapy with ASA, Plavix, and a vitamin K antagonist for at least 1 month for patients treated with coronary stent implantation, irrespective of type of stent used; (2) triple therapy for 1 to 6 months is recommended for those with high ischemic risk due to ACS or other characteristics, when the benefits of therapy outweigh the bleeding risk; (3) dual therapy with a vitamin K antagonist and Plavix should be considered for patients in whom the bleeding risk outweighs the ischemic risk. The following are recommendations for patients with bioprostheses: (1) dual antiplatelet therapy should be considered for the first 3 to 6 months after transcatheter aortic valve implantation, followed by lifelong single antiplatelet therapy (in patients who do not need oral anticoagulation for other reasons); (2) antiplatelet therapy with a single agent can be considered after transcatheter aortic valve implantation for patients with a high risk of bleeding) (*Baumgartner et al 2018*).
- The updated 2019 Beers Criteria published by the American Geriatric Society (AGS) recommends avoiding short-acting dipyridamole and cilostazol in elderly patients, and recommends cautious use of ASA and Effient in older adults (*AGS 2019*). The criteria also recommends against scheduled use of proton-pump inhibitors, such as omeprazole, for more than 8 weeks unless they are used for high-risk patients.

SAFETY SUMMARY

- Boxed warnings associated with antiplatelet treatment include significant, sometimes fatal, bleeding with Brilinta, Effient, and Zontivity treatment. Additionally, Effient should not be prescribed in patients ≥ 75 years of age, body weight < 60 kg, those with a propensity to bleed, and with concomitant use of medications that increase the risk of bleeding. Brilinta should not be used with ASA in doses > 100 mg due to reduced effectiveness. The effectiveness of Plavix is dependent on the activation of CYP2C19; therefore, there is a reduced effect on platelet activity in patients who are homozygous for nonfunctional alleles of the CYP2C19 gene (termed “CYP2C19 poor metabolizers”). The use of another platelet $P2Y_{12}$ inhibitor should be considered in patients identified as CYP2C19 poor metabolizers. Additionally, Plavix has a warning and precaution for diminished antiplatelet activity with concomitant use of drugs that interfere with CYP2C19 (e.g.,

omeprazole, esomeprazole). Concomitant use with omeprazole or esomeprazole and Plavix should be avoided. Cilostazol is contraindicated in patients with heart failure of any severity.

- Plavix, Effient, Brilinta, and Zontivity are contraindicated in patients with active pathological bleeding such as bleeding peptic ulcer or ICH, and active pathologic bleeding is cited as a warning and precaution within the cilostazol labeling. Withholding Zontivity for a brief period will not be useful in managing an acute bleeding event because of its long half-life. There is no known treatment to reverse the antiplatelet effect of Zontivity, and significant inhibition of platelet aggregation remains 4 weeks after discontinuation. Because of the short half-life of Plavix's active metabolite, it may be possible to restore hemostasis by administering exogenous platelets; however, platelet transfusions within 4 hours of the loading dose or 2 hours of the maintenance dose may be less effective.
- Effient and Zontivity are also contraindicated in patients with a history of prior TIA or stroke, and Brilinta and Zontivity are contraindicated in patients with a history of ICH. Aggrenox, Durlaza, and Yosprala are contraindicated in patients with a known allergy to NSAIDs, in patients with asthma, rhinitis, and nasal polyps, or in children or adolescents with viral infections due to the risk of Reye's syndrome. Other contraindications are included within boxed warnings.
- Agrylin has no contraindications.
- Plavix, Brilinta, and Effient should be discontinued prior to surgery. Thrombotic thrombocytopenic purpura (TTP) may occur after brief exposure (< 2 weeks) of Plavix, Brilinta, or Effient. Premature discontinuation of Plavix, Brilinta, or Effient may increase the risk of CV events. Dyspnea has been reported in patients administered Brilinta; continuation with Brilinta without interruption or another antiplatelet should be considered. Brilinta can cause ventricular pauses, bradyarrhythmias including AV block. Brilinta has not been studied in patients with severe hepatic impairment. The concentrations of Brilinta and its metabolite and platelet inhibition are expected to be similar in patients with end-stage renal disease on intermittent hemodialysis vs patients with normal renal function. In patients with severe hepatic impairment, concentrations of Brilinta are likely to be increased. Brilinta may cause false negative platelet functional test results in patients with heparin-induced thrombocytopenia. Hypersensitivity reactions, including rash and angioedema, have been reported with Plavix and Effient use in patients with a history of prior thienopyridine hypersensitivity.
- Aggrenox, Durlaza, and Yosprala should be used with caution in patients at increased bleeding risk such as patients with GI ulcers, a history of active peptic ulcer disease, and/or concomitant alcohol (≥ 3 drinks daily). Agents containing ASA may cause fetal harm, especially during the third trimester. ASA and Agrylin should not be co-administered as use increases the risk of bleeding.
- Concomitant use of Yosprala with Plavix should be avoided, as omeprazole reduces the pharmacologic activity of Plavix. Omeprazole has also been associated with acute interstitial nephritis, *Clostridium difficile*-associated diarrhea, increased risk of bone fracture, cutaneous and systemic lupus erythematosus, hypomagnesemia, and vitamin B-12 deficiency. Concomitant Yosprala and PPI use is associated with an increased risk of fundic gland polyps that increase with long-term use, especially beyond 1 year.
- Agrylin may cause vasodilation, tachycardia, palpitations, pulmonary hypertension, and congestive heart failure (CHF). Other drugs that inhibit PDE-3 have caused decreased survival when compared with placebo in patients with CHF (Class III to IV). Because of the positive inotropic effects and side effects of Agrylin, a pre-treatment CV examination is recommended in addition to careful monitoring during treatment. Agrylin increased QT prolongation in healthy volunteers; therefore, Agrylin should not be used in patients with known risk factors for QT prolongation. In addition, interstitial lung diseases, mostly as progressive dyspnea with lung infiltrations, have been reported to be associated with the use of Agrylin in postmarketing reports.
- Cilostazol may induce tachycardia, palpitation, tachyarrhythmia or hypotension, with an associated increase in heart rate of approximately 5 to 7 bpm. Increased risks of exacerbations of angina pectoris or MI may occur in patients with a history of ischemic heart disease. Left ventricular outflow tract obstruction has been reported in patients with sigmoid shaped interventricular septum after starting cilostazol. Patients should be monitored for the development of a new systolic murmur or cardiac symptoms. Cilostazol has not been studied in patients with hemostatic disorders or active bleeding and should be avoided in these groups. Patients should be monitored periodically for complete blood count (CBC) abnormalities. Cilostazol has not been studied in patients with moderate or severe hepatic impairment.
- Dipyridamole has a vasodilatory effect and should be used with caution in patients with severe CAD or in patients with hypotension. Chest pain may be aggravated in patients with underlying CAD who are receiving dipyridamole. Elevations of hepatic enzymes and hepatic failure have been reported in association with dipyridamole administration.
- Patients undergoing pharmacological stress testing with adenosinergic agents should not take Aggrenox or dipyridamole within 48 hours prior to stress testing.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Agrylin (anagrelide)	Capsules	Oral	Pediatric: Once daily Adult: 2 to 4 times daily	Adjust to the lowest effective dosage required to reduce and maintain platelet count <600,000/µL in adults. Avoid with severe hepatic impairment.
Durlaza (ASA ER)	Capsules	Oral	Once daily	Do not take 2 hours before or 1 hour after consuming alcohol. Avoid with severe renal or hepatic impairment.
cilostazol	Tablets	Oral	Twice daily	Reduce dose with concomitant CYP3A4 or CYP2C19 inhibitors. Take at least half an hour before or 2 hours after breakfast and dinner. If symptoms are not improved after 3 months, discontinue treatment. Moderate or severe hepatic impairment have not been studied.
Plavix (clopidogrel)	Tablets	Oral	Once daily†	--
dipyridamole	Tablets, IV solution	Oral, IV	Tablets: Four times daily‡	--
Effient (prasugrel)	Tablets	Oral	Once daily§‖	Take with or without food. Consider a lower dose for patients < 60 kg. Patients should also take ASA daily. Not studied in severe hepatic impairment, generally at higher risk of bleeding.
Brilinta (ticagrelor)	Tablets	Oral	Twice daily	Take with or without food. Administer with ASA. May be crushed, mixed with water, and drunk or administered via nasogastric tube. Avoid with severe hepatic impairment.
Zontivity* (vorapaxar)	Tablets	Oral	Once daily	Take with or without food. Use with ASA and/or Plavix according to their indications or standard of care. There is limited experience with other antiplatelets

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				and none with Zontivity as the only antiplatelet agent. Avoid with severe hepatic impairment.
Aggrenox (ASA/ ER dipyridamole)	Capsules	Oral	Twice daily	Take with or without food. In case of intolerable headaches during initial treatment, switch to 1 capsule at bedtime and low-dose ASA in the morning; resume twice daily dosing within 1 week. Avoid with severe renal and hepatic impairment.
Yosprala (ASA DR/ omeprazole)	Tablets	Oral	Once daily	Take at least 60 minutes before a meal. Avoid with severe renal impairment and any degree of hepatic impairment.

See the current prescribing information for full details
*There is limited clinical experience with other antiplatelet drugs or with Zontivity as a monotherapy agent. Also due to the risk of bleeding, Zontivity should be avoided in patients taking warfarin or other anticoagulants. Withholding Zontivity for a brief period will not be useful in managing acute bleeding events because of its long half-life. Significant inhibition of platelet aggregation remains 4 weeks after discontinuation. Also, the optimal time for initiation and duration of Zontivity therapy also remain poorly defined.
† Initiating Plavix without a loading dose will delay establishment of an antiplatelet effect by several days for certain indications.
‡ As adjunct to the usual warfarin therapy. ASA is not to be administered concomitantly with coumarin anticoagulants.
§ In the clinical trial, the loading dose of Effient was not administered until coronary anatomy was established in UA/NSTEMI patients and in STEMI patients presenting >12 hours after symptom onset. In STEMI patients presenting within 12 hours of symptom onset, the loading dose was administered at the time of diagnosis, although most received Effient at the time of PCI. For the small fraction of patients that required urgent CABG after treatment with Effient, the risk of significant bleeding was substantial.
‖ The safety and efficacy of the 5 mg dose have not been prospectively studied.

CONCLUSION

- The platelet inhibitors play an important role in the treatment and prevention of cerebrovascular and CV diseases.
- Antiplatelet agents have different sites of action. ASA is a COX-1 inhibitor. Plavix and Effient irreversibly block $P2Y_{12}$, a key adenosine phosphate receptor on the platelet surface. Brilinta is a reversible inhibitor of $P2Y_{12}$. Zontivity is a first-in-class selective antagonist of the PAR-1, which is a receptor on thrombin. The mechanism of action of dipyridamole, Agrylin, and cilostazol are not completely understood, but each is believed to inhibit platelet aggregation. Plavix has incomplete platelet inhibition, a slower onset of action, and poor response in some patients.
- Plavix has been shown to significantly reduce the odds of a serious vascular event in high-risk patients. Study data has demonstrated that Plavix significantly reduced the risk of stroke, MI, and vascular death compared to ASA in patients with a recent ischemic stroke, MI, or established peripheral vascular disease. On the basis of the CURE, COMMIT, and CLARITY studies, Plavix received an FDA-approved indication for the reduction of atherothrombotic events in patients with ACS and MI, and Plavix has been incorporated into the current treatment guidelines for the management of these conditions (*Amsterdam et al 2014, COMMIT 2005, Culebras et al 2014, CURE 2001, Gerhard-Herman et al 2016, Ibanez et al 2018, January et al 2014, January et al 2019, Lip et al 2018, O'Gara et al 2013, Roffi et al 2016, Sabatine et al 2005a, Sabatine et al 2005b, Valgimigli et al 2018*).
- Plavix's effectiveness is dependent on its conversion to its active metabolite mostly by CYP2C19. Patients with genetically reduced CYP2C19 function have lower systemic exposure to the active metabolite of clopidogrel, diminished antiplatelet responses, and generally exhibit higher CV event rates following MI than patients with normal CYP2C19 function. In addition, concomitant use of Plavix with proton pump inhibitors, particularly those extensively inhibiting CYP2C19, may also increase CV events.
- Effient may be the most potent of these agents, with more desirable characteristics compared to Plavix with regard to drug-drug interactions and interpatient enzyme variability (*Serebruany et al 2009, Wiviott et al 2007*). FDA-approval of Effient was based on the results from the TRITON-TIMI 38 study, which compared Plavix to Effient. Effient has

demonstrated efficacy in reducing ischemic events in patients with ACS who underwent PCI. Although compared to Plavix, there were no differences in the important outcomes of all-cause and CV mortality, and Effient demonstrated more major bleeding. The overall recommendation is for a thienopyridine to be used in ACS patients who are managed with PCI, with Plavix, Effient, and Brilinta listed as potential options. Of note, the use of Effient in STEMI patients with a prior history of stroke or TIA for which primary PCI is planned is not recommended (*Levine et al 2011, Levine et al 2016b*).

- Brilinta is FDA-approved to reduce the rate of thrombotic CV events in patients with ACS, including UA, NSTEMI, and STEMI. Brilinta works in a similar manner to the other thienopyridine platelet inhibitors (Plavix and Effient). Brilinta is not a prodrug; therefore, it is not subject to potential drug interactions associated with the other agents (*Micromedex 2020*). PLATO was a pivotal clinical study establishing the safety and efficacy of Brilinta in reducing the rate of thrombotic CV events in patients with ACS, which compared Brilinta and Plavix in hospitalized patients with documented ACS, with or without ST-segment elevation. After 12 months of treatment, there was no difference in major bleeding; however, Brilinta significantly reduced all-cause and CV mortality. This efficacy benefit was not observed in North American patients (*Mahaffey et al 2011, Wallentin et al 2009*). The PEGASUS TIMI-54 trial reinforced benefit in patients with a history of MI in which a reduction in the rate of CV death, MI, and stroke was observed in patients treated with Brilinta 60 mg twice daily plus ASA over ASA monotherapy. The rates of CV mortality or all-cause mortality alone were not significantly different between groups, and increased risk of major bleeding was observed with Brilinta treatment (*Bonaca et al 2015*).
- Zontivity is FDA-approved for use in patients with a history of MI or PAD. Zontivity should be prescribed with ASA and/or Plavix according to their indications or standard of care, and not be used as monotherapy or concomitantly with warfarin or other anticoagulants. There is limited clinical experience with other antiplatelet drugs or with Zontivity as a monotherapy agent. Increased hemorrhagic stroke and bleeding rates in patients with a history of stroke or TIA caused the Zontivity phase 3 studies to be terminated early. In the TRA2°P-TIMI 50 trial, Zontivity demonstrated lower rates of the composite of CV mortality, MI, or stroke vs placebo when added to standard antiplatelet therapy for secondary prevention of CV events in PAD or MI who have not undergone PCI. Significance was driven by MI reductions (*Morrow et al 2012, Tricoci et al 2012, FDA Summary Review [Zontivity] 2014, FDA Advisory Committee Transcript [Zontivity] 2014*).
  - When managing acute bleeding events, withholding Zontivity may not be helpful because of its long half-life. Significant inhibition of platelet aggregation remains 4 weeks after discontinuation. Also, the optimal time for initiation and duration of Zontivity therapy also remain poorly defined (*FDA Summary Review [Zontivity] 2014, Morrow et al 2012, Tricoci et al 2012*).
  - The 2016 ESC guidelines for CV disease prevention stipulate that Zontivity cannot be recommended systematically in patients with stable atherosclerotic disease; however, the 2015 ESC guidelines state Zontivity may be added to ASA and Plavix for patients with a history of MI. The ESC acknowledges that efficacy is modest and must be weighed against the risk for bleeds (*Piepoli et al 2016, Roffi et al 2016*).
- Dipyridamole has been shown to reduce stroke recurrence in patients with previous ischemic cerebrovascular disease compared to placebo, but has not been shown to be more effective than ASA (*Diener et al 1996, Leonardi-Bee et al 2005*). Aggrenox significantly reduced the risk of stroke by 37% compared to 18% with ASA and 16% with ER dipyridamole. There was no significant difference in all-cause mortality among the active treatment groups (*Diener et al 1996*). Aggrenox significantly reduced the composite of death, nonfatal stroke or MI and major bleeding to 13% of patients compared to 16% for ASA monotherapy; however, the combination regimen was discontinued more often, mainly because of headache (*Halkes et al 2006*).
- Cilostazol is used for the symptomatic treatment of intermittent claudication and is recommended as an effective therapy to improve symptoms and increase walking distance in patients with claudication due to lower extremity PAD (*Gerhard-Herman et al 2016*). Long-term effects of the drug on limb preservation and hospitalization have not been fully elucidated. Recent studies and SRs have failed to demonstrate or exclude a beneficial effect of cilostazol on clinical outcomes when added to Plavix and ASA therapy. Currently, experts generally do not recommend the use of cilostazol for the prevention of postprocedural complications in patients undergoing coronary artery stent placement, with the possible exception of those with an allergy or intolerance to ASA or Plavix. In such cases, ACCP states that cilostazol may be used as a substitute for either ASA or Plavix as part of the DAPT regimen (*Alonso-Coello et al 2012, Guyatt et al 2012, Levine et al 2011, Levine et al 2016b*).
- Agrylin is the only platelet inhibitor to be FDA-approved for the treatment of thrombocythemia associated with myeloproliferative disorders, and the agent has demonstrated safety and efficacy for this indication (*Anagrelide study*

group 1992, Birgegard et al 2004, Dombi et al 2017, Harrison et al 2005, Penninga et al 2004, Silver 2005, Steurer et al 2004, Wiviott et al 2007).

- ASA is the most frequently studied platelet inhibitor and is generally the reference drug to which other treatments are compared. ASA is the platelet inhibitor recommended as first-line in most treatment guidelines for general use, including initial management of noncardioembolic stroke or TIA, ACS, and MI, and for primary and secondary prevention in patients with cerebrovascular, CV, and peripheral vascular diseases (*Aboyans et al 2018*, *Amsterdam et al 2014, Culebras et al 2014, Gagne et al 2013, Gerhard-Herman et al 2016, Guyatt et al 2012, Ibanez et al 2018, Lip et al 2018, January et al 2014, January et al 2019, Kernan et al 2014, Knuuti et al 2020, Kohli et al 2014, O'Gara et al 2013, Powers et al 2018, Powers et al 2019, Roffi et al 2016, Smith et al 2011, Smith et al 2017, Valgimigli et al 2018*). Evidence supporting the efficacy of ASA has demonstrated a reduction in vascular death of ~15% and in nonfatal vascular events of ~30% (*Eikelboom et al 2012*). In the US, nearly 40% of adults > 50 years of age use ASA for the primary or secondary prevention of CV disease (*Bibbins-Domingo et al 2016*).

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Publication Date: March 23, 2020

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] 2020*).
- 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 2020*).
- 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 2020*).
- 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. All GLP-1 receptor agonists are administered via subcutaneous injection, with the exception of Rybelsus (semaglutide) tablets, which are administered orally. As of 2018, albiglutide was discontinued by the manufacturer due to limited prescribing of the drug and not because of safety concerns (*DRUGS@FDA 2020*).
- 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)	-
Rybelsus (semaglutide)	-
Symlin (pramlintide)	-
Trulicity (dulaglutide)	-
Victoza (liraglutide)*	-

*As a result of a generic settlement agreement, a generic version of liraglutide may enter the market as early as December 22, 2023 (*Coppock 2019*).

(*DRUGS@FDA 2020*, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. FDA Approved Indications

Indication	Adlyxin (lixisenatide)	Byetta (exenatide)	Bydureon (exenatide ER)	Bydureon BCise (exenatide ER)	Ozempic (semaglutide)	Rybelsus (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	✔	✔	✔	✔	✔	✔		✔	✔
Adjunct to diet and exercise to improve glycemic control in patients 10 years and older with T2DM									✔
Reduce the risk of major adverse cardiovascular (CV) events (MACE; CV death, non-fatal myocardial infarction [MI], or non-fatal stroke) in adults with T2DM and established CV disease (CVD)					✔				✔
Reduce the risk of MACE (CV death, non-fatal MI, or non-fatal stroke) in adults with T2DM who have established CVD or multiple CV risk factors								✔	
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.	✔	✔	✔	✔	✔	✔		✔	

Indication	Adlyxin (lixisenatide)	Byetta (exenatide)	Bydureon (exenatide ER)	Bydureon BCise (exenatide ER)	Ozempic (semaglutide)	Rybelsus (semaglutide)	Symlin (pramlintide)	Trulicity (dulaglutide)	Victoza (liraglutide)
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.								✔	
Has not been studied in patients with gastroparesis. Not recommended in patients with gastroparesis.	✔								
Not studied in combination with prandial/short-acting insulin.	✔	✔	✔	✔					✔

(Prescribing information: *Adlyxin 2019*, *Bydureon 2019, Bydureon BCise 2019, Byetta 2018, Ozempic 2020, Rybelsus 2020, Symlin 2019, Trulicity 2019, Victoza 2019*)

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 double-blind (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 placebo-controlled (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*).

- Liraglutide was studied in children and adolescents aged 10 to less than 17 years with T2DM in the PC Ellipse trial (*Tamborlane et al 2019*). After 26 weeks of DB treatment, liraglutide was associated with a significantly greater decrease in HbA1c vs placebo (mean difference, -1.06%; 95% CI, -1.65 to -0.46; p < 0.001), which was maintained over an additional 26-week OL extension (mean difference, -1.30%; 95% CI, -1.89 to -0.70).

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).*

Oral Semaglutide

- The Peptide Innovation for Early Diabetes Treatment (PIONEER) clinical development program for oral semaglutide consisted of 10 clinical trials that enrolled a total of 9543 adult patients with T2DM *(Novo Nordisk news release 2019).*
- PIONEER 1, 5, and 8 were Phase 3a, DB, PC, MC, RCTs that evaluated the glycemic efficacy of Rybelsus compared to placebo in various settings. The primary endpoint was the change from baseline to Week 26 in HbA1c. Secondary endpoints included body weight, FPG, and the proportion of patients achieving HbA1c < 7.0%. Overall, Rybelsus improved HbA1c, FPG, and body weight (at higher doses) with a similar safety profile to other GLP-1RAs *(Buse et al 2019, Novo Nordisk medical information 2019)*.
  - PIONEER 1 (N = 703) compared 3 doses of Rybelsus to placebo as monotherapy for 26 weeks in treatment-naïve patients managed by diet and exercise alone *(Aroda et al 2019)*.
  - PIONEER 5 (N = 324) evaluated the effect of Rybelsus 14 mg compared to placebo for 26 weeks in patients with moderate renal impairment (estimated glomerular filtration rate [eGFR] ≥ 30 and < 60 mL/min/1.73 m^2) receiving a stable dose of metformin, SU, and/or basal insulin *(Mosenzon et al 2019).*
  - PIONEER 8 (N = 731) assessed the safety and efficacy of 3 doses of Rybelsus compared to placebo for 52 weeks as add-on therapy in patients with T2DM inadequately controlled on insulin with or without metformin *(Zinman et al 2019)*.
- PIONEER 2, 3, 4, and 7 evaluated the glycemic efficacy of Rybelsus compared to other antidiabetic agents *(Pieber et al 2019, Pratley et al 2019, Rodbard et al 2019, Rosenstock et al 2019)*. For HbA1c reduction, Rybelsus was superior to empagliflozin 25 mg and sitagliptin 100 mg, and noninferior to liraglutide 1.8 mg. For body weight reduction, Rybelsus was superior to sitagliptin and liraglutide, but not significantly different from empagliflozin *(Buse et al 2019)*. The incidences of AEs were similar for Rybelsus compared to empagliflozin, sitagliptin, and liraglutide. The hypoglycemia risk was low with Rybelsus, empagliflozin, sitagliptin, and liraglutide. Rates of GI AEs were consistent with the GLP-1RA class and higher than those observed with empagliflozin and sitagliptin *(Buse et al 2019).*
  - PIONEER 2 (N = 822) was a 52-week, Phase 3a, open-label (OL), MC RCT that compared Rybelsus 14 mg (n = 412) to the SGLT2i empagliflozin 25 mg (n = 410) as add-on therapy in patients with T2DM inadequately controlled by metformin *(Rodbard et al 2019).*
  - PIONEER 3 (N = 1864) was a 78-week, Phase 3a, DB, double dummy (DD), parallel-group (PG), MC RCT that compared Rybelsus 3 mg (n = 466), 7 mg (n = 466), or 14 mg (n = 465) to the DPP-4i sitagliptin 100 mg (n = 467) as

add-on therapy in patients with T2DM inadequately controlled by metformin with or without an SU *(Rosenstock et al 2019).*

- PIONEER 4 (N = 711) was a 52-week, Phase 3a, DB, DD, PG, MC RCT that evaluated the effect of Rybelsus 14 mg (n = 285), the injectable GLP-1RA liraglutide 1.8 mg (n = 284), or placebo (n = 142) as add-on therapy in patients with T2DM inadequately controlled by metformin with or without an SGLT2i *(Pratley et al 2019).*
- PIONEER 7 (N = 504) was a 52-week, Phase 3a, OL, MC RCT that compared flexible dose adjustments of daily Rybelsus (n = 253) to a fixed dose of daily sitagliptin 100 mg (n = 251) in patients with T2DM inadequately controlled on stable daily doses of 1 or 2 oral antidiabetic drugs (OADs) *(Pieber et al 2019).*

Cardiovascular (CV) outcomes

- A MC, DB, PC, RCT (REWIND trial; N = 9901) evaluated the long-term effects of dulaglutide vs placebo in patients with T2DM who had either a previous CV event or CV risk factors. A total of 31.5% of patients reported previous CV disease and 22.2% had baseline eGFR < 60 mL/min per 1.73 m^2. The median follow-up was 5.4 years. The primary composite outcome (CV death, non-fatal MI, or non-fatal stroke) occurred 12.0% of patients in the dulaglutide group vs 13.4% in the placebo group (hazard ratio [HR], 0.88; 95% confidence interval [CI], 0.79 to 0.99; p = 0.026). All-cause mortality did not differ between groups (10.8% in the dulaglutide group vs 12.0% in the placebo group (HR, 0.90; 95% CI 0.80 to 1.01; p = 0.067). The rates of death from CV causes, nonfatal MI, and hospitalization for heart failure did not differ significantly between groups, while non-fatal MI was statistically significantly different in favor of dulaglutide (*Gerstein et al 2019*).
- 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 (HR, 0.91; 95% 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 CVD (ASCVD) (without a MI/stroke) (HR, 0.76; 95% CI, 0.62 to 0.94) (*Mann et al 2018, Verma et al 2018*).
  - The risk of acute gallbladder or biliary disease was increased with liraglutide vs placebo (HR, 1.60; 95% CI, 1.23 to 2.09) *(Nauck et al 2019)*.
- 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 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*).
- PIONEER 6 (N = 3183) was an event-driven, Phase 3a, DB, PC, MC RCT designed to confirm the CV safety of Rybelsus (n = 1591) vs placebo (n = 1592) as add-on therapy to standard of care in T2DM patients ≥ 50 years of age with established CVD/CKD or ≥ 60 years of age with CV risk factors (CVRFs) *(Husain et al 2019)*. After a median follow-up of 15.9 months (range, 0.4 to 20.0), Rybelsus demonstrated noninferiority to placebo with respect to 3-point MACE. A primary outcome event (CV death, nonfatal MI, or nonfatal stroke) occurred in 3.8% of patients in the Rybelsus group vs 4.8% in the placebo group (hazard ratio [HR], 0.79; 95% confidence interval [CI], 0.57 to 1.11; p < 0.001 for noninferiority; p = 0.17 for superiority).
  - The ongoing SOUL CVOT will evaluate > 9000 patients for 3.5 to 5 years to determine whether Rybelsus provides a CV benefit. The estimated study completion date is in 2024 *(ClinicalTrials.gov 2020)*.

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*).
- A meta-analysis found that treatment with exenatide ER did not increase the risk of CV events compared with placebo or active comparators, and may reduce the risk of all-cause mortality *(Bonora et al 2019)*.

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

- Professional society guidelines emphasize individualized therapy based upon patient- and drug-specific factors such as comorbidities, weight, hypoglycemia risk, propensity for AEs, drug interactions, and patient preferences *(ADA 2020, Copeland et al 2013, Davies et al 2018, Garber et al 2020)*.
- Metformin is recommended for first-line pharmacologic therapy in treatment-naïve patients with T2DM, unless the patient has contraindications or intolerance. SGLT2 inhibitors or GLP-1 receptor agonists should be considered for patients with atherosclerotic CV disease (ASCVD), heart failure, or chronic kidney disease, independent of HbA1c. Metformin is considered the drug of choice for children with T2DM *(ADA 2020, Copeland et al 2013, Garber et al 2020)*.

- **ADA: Standards of Medical Care in Diabetes – 2020** *(ADA 2020)*
  - 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).
    - Early combination therapy can be considered in some patients at treatment initiation to extend the time to treatment failure (level A).
    - 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 or indicators of high risk, established kidney disease, or HF, SGLT2 inhibitors or GLP-1 receptor agonists with demonstrated CVD benefit are recommended as part of the antihyperglycemic regimen, independent of HbA1c (level A).

- In patients with T2DM who need greater glucose lowering than can be obtained with oral agents, GLP-1 receptor agonists are preferred to insulin when possible (level B).
- Intensification of treatment for patients with T2DM not meeting treatment goals should not be delayed (level B).
- The medication regimen and medication-taking behavior should be reevaluated at regular intervals (every 3 to 6 months) and adjusted as needed to incorporate specific factors that impact treatment choice (level E).

○ For patients with indicators of high-risk or established ASCVD, CKD, or HF, SGLT2 inhibitors or GLP-1 receptor agonists with proven benefit should be considered independently of baseline HbA1c or individualized HbA1c target.

- If ASCVD predominates, a GLP-1 receptor agonist with proven CVD benefit is preferred. Alternatively, an SGLT2 inhibitor with proven CVD benefit is recommended if eGFR is adequate.
- If HF or CKD predominates, an SGLT2 inhibitor with evidence of reducing HF and/or CKD in CV outcome trials is preferred if eGFR is adequate. If SGLT2 inhibitors are contraindicated, not tolerated, or if eGFR Is not adequate, a GLP-1 receptor agonist with proven CVD benefit should be added.

Table 3. ADA Factors to Consider for Antihyperglycemic Therapies in T2DM

Class*	Efficacy	Hypoglycemia	Weight	ASCVD	CHF	Route	DKD Progression
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Oral	Neutral
SGLT2i	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin, dapagliflozin‡	Oral	Benefit: canagliflozin§, empagliflozin, dapagliflozin
GLP-1ra	High	No	Loss	Benefit: See labeled indication Neutral: lixisenatide	Neutral	SQ, oral	Benefit: liraglutide
DPP-4i	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin	Oral	Neutral
TZD	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Oral	Neutral
SFU (2nd generation)	High	Yes	Gain	Neutral	Neutral	Oral	Neutral
Insulin	Highest	Yes	Gain	Neutral	Neutral	SQ	Neutral

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; DKD = diabetic kidney disease; DPP-4i = dipeptidyl peptidase 4 inhibitor; 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.

† FDA approved for CVD benefit

‡ FDA approved for HF indication

§ FDA approved for CKD indication

- **American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) - Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm** *(Garber et al 2020)*

○ 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 HbA1c, 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.
- The therapeutic regimen should be as simple as possible to optimize adherence.

○ For patients with recent-onset T2DM or mild hyperglycemia (HbA1c < 7.5%), lifestyle therapy plus antihyperglycemic monotherapy (preferably with metformin) is recommended.

- For patients with established or high ASCVD risk, stage 3 CKD, or HF with reduced ejection fraction, an SGLT2 inhibitor or long-acting GLP-1 receptor agonist with proven efficacy is recommended independent of glycemic control.
- Other acceptable alternatives to metformin as initial therapy include DPP-4 inhibitors and TZDs. Alpha-glucosidase inhibitors, SFUs, and meglitinides may also be appropriate as monotherapy for select patients.

○ GLP-1 receptor agonists have robust HbA1c-lowering properties, are usually associated with weight loss, lipid, and blood pressure reductions, and are available in several formulations. The risk of hypoglycemia with GLP-1 receptor agonists is low, and they reduce fluctuations in both fasting and postprandial glucose levels by stimulating glucose-dependent insulin secretion and suppressing glucagon secretion.

- In the LEADER trial, liraglutide significantly reduced the risk of nephropathy and of death from certain CV causes.
- Data from the SUSTAIN 6, REWIND and HARMONY trials with injectable semaglutide, dulaglutide, and albiglutide, respectively, suggest other GLP1 receptor agonists also have cardiovascular disease benefits.
- GLP-1 receptor agonists based on exendin-4 have been proven to be safe in cardiovascular disease, but they have not been shown to confer cardiovascular benefits.
- No studies have confirmed that incretin agents cause pancreatitis; however, GLP-1 receptor agonists should be used cautiously, if at all, in patients with a history of pancreatitis and discontinued if pancreatitis develops.

Table 4. AACE/ACE Profiles of Antidiabetic Medications

Drug Class	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: long-acting GLP-1ra Exenatide not indicated CrCl < 30	Moderate	Potential benefit of long-acting GLP-1ra in ASCVD Neutral for HF	Neutral	Neutral
SGLT2i	Neutral	Loss	Genital mycotic infections Not indicated eGFR < 45* Potential CKD benefit*	Neutral	Prevent HHF; Manage HFrEF† Empagliflozin FDA approved to reduce CV mortality Canagliflozin FDA approved to reduce MACE	Neutral	DKA can occur in various stress settings
DPP-4i	Neutral	Neutral	Dose adjustment necessary (except linagliptin) Albuminuria reduction	Neutral	Possible increased HHF with alogliptin and saxagliptin	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 for HF	Neutral	Neutral
Meglitinide	Mild	Gain	More hypoglycemia risk	Neutral	Possible ASCVD risk	Neutral	Neutral
Colesevelam	Neutral	Neutral	Neutral	Mild	Lowers LDL-C	Neutral	Neutral
Bromocriptine QR	Neutral	Neutral	Neutral	Moderate	Safe in ASCVD	Neutral	Neutral
Insulin	Moderate to severe	Gain	More hypoglycemia risk	Neutral	CHF risk Neutral for ASCVD	Neutral	Neutral
Pramlintide	Neutral	Loss	Neutral	Moderate	Neutral	Neutral	Neutral

Abbreviations: AGI = alpha-glucosidase inhibitor; ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; CKD = chronic kidney disease; 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; HFrEF = heart failure reduced ejection fraction; HHF = hospitalization for heart failure; LDL-C = low density lipoprotein-cholesterol; MACE = major adverse cardiovascular events; QR = quick release; SFU = sulfonylurea; SGLT2i = sodium-glucose cotransporter-2 inhibitor; TZD = thiazolidinedione

* Canagliflozin indicated for eGFR ≥ 30 mL/min/1.73 m^2 in patients with CKD 3 and albuminuria.

† Dapagliflozin has a potential benefit in primary prevention of HHF and demonstrated efficacy in HFrEF.

- **Endocrine Society: Guideline for Treatment of Diabetes in Older Adults** (*LeRoith et al 2019*)
  - Glycemic management strategies must be adjusted to the individual needs of older patients. Specific factors regarding certain drug classes are particularly important for older patients with diabetes, especially those with CKD and heart disease.
    - In T2DM patients ≥ 65 years of age, metformin is recommended as the initial oral medication chosen for glycemic management in addition to lifestyle management (unless the patient has significantly impaired kidney function or gastrointestinal intolerance).
    - Patients who are not able to achieve glycemic targets with metformin and lifestyle changes can receive add-on therapy with oral or injectable agents and/or insulin.
      - GLP-1 receptor agonists and SGLT2 inhibitors should be prescribed early, given their beneficial CV outcomes.
      - SFUs and meglitinides should be avoided and insulin should be used sparingly to reduce the risk of hypoglycemia.
      - Glycemic treatment regimens should be kept as simple as possible.
  - GLP-1 receptor agonists increase insulin release, decrease glucagon secretion, delay gastric emptying, suppress appetite, and do not cause hypoglycemia. Nausea is a common side effect, and initial concern about an increased risk for pancreatitis has not been proven. Liraglutide and semaglutide have been found to improve cardiovascular outcomes.

- **American College of Cardiology (ACC)/American Heart Association (AHA): Guideline on the Primary Prevention of CV Disease** *(Arnett et al 2019)*
  - For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk.
  - For adults with T2DM and additional ASCVD risk factors who require glucose lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate an SGLT2 inhibitor or GLP-1 receptor agonist to improve glycemic control and reduce CVD risk.
    - SGLT2i act in the proximal tubule to increase urinary excretion of glucose and sodium, leading to a reduction in HbA1c, body weight, and blood pressure. Three RCTs have shown a significant reduction in ASCVD events and HF with use of an SGLT2i. Although most patients studied had established CVD at baseline, the reduction in HF has been shown to extend to primary prevention populations.
    - The GLP-1RAs increase insulin and glucagon production in the liver, increase glucose uptake in muscle and adipose tissue, and decrease hepatic glucose production. Three GLP-1RAs have been found to significantly reduce the risk of ASCVD in adults with T2DM who are at high ASCVD risk.

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 and exenatide ER have 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.
- Pramlintide is Pregnancy Category C. Dulaglutide, exenatide, 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 5. 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.
Rybelsus (semaglutide)	Tablets	Oral	Once Daily	Must be taken at least 30 minutes before the first food, beverage or other oral medications of the day with no more than 4 ounces of plain water only. Swallow whole. Do not crush or chew tablets
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, lixisenatide, and semaglutide are incretin-based antidiabetic therapies that are FDA-approved as adjunctive therapy to diet and exercise in adult patients with T2DM; liraglutide is approved for patients 10 years and older. Additionally, liraglutide, dulaglutide, and subcutaneous semaglutide are 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. Semaglutide is additionally available in an oral formulation. 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, Harmony Outcomes, REWIND, and SUSTAIN 6 trials demonstrated a statistically significant CV risk reduction with liraglutide, albiglutide, dulaglutide, and subcutaneous semaglutide, respectively, vs placebo (*Gerstein et al 2019, Hernandez et al 2018, Marso et al 2016a, Marso et al 2016b*). The ELIXA, EXSCEL, and POINEER 6 CV outcome trials did not demonstrate statistically significant reductions in MACE with lixisenatide, exenatide ER, or oral semaglutide, respectively, vs placebo (*Holman et al 2017, Husain et al 2019, Pfeffer et al 2015*).
- 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 and exenatide ER also have a warning for acute gallbladder disease, while semaglutide has a warning for diabetic retinopathy complications.
- The 2020 ADA and AACE/ACE guidelines recommend metformin for first-line pharmacologic therapy in treatment-naïve patients with T2DM. SGLT2 inhibitors or GLP-1 receptor agonists should be considered for patients with atherosclerotic CV disease (ASCVD), heart failure, or chronic kidney disease, independent of HbA1c *(ADA 2020, Garber et al 2020)*.
- 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 2020, Garber et al 2020*).

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Publication Date: 31st March 2020

OPTUMRx

Therapeutic Class Overview
Sodium-Glucose Cotransporter-2 Inhibitors

INTRODUCTION

- In the United States, diabetes mellitus affects more than 30 million people and is the 7th leading cause of death (*Centers for Disease Control and Prevention [CDC] 2019*).
- 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] 2020a)*. 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 2020b)*.
  - Complications of T2DM include hypertension, heart disease, stroke, vision loss, nephropathy, and neuropathy *(ADA 2020a)*.
- 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 2020)*.
- 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 2020)*.
- 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)	-
Qternmet XR (dapagliflozin/saxagliptin/metformin)	-
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)	-

Drug	Generic Availability
Trijardy XR (empagliflozin/linagliptin/metformin ER)	-
Ertugliflozin products	
Steglatro (ertugliflozin)	-
Segluromet (ertugliflozin/metformin)	-
Steglujan (ertugliflozin/sitagliptin)	-

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration (FDA) Approved Indications for Single-Entity Products

Indications	Farxiga (dapagliflozin)	Invokana (canagliflozin)	Jardiance (empagliflozin)	Steglatro (ertugliflozin)
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		✓		
To reduce the risk of end-stage kidney disease, doubling of serum creatinine, CV death, and HHF in adults with T2DM and diabetic nephropathy with albuminuria		✓		
To reduce the risk of HHF in adults with T2DM and established CVD or multiple CV risk factors	✓			

Abbreviations: CV = cardiovascular; CVD = cardiovascular disease; HHF = hospitalization for heart failure; MACE = major adverse cardiovascular events; T2DM = type 2 diabetes mellitus

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).

(*Prescribing information: Farxiga 2020, Invokana 2020, Jardiance 2020, Steglatro 2020*)

Table 3. FDA Approved Indications for Combination Products

Indications	Invokamet, Invokamet XR* (canagliflozin/metformin)	Synjardy, Synjardy XR* (empagliflozin/metformin)	Xigduo XR* (dapagliflozin/ metformin ER)	Segluromet (ertugliflozin/metformin)	Glyxambi (empagliflozin/ linagliptin)	Qtern (dapagliflozin/ saxagliptin)	Qternmet XR* (dapagliflozin/ saxagliptin/metformin)	Steglujan (ertugliflozin/sitagliptin)	Trijardy XR* (empagliflozin/linagliptin/ metformin)
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 components is appropriate	✓	✓						✓	

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: T2DM = type 2 diabetes mellitus
* These combination products contain metformin ER.

Limitations of use: Canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin are not recommended in patients with T1DM or for the treatment of DKA. Glyxambi and Steglujan have not been studied in patients with a history of pancreatitis. Qternmet XR should be started only in patients currently taking metformin.

(Prescribing information: Glyxambi 2020, Invokamet/Invokamet XR 2020, Qtern 2020, Qternmet XR 2020, Segluromet 2020, Steglujan 2020, Synjardy 2020, Synjardy XR 2020, Trijardy XR 2020, Xigduo XR 2020)

- 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

Type 2 diabetes mellitus (T2DM)

- The safety and efficacy of the SGLT2 inhibitors for T2DM 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 2015a)*
  - 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 2015a, Schernthaner et al 2013)*
  - As add-on therapy to insulin *(Neal et al 2015, Rosenstock et al 2014, Rosenstock et al 2015b, 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, Synjardy XR, and Trijardy XR to their individual components in healthy subjects was used to support the 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 2015b)* 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 2015a, Rosenstock et al 2019)*. 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)*.

- Qternmet XR (dapagliflozin/metformin/saxagliptin) was approved in May 2019; the dapagliflozin/saxagliptin/metformin combination improved glycemic control at week 24 compared to dapagliflozin plus metformin or saxagliptin plus metformin *(Rosenstock et al 2019, Matthaei et al 2015b)*.
- 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 (CKD) *(Barnett et al 2014, Fioretto et al 2018, Grunberger et al 2018, Kohan et al 2014, Perkovic et al 2019, 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 *(Feng et al 2019, 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) and renal 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 2020b, Das et al 2018, Davies et al 2018, Garber et al 2020)*.
  - 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 2020b, Das et al 2018, Davies et al 2018, Garber et al 2020)*.
- 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. This study was completed in December 2019; results are not yet available *(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.
- The double-blind CREDENCE trial (N = 4401) evaluated renal outcomes in patients with T2DM and albuminuric chronic kidney disease. Patients with an estimated glomerular filtration rate (eGFR) ≥ 30 and < 90 mL/min/1.73 m^2, albuminuria, and treated with renin–angiotensin system blockade were randomized to receive canagliflozin 100 mg or placebo for a median follow-up of 2.6 years *(Perkovic et al 2019).*
  - A primary outcome event (composite of end-stage kidney disease [dialysis, transplantation, or a sustained eGFR of < 15 mL/min/1.73 m^2], a doubling of the serum creatinine level, or death from renal or CV causes) was observed in fewer patients treated with canagliflozin vs placebo (43.2 vs 61.2 per 1000 patient-years, respectively; HR, 0.70; 95% CI, 0.59 to 0.82; p = 0.00001).
  - Results also favored canagliflozin for the renal-specific composite of end-stage kidney disease, a doubling of the creatinine level, or death from renal causes (HR, 0.66; 95% CI, 0.53 to 0.81; p < 0.001), end-stage kidney disease (HR, 0.68; 95% CI, 0.54 to 0.86; p = 0.002)., composite of CV death, MI, or stroke (HR, 0.80; 95% CI, 0.67 to 0.95; p = 0.01), and HHF (HR, 0.61; 95% CI, 0.47 to 0.80; p < 0.001).
  - No significant differences were observed in the rates of amputation or fracture with canagliflozin vs placebo.

Heart failure (HF)

- DAPA-HF (N = 4744) was a Phase 3, event-driven, international, multicenter, double-blind, placebo-controlled RCT that evaluated dapagliflozin vs placebo added to standard of care in patients with established HF and a reduced ejection fraction (≤ 40%), with or without T2DM *(McMurray et al 2019)*.
  - After a median follow-up of 18.2 months, a primary outcome event (composite of worsening HF [ie, hospitalization or an urgent visit resulting in intravenous therapy for HF] or CV death) occurred in 386 of 2373 patients (16.3%) in the dapagliflozin group and 502 of 2371 patients (21.2%) in the placebo group (HR, 0.74; 95% CI, 0.65 to 0.85; p < 0.001).
  - Findings in patients with diabetes were similar to those in patients without diabetes.

- The frequency of adverse events related to volume depletion, renal dysfunction, and hypoglycemia did not differ between treatment groups.

CLINICAL GUIDELINES

Overview

- Professional society guidelines emphasize individualized therapy based upon patient- and drug-specific factors such as comorbidities, weight, hypoglycemia risk, propensity for AEs, drug interactions, and patient preferences *(ADA 2020b, Copeland et al 2013, Davies et al 2018, Garber et al 2020)*.
- Metformin is recommended for first-line pharmacologic therapy in treatment-naïve patients with T2DM, unless the patient has contraindications or intolerance. SGLT2 inhibitors or GLP-1 receptor agonists should be considered for patients with established atherosclerotic CV disease (ASCVD), high ASCVD risk, HF, or CKD, independent of HbA1c. Metformin is considered the drug of choice for children with T2DM *(ADA 2020b, Copeland et al 2013, Garber et al 2020)*.

- **ADA: Standards of Medical Care in Diabetes – 2020** *(ADA 2020b)*
  - Pharmacological therapy for T2DM:
    - Metformin (if not contraindicated and if tolerated) is the preferred initial pharmacological agent for T2DM (level A; refer to guideline for description of levels of evidence).
    - Metformin should be continued when used in combination with other agents, including insulin, if not contraindicated and if tolerated (level A).
    - Early combination therapy can be considered in some patients at treatment initiation to extend the time to treatment failure (level A).
    - 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 or indicators of high risk, established kidney disease, or HF, SGLT2 inhibitors or GLP-1 receptor agonists with demonstrated CVD benefit are recommended as part of the antihyperglycemic regimen, independent of HbA1c (level A).
    - In patients with T2DM who need greater glucose lowering than can be obtained with oral agents, GLP-1 receptor agonists are preferred to insulin when possible (level B).
    - Intensification of treatment for patients with T2DM not meeting treatment goals should not be delayed (level B).
    - The medication regimen and medication-taking behavior should be reevaluated at regular intervals (every 3 to 6 months) and adjusted as needed to incorporate specific factors that impact treatment choice (level E).
  - For patients with indicators of high-risk or established ASCVD, CKD, or HF, SGLT2 inhibitors or GLP-1 receptor agonists with proven benefit should be considered independently of baseline HbA1c or individualized HbA1c target.
    - If ASCVD predominates, a GLP-1 receptor agonist with proven CVD benefit is preferred. Alternatively, an SGLT2 inhibitor with proven CVD benefit is recommended if eGFR is adequate.
    - If HF or CKD predominates, an SGLT2 inhibitor with evidence of reducing HF and/or CKD in CV outcome trials is preferred if eGFR is adequate. If SGLT2 inhibitors are contraindicated, not tolerated, or if eGFR Is not adequate, a GLP-1 receptor agonist with proven CVD benefit should be added.

Table 4. ADA Factors to Consider for Antihyperglycemic Therapies in T2DM

Class*	Efficacy	Hypoglycemia	Weight	ASCVD	CHF	Route	DKD Progression
Metformin	High	No	Neutral (potential for modest loss)	Potential benefit	Neutral	Oral	Neutral
SGLT2i	Intermediate	No	Loss	Benefit: empagliflozin†, canagliflozin	Benefit: empagliflozin†, canagliflozin, dapagliflozin‡	Oral	Benefit: canagliflozin§, empagliflozin, dapagliflozin
GLP-1ra	High	No	Loss	Benefit: See labeled indication	Neutral	SQ, oral	Benefit: liraglutide

				Neutral: lixisenatide			
DPP-4i	Intermediate	No	Neutral	Neutral	Potential risk: saxagliptin	Oral	Neutral
TZD	High	No	Gain	Potential benefit: pioglitazone	Increased risk	Oral	Neutral
SFU (2nd generation)	High	Yes	Gain	Neutral	Neutral	Oral	Neutral
Insulin	Highest	Yes	Gain	Neutral	Neutral	SQ	Neutral

Abbreviations: ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; DKD = diabetic kidney disease; DPP-4i = dipeptidyl peptidase 4 inhibitor; 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.

† FDA approved for CVD benefit

‡ FDA approved for HF indication

§ FDA approved for CKD indication

- **American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) - Consensus Statement on the Comprehensive Type 2 Diabetes Management Algorithm** *(Garber et al 2020)*
  - 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 HbA1c, 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.
    - The therapeutic regimen should be as simple as possible to optimize adherence.
  - For patients with recent-onset T2DM or mild hyperglycemia (HbA1c < 7.5%), lifestyle therapy plus antihyperglycemic monotherapy (preferably with metformin) is recommended.
    - For patients with established or high ASCVD risk, stage 3 CKD, or HF with reduced ejection fraction, an SGLT2 inhibitor or long-acting GLP-1 receptor agonist with proven efficacy is recommended independent of glycemic control.
    - Other acceptable alternatives to metformin as initial therapy include DPP-4 inhibitors and TZDs. Alpha-glucosidase inhibitors, SFUs, and meglitinides may also be appropriate as monotherapy for select patients.
  - 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 MACE risk, as well as a lower risk for HHF. Canagliflozin was also associated with an increased risk of amputation in the CANVAS trial.
      - The CREDENCE trial specifically assessed kidney benefits in patients with stage 3 CKD and albuminuria. Canagliflozin significantly reduced the risk of a composite of end-stage kidney disease (dialysis, transplantation, or a sustained eGFR of <15 mL/min/1.73 m^2), a doubling of the serum creatinine level, or death from renal or CV causes by 30%. HHF was also reduced by 39%.
    - 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 MACE.
      - The DAPA-HF trial involved patients who had HF with reduced ejection fraction (58% of whom did not have diabetes). Dapagliflozin was associated with a 26% reduction in risk of worsening HF or CV death
    - HF-related endpoints appear to account for most of the observed benefits in the published studies.
    - In their respective CV outcomes trials, canagliflozin, dapagliflozin, and empagliflozin reduced progression of kidney disease.
    - Safety concerns with treatment include increased risks of mycotic genital infections, slightly increased LDL-C levels, limited efficacy in patients with an eGFR < 45 mL/min/1.73 m^2, and dehydration due to increased diuresis leading to initial renal impairment, hypotension, syncope, and falls. Postmarketing reports of SGLT2 inhibitor-associated DKA are still being investigated. The class is also associated with an increased risk of necrotizing fasciitis of the perineum (Fournier's gangrene), a rare but serious genital infection.

Table 5. AACE/ACE Profiles of Antidiabetic Medications

Drug Class	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: long-acting GLP-1ra Exenatide not indicated CrCl < 30	Moderate	Potential benefit of long-acting GLP-1ra in ASCVD Neutral for HF	Neutral	Neutral
SGLT2i	Neutral	Loss	Genital mycotic infections Not indicated eGFR < 45* Potential CKD benefit*	Neutral	Prevent HHF; Manage HFrEF† Empagliflozin FDA approved to reduce CV mortality Canagliflozin FDA approved to reduce MACE	Neutral	DKA can occur in various stress settings
DPP-4i	Neutral	Neutral	Dose adjustment necessary (except linagliptin) Albuminuria reduction	Neutral	Possible increased HHF with alogliptin and saxagliptin	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 for HF	Neutral	Neutral
Meglitinide	Mild	Gain	More hypoglycemia risk	Neutral	Possible ASCVD risk	Neutral	Neutral
Colesevelam	Neutral	Neutral	Neutral	Mild	Lowers LDL-C	Neutral	Neutral
Bromocriptine QR	Neutral	Neutral	Neutral	Moderate	Safe in ASCVD	Neutral	Neutral
Insulin	Moderate to severe	Gain	More hypoglycemia risk	Neutral	CHF risk Neutral for ASCVD	Neutral	Neutral
Pramlintide	Neutral	Loss	Neutral	Moderate	Neutral	Neutral	Neutral

Abbreviations: AGI = alpha-glucosidase inhibitor; ASCVD = atherosclerotic cardiovascular disease; CHF = congestive heart failure; CKD = chronic kidney disease; 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; HFrEF = heart failure reduced ejection fraction; HHF = hospitalization for heart failure; LDL-C = low density lipoprotein-cholesterol; MACE = major adverse cardiovascular events; QR = quick release; SFU = sulfonylurea; SGLT2i = sodium-glucose cotransporter-2 inhibitor; TZD = thiazolidinedione

* Canagliflozin indicated for eGFR ≥ 30 mL/min/1.73 m^2 in patients with CKD 3 and albuminuria.

† Dapagliflozin has a potential benefit in primary prevention of HHF and demonstrated efficacy in HFrEF.

- **Endocrine Society: Guideline for Treatment of Diabetes in Older Adults** (*LeRoith et al 2019*)
  - Glycemic management strategies must be adjusted to the individual needs of older patients. Specific factors regarding certain drug classes are particularly important for older patients with diabetes, especially those with CKD and heart disease.
    - In T2DM patients ≥ 65 years of age, metformin is recommended as the initial oral medication chosen for glycemic management in addition to lifestyle management (unless the patient has significantly impaired kidney function or gastrointestinal intolerance).
    - Patients who are not able to achieve glycemic targets with metformin and lifestyle changes can receive add-on therapy with oral or injectable agents and/or insulin.
      - GLP-1 receptor agonists and SGLT2 inhibitors should be prescribed early, given their beneficial CV outcomes.
      - SFUs and meglitinides should be avoided and insulin should be used sparingly to reduce the risk of hypoglycemia.
      - Glycemic treatment regimens should be kept as simple as possible.
  - SGLT2 inhibitors reduce HbA1c by approximately 0.8%, can reduce weight, and do not cause hypoglycemia.
    - Empagliflozin and canagliflozin have been shown to decrease MACE, HF, and the progression of CKD.
    - SGLT2 inhibitors cause an obligate increase in urine volume and an increase in urogenital candida infections.
    - Canagliflozin has also been shown to be associated with a decrease in bone mineral density at the hip, but not the femoral neck, lumbar spine, or distal radius, with a significant increase in fractures of arms and legs but not the spine.

- **American College of Cardiology (ACC)/American Heart Association (AHA): Guideline on the Primary Prevention of CV Disease** *(Arnett et al 2019)*
  - For adults with T2DM, it is reasonable to initiate metformin as first-line therapy along with lifestyle therapies at the time of diagnosis to improve glycemic control and reduce ASCVD risk.
  - For adults with T2DM and additional ASCVD risk factors who require glucose lowering therapy despite initial lifestyle modifications and metformin, it may be reasonable to initiate an SGLT2 inhibitor or GLP-1 receptor agonist to improve glycemic control and reduce CVD risk.
    - SGLT2i act in the proximal tubule to increase urinary excretion of glucose and sodium, leading to a reduction in HbA1c, body weight, and blood pressure. Three RCTs have shown a significant reduction in ASCVD events and HF with use of an SGLT2i. Although most patients studied had established CVD at baseline, the reduction in HF has been shown to extend to primary prevention populations.
    - The GLP-1RAs increase insulin and glucagon production in the liver, increase glucose uptake in muscle and adipose tissue, and decrease hepatic glucose production. Three GLP-1RAs have been found to significantly reduce the risk of ASCVD in adults with T2DM who are at high ASCVD risk.

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, Xigduo XR, Trijardy XR: eGFR < 30 mL/min/1.73 m^2; Invokamet, Invokamet XR, Qtern, Qternmet XR, Synjardy, Synjardy XR: eGFR < 45 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 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 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 2016b)*.

- 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 2016a 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 6. 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)	Qternmet XR (dapagliflozin/ saxagliptin/metformin)	Invokamet, Invokamet XR (canagliflozin/ metformin)	Synjardy, Synjardy XR (empagliflozin/ metformin)	Xigduo XR (dapagliflozin/metformin ER)	Segluromet (ertugliflozin/ metformin)	Steglujan (ertugliflozin/ sitagliptin)	Trijardy XR (empagliflozin/linagliptn /metformin ER)
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 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.	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
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 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. Do not use in patients with active bladder cancer and use 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 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.													
Lactic acidosis/radiologic studies with intravascular iodinated contrast materials: metformin can lead to acute alteration of renal function and has been associated with lactic acidosis. Metformin-containing agents should be withheld at the time of or prior to a radiological study with contrast (and withheld for 48 hours subsequent to the procedure) in certain patients. Metformin-containing products should be reinstituted only after renal function is stable.							✔	✔	✔	✔	✔		✔

† 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.
- When 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.

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 200 mg and then 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. For patients with an eGFR < 60 mL/min/1.73 m^2, if an inducer of UGT is co-administered, increase the canagliflozin dose to 200 mg once daily in patients currently tolerating 100 mg. Consider adding another antihyperglycemic agent in patients who require additional glycemic control.
- Co-administration of canagliflozin 300 mg with digoxin has been reported to increase the AUC and mean peak drug concentration of digoxin (20% and 36%, respectively).

Empagliflozin:

- Diuretics: Co-administration results in an increased urine volume and frequency of voids, which may increase the potential for volume depletion.

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.

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 7. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single entity products				
Farxiga (dapagliflozin)	Tablets	Oral	Daily	Use is not recommended if eGFR is < 45 mL/min/1.73 m^2.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Contraindicated in patients with eGFR below 30 mL/min/1.73 m^2, end-stage renal disease, or on dialysis.
Invokana (canagliflozin)	Tablets	Oral	Daily	Limit dose to 100 mg once daily in patients who have an eGFR of 30 to < 60 mL/min/1.73 m^2. Contraindicated in patients with eGFR below 30 mL/min/1.73 m^2 who are being treated for glycemic control and on dialysis. 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 m2, end-stage renal disease, or on dialysis.
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. Contraindicated in patients with eGFR below 30 mL/min/1.73 m^2, end-stage renal disease, or on dialysis. 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. Avoid use 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. Avoid use 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, end-stage renal disease, or on dialysis. Avoid use in hepatic impairment.
Qtern (dapagliflozin/ saxagliptin)	Tablets	Oral	Daily	Contraindicated in patients with eGFR < 45 mL/min/1.73 m^2, end-stage renal disease, or on dialysis.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Qternmet XR (dapagliflozin/saxagliptin/ metformin)	Tablets	Oral	Daily	Contraindicated in patients with eGFR < 45 mL/min/1.73 m^2, end-stage renal disease, or on dialysis. Avoid use in hepatic impairment.
Glyxambi (empagliflozin/ linagliptin)	Tablets	Oral	Daily	Contraindicated in patients with severe renal impairment, end-stage renal disease, or on dialysis. Do not initiate 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 m2, end-stage renal disease, or on dialysis. Advise premenopausal females of the potential for an unintended pregnancy. Avoid use in hepatic impairment.
Synjardy XR (empagliflozin/ metformin ER)	Tablets	Oral	Daily	Contraindicated in patients with eGFR < 45 mL/min/1.73 m^2, end-stage renal disease, or on dialysis. Advise premenopausal females of the potential for an unintended pregnancy. Avoid use in hepatic impairment.
Trijardy XR (empagliflozin/linagliptin/ metformin ER)	Tablets	Oral	Daily	Contraindicated in patients with eGFR < 30 mL/min/1.73 m^2, end-stage renal disease, or on dialysis. Do not initiate or continue in patients with an eGFR < 45 mL/min/1.73 m^2. Not recommended in patients with hepatic impairment.
Segluromet (ertugliflozin/metformin)	Tablets	Oral	Two times daily	Contraindicated in patients with eGFR < 30 mL/min/1.73 m^2, end-stage renal disease, or on dialysis. 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. Avoid use in hepatic impairment.
Steglujan (ertugliflozin/sitagliptin)	Tablets	Oral	Daily	Contraindicated in patients with eGFR < 30 mL/min/1.73 m^2, end-stage renal disease, or on dialysis. 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. Qternmet XR (dapagliflozin/saxagliptin/metformin) and Trijardy XR (empagliflozin/linagliptin/metformin ER) are SGLT2 inhibitor/DDP-4 inhibitor/metformin combinations.
- 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 and renal function should be monitored prior to and during therapy for all agents. Volume depletion issues should be corrected prior to initiation of SGLT2 therapy.
- The SGLT2 inhibitors share a similar safety profile, including 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.
- 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.
- According to current clinical guidelines for the management of T2DM, metformin is recommended first-line for the initial pharmacologic treatment of T2DM, and SGLT2 inhibitors are among the second-line options. SGLT2 inhibitors or GLP-1 receptor agonists should be considered for patients with established ASCVD, high ASCVD risk, HF, or CKD, independent of HbA1c *(ADA 2020b, Garber et al 2020).*

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Publication Date: April 1, 2020

Therapeutic Class Overview
Antiasthmatic – Monoclonal Antibodies

INTRODUCTION

- Asthma is a chronic lung disease that inflames and narrows the airways, making it difficult to breathe. 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 2018, asthma affected an estimated 19.2 million adults and 5.5 million children in the United States (U.S.). The exact cause(s) of asthma are unknown. A combination of factors such as genetics, certain respiratory infections during childhood, and contact with airborne allergens can contribute to its development. Most patients with asthma have allergies (*Centers for Disease Control and Prevention [CDC] 2020, National Heart, Lung, and Blood Institute [NHLBI] Web site*).
- Current pharmacologic options for asthma management are categorized as: (1) control medications to achieve and maintain control of persistent asthma or prevent exacerbations, and (2) quick-relief medications used to treat acute symptoms and exacerbations (*NHLBI 2007, Global Initiative for Asthma [GINA] 2020*).
  - Control medications include:
    - Corticosteroids (inhaled corticosteroids [ICSs], or oral corticosteroids for severe exacerbations)
    - Long-acting beta$_2$-agonists (LABAs)
    - Leukotriene receptor antagonists (LTRAs)
    - Methylxanthines (ie, theophylline)
    - Cromolyn sodium and nedocromil
    - Add-on immunomodulators (ie, omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab) in patients with severe asthma
    - Add-on tiotropium in patients whose asthma is not well-controlled with ICS/LABA
    - Add-on azithromycin in patients whose asthma is not well-controlled with moderate-high dose ICS/LABA
  - Quick-relief/reliever medications include:
    - Short-acting beta$_2$-agonists (SABAs) for relief of acute symptoms and prevention of exercise-induced bronchospasm
    - ICS-formoterol (per GINA recommendations on the basis of the safety concerns about SABA-only treatment and the fact that ICS and ICS/LABA already have an effective safety record)
    - Anticholinergics (ie, ipratropium bromide) as an alternative bronchodilator for those not tolerating a SABA
    - Systemic corticosteroids, although not short-acting, are used for moderate and severe exacerbations as part of initial treatment.
- Approximately 3.7% of asthma patients have severe disease and 17% have difficult-to-treat asthma. Severe asthma includes various clinical phenotypes of poorly controlled asthma characterized by frequent use of high-dose ICS and/or oral corticosteroids (*Chung et al 2014; GINA 2019; GINA 2020*).
- While there are currently no widely accepted definitions of specific asthma phenotypes, several strategies have been proposed to categorize severe asthma phenotypes based on characteristics such as patient age, disease onset, corticosteroid resistance, chronic airflow obstruction, or type of cellular infiltrate in the airway lumen or lung tissue (*Walford et al 2014*). The most recent GINA guideline on severe or difficult-to-treat asthma recommends assessing for Type 2 inflammation through blood and sputum eosinophil levels, exhaled nitric oxide level and allergic triggers to asthma (*GINA 2019*).
- Chronic idiopathic urticaria (CIU), also called chronic urticaria or spontaneous urticaria, is defined by the presence of hives on most days of the week for 6 weeks or longer, with or without angioedema. The hives are circumscribed, raised, erythematous plaques, often with central pallor and variable in size. No external allergic cause or contributing disease process can be identified in 80 to 90% of adults and children with CIU (*Khan 2020, Saini 2020*).
- CIU affects up to 1% of the general population in the United States, and the prevalence is believed to be similar in other countries. The condition is more common in adults than children and typically begins in the third to fifth decades of life. CIU is a self-limited disorder in most patients although the condition generally has a prolonged duration of 2 to 5 years (*Saini 2020*).

- Non-sedating H_1-antihistamines are the cornerstone of therapy for CIU. Limited courses of oral glucocorticoids are often used in combination with antihistamines for refractory symptoms. Other pharmacologic options for patients who do not respond to H_1-antihistamines include the use of H_2-antihistamines, leukotriene modifiers, cyclosporine, tacrolimus, mycophenolate, hydroxychloroquine, sulfasalazine, dapsone, and omalizumab (*Khan 2020, Maurer et al 2013*).
- Eosinophilic granulomatosis with polyangiitis (EGPA), previously called Churg-Strauss syndrome, is a systemic necrotizing vasculitis that affects small-to-medium-sized vessels. It is typically associated with eosinophilia and severe asthma (*Groh et al 2015, Padmanabhan et al 2019).*
- EGPA is a rare condition with a prevalence of approximately 13 cases per 1 million persons and an annual incidence of approximately 7 new cases per 1 million persons. It has a higher incidence in patients with asthma (*Groh et al 2015*).
- Systemic glucocorticoids are the mainstay of treatment for EGPA. For refractory EGPA, the addition of cyclophosphamide, azathioprine, methotrexate, rituximab, or intravenous immunoglobulins (IVIG) can be considered *(Groh et al 2015).* In more than 85% of patients with EGPA, remission can be achieved with glucocorticoids with or without an immunosuppressant; however, relapses occur in more than 33% of patients (*Pagnoux and Groh 2016*).
- Atopic dermatitis (AD) is a chronic inflammatory skin condition characterized by dry skin, erythema, oozing, crusting, and severe pruritus exacerbated by various environmental stimuli. It is associated with increased immunoglobulin E (IgE) levels and a history of atopy (asthma, allergic rhinitis, or eczema). A genetic defect that leads to dysfunction of the epidermal skin barrier along with an impaired immune response to microbial entry through the epidermis are believed to be the underlying causes of the condition (*Weston and Howe 2019*).
- AD affects up to 25% of children and 2 to 3% of adults. It can manifest at different sites depending on the age at onset. The prevalence appears to be increasing especially in Western societies (*Sidbury et al 2014*, *Weston and Howe 2019*).
- Topical emollients and topical corticosteroids are first-line treatments for AD. Topical calcineurin inhibitors are generally reserved as a second-line treatment option. The use of systemic therapies is reserved for patients with moderate to severe disease and can include phototherapy, oral cyclosporine, or other systemic immunosuppressants (*Weston and Howe 2020*).
- Chronic rhinosinusitis with nasal polyposis (CRSwNP) has a prevalence of approximately 2.7% in adults, and peaks in the sixth decade of life. Symptoms include nasal obstruction, reduced sense of smell, and sleep disturbance, all of which can substantially impact the quality of life. The majority of cases are idiopathic, but may be due to genetic, metabolic, or immunologic causes, resulting in inflammation characterized by eosinophilia and elevated levels of IL-4, IL-5, and IL-13 *(Hopkins 2019)*.
- Common treatment options for CRSwNP include saline irrigation and intranasal glucocorticoids in patients with mild symptoms, and short-term systemic glucocorticoids, surgery, and biologic agents in patients with severe symptoms *(Hopkins 2019)*.
- This monograph describes the use of Cinqair (reslizumab), Dupixent (dupilumab), Fasenra (benralizumab), Nucala (mepolizumab), and Xolair (omalizumab).
  - Cinqair, Fasenra, and Nucala are humanized monoclonal antibody interleukin-5 (IL-5) antagonists. The mechanism of action of Fasenra is slightly different, in that it binds to the IL-5 receptor on immune effector cells, whereas Cinqair and Nucala bind to the IL-5 cytokine. Eosinophils play a key role in the pathobiology of airway disorders by contributing to inflammation through the release of leukotrienes and pro-inflammatory cytokines. Increases in eosinophils are often correlated with greater asthma severity. IL-5, a cytokine critical to eosinophil differentiation and survival, has been isolated as a potential target in eosinophilic asthma. Nucala is also approved for the treatment of adult patients with EGPA.
  - Xolair is a recombinant DNA-derived monoclonal antibody that selectively binds to human IgE. Xolair, which reduces the allergic response mediators, is useful in a subset of patients with allergic asthma. In addition, Xolair has been shown to improve symptoms in patients with CIU.
  - Dupixent is a human monoclonal antibody that inhibits signaling of IL-4 and IL-13. This results in a reduction of the release of inflammatory mediators including cytokines, chemokines, nitric oxide, and IgE. These actions are useful for eosinophilic asthma, controlling symptoms of moderate to severe AD, and add-on therapy for inadequately controlled CRSwNP.
- Medispan class: Antiasthmatic – Monoclonal Antibodies

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Cinqair (reslizumab)	--

Drug	Generic Availability
Dupixent (dupilumab)	--
Fasenra (benralizumab)	--
Nucala (mepolizumab)	--
Xolair (omalizumab)	--

(*Drugs@FDA 2020, Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations 2020*)

INDICATIONS

Table 2: Food and Drug Administration Approved Indications*

Indication	Cinqair† (reslizumab)	Dupixent (dupilumab)	Fasenra† (benralizumab)	Nucala (mepolizumab)	Xolair‡ (omalizumab)
Moderate to severe persistent asthma in patients 6 years of age and older with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with ICS					✔
Add-on maintenance treatment for patients 12 years of age and older with severe asthma with an eosinophilic phenotype			✔		
Add-on maintenance treatment for patients 6 years of age and older with severe asthma with an eosinophilic phenotype				✔	
Add-on maintenance treatment for patients 12 years of age and older with moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma		✔			
Add-on maintenance treatment for patients 18 years of age and older with severe asthma with an eosinophilic phenotype	✔				
Treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA)				✔	
The treatment of adults and adolescents 12 years of age and older with CIU					✔

Indication	Cinqair† (reslizumab)	Dupixent (dupilumab)	Fasenra† (benralizumab)	Nucala (mepolizumab)	Xolair‡ (omalizumab)
who remain symptomatic despite H_1-antihistamine treatment.					
Treatment of patients 6 years of age and older with moderate-to-severe AD not adequately controlled with topical prescription therapies or when those therapies are not advisable		✔			
Add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP)		✔			

*None of the agents are indicated for the relief of acute bronchospasm or status asthmaticus.
†Not indicated for the treatment of other eosinophilic conditions
‡Not indicated for other allergic conditions or other forms of urticaria

(*Prescribing information: Cinqair 2020, Dupixent 2020, Fasenra 2019, Nucala 2019, Xolair 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

OMALIZUMAB

Asthma

- The original Food and Drug Administration (FDA) approval of omalizumab was based on the results of 3 randomized, double-blind, placebo-controlled, multicenter trials conducted in patients ≥ 12 years of age with moderate to severe asthma for ≥ 1 year and a positive skin test reaction to a perennial aeroallergen. All patients were required to have a baseline IgE between 30 and 700 international unit (IU)/mL and body weight not more than 150 kg. Patients were treated according to a dosing table to administer at least 0.016 mg/kg/IU (IgE/mL) of omalizumab or placebo over each 4-week period.
  - Each study was comprised of a run-in period to achieve a stable conversion to a common ICS, followed by randomization to omalizumab or placebo. Patients received omalizumab for 16 weeks with an unchanged ICS dose unless an acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase of 12 (*Busse et al 2001, Solèr et al 2001*) and 16 weeks (*Holgate et al 2004*) during which ICS dose reduction was attempted in a stepwise manner.
  - In the 28-week study by Busse et al (N = 525), during the steroid stable phase, patients treated with omalizumab had fewer mean exacerbations/subject (0.28 vs 0.54; p = 0.006) and decreased mean duration of exacerbations (7.8 vs 12.7 days; p < 0.001) compared with placebo-treated patients. Similarly, during the steroid reduction phase, omalizumab was associated with fewer exacerbations/subject (0.39 vs 0.66; p = 0.003), and a shorter mean duration of exacerbations (9.4 vs 12.6 days; p = 0.021) (*Busse et al 2001*).
  - In the 28-week study by Solèr et al (N = 546), asthma exacerbations/patient, the primary endpoint, decreased more in the omalizumab group compared to placebo during both the stable steroid (0.28 vs 0.66; p < 0.001) and steroid reduction phases (0.36 vs 0.75; p < 0.001) (*Solèr et al 2001*).
  - In the 32-week study by Holgate et al (N = 246), the percentage reduction in ICS dose, the primary endpoint, was greater among patients treated with omalizumab than among patients treated with placebo (median, 60 vs 50%; p = 0.003). The percentages of patients with ≥ 1 asthma exacerbation were similar between omalizumab and placebo

groups during both the stable steroid and steroid reduction phases (p-value not reported). The absence of an observed treatment effect may be related to differences in the patient population compared with the first 2 studies, study sample size, or other factors (*Holgate et al 2004*).

- A meta-analysis of 3 of the previously mentioned trials (*Busse et al 2001, Holgate et al 2004, Solèr et al 2001*) and their extension studies assessed the efficacy of omalizumab in a subgroup of 254 patients at high risk of serious asthma-related mortality and morbidity. Patients were defined as high-risk due to asthma histories that included the following: intubation history, emergency room visit within the last year, overnight hospitalization, or intensive care unit treatment. The primary outcome was an annualized rate of acute exacerbation episodes based on data from the initial 16-week stable steroid phase for high-risk patients. Two kinds of acute exacerbation episodes were considered as endpoints: significant acute exacerbation episodes and all acute exacerbation episodes (ie, all episodes recorded by the investigator). Significant acute exacerbation episodes were defined as those requiring a doubling of baseline ICS dose (*Busse et al 2001, Solèr et al 2001*) or use of systemic steroids (all 3 studies). During the stable steroid phase, mean significant acute exacerbation episode rates were 1.56 and 0.69/patient-year, respectively, a reduction of 56% with omalizumab (p = 0.007). Similar reductions in exacerbations in favor of omalizumab were observed for the whole study period and for all acute exacerbation episodes. The authors concluded that 113 significant acute exacerbation episodes were prevented for every 100 patients treated with omalizumab for 1 year (*Holgate et al 2001*).
- A Cochrane Review conducted in 2014 evaluated the efficacy of omalizumab in patients with allergic asthma. Treatment with omalizumab was associated with a significant reduction in the odds of a patient having an asthma exacerbation (odds ratio [OR], 0.55; 95% confidence interval [CI], 0.42 to 0.6; 10 studies; 3261 participants). This represents an absolute reduction from 26% for participants suffering an exacerbation on placebo to 16% on omalizumab, over 16 to 60 weeks. Additionally, in patients with moderate to severe asthma and in those who were receiving background ICS therapy, treatment with omalizumab resulted in a significant reduction in the odds of having an asthma exacerbation (OR, 0.50; 95% CI, 0.42 to 0.6; 7 studies; 1889 participants). A significant benefit was noted for subcutaneous (SC) omalizumab vs placebo with regard to reducing hospitalizations (OR, 0.16, 95% CI, 0.06 to 0.42; 4 studies; 1824 participants), representing an absolute reduction in risk from 3% with placebo to 0.5% with omalizumab over 28 to 60 weeks. The authors concluded that omalizumab was effective in reducing asthma exacerbations and hospitalizations as an adjunctive therapy to ICS and significantly more effective than placebo in increasing the numbers of participants who were able to reduce or withdraw their ICS. Omalizumab was generally well tolerated, although there were more injection site reactions with omalizumab. However, the clinical value of the reduction in steroid consumption has to be considered in light of the high cost of omalizumab (*Normansell et al 2014*).
- A systematic review of 8 randomized, placebo-controlled trials (N = 3429) evaluated the efficacy and safety of SC omalizumab as add-on therapy to corticosteroids in children and adults with moderate to severe allergic asthma. At the end of the steroid reduction phase, patients taking omalizumab were more likely to be able to withdraw corticosteroids completely compared with placebo (relative risk [RR], 1.8; 95% CI, 1.42 to 2.28; p = 0.00001). Omalizumab patients showed a decreased risk for asthma exacerbations at the end of the stable (RR, 0.57; 95% CI, 0.48 to 0.66; p = 0.0001) and adjustable-steroid phases (RR, 0.55; 95% CI, 0.47 to 0.64; p = 0.0001); post-hoc analysis suggests this effect was independent of duration of treatment, age, severity of asthma, and risk of bias. The frequency of serious adverse effects was similar between omalizumab (3.8%) and placebo (5.3%). However, injection site reactions were more frequent in the omalizumab patients (19.9 vs 13.2%). Omalizumab was not associated with an increased risk of hypersensitivity reactions, cardiovascular effects, or malignant neoplasms (*Rodrigo et al 2011*).
- In July 2016, the FDA expanded the indication of omalizumab to patients 6 to 11 years of age with moderate to severe persistent asthma. The approval was based primarily on a 52-week, randomized, double-blind, placebo-controlled, multicenter trial. The study evaluated the safety and efficacy of omalizumab as add-on therapy in 628 pediatric patients 6 to < 12 years of age with moderate to severe asthma inadequately controlled despite the use of an ICS (*Lanier et al 2009*).
  - Over the 24-week fixed-steroid phase, omalizumab reduced the rate of clinically significant asthma exacerbations (worsening symptoms requiring doubling of baseline ICS dose and/or systemic steroids) by 31% vs placebo (0.45 vs 0.64; RR, 0.69; p = 0.007). Over a period of 52 weeks, the exacerbation rate was reduced by 43% (p < 0.001). Other efficacy variables such as nocturnal symptom scores, beta-agonist use, and forced expiratory volume in 1 second (FEV_1) were not significantly different in omalizumab-treated patients compared to placebo.
- A 2017 systematic review of 3 randomized, placebo-controlled trials and 5 observational studies evaluated the safety and efficacy of omalizumab in children and adolescents. Omalizumab reduced exacerbations compared with placebo or baseline in all studies that included this outcome. The randomized controlled trials did not identify significant differences

in FEV_1; however, 3 of the 4 observational studies that included this outcome did find significant FEV_1 improvement with omalizumab. Generally, ICS and rescue medication use were reduced with omalizumab in the studies. The authors concluded that the evidence strongly supports omalizumab safety and efficacy in patients 6 to 11 years *(Corren et al 2017)*.

- The EXCELS study was a multicenter, observational cohort study to evaluate the clinical effectiveness and long-term safety of omalizumab in patients with moderate-to-severe allergic asthma. Patients were evaluated as part of 3 groups: non-omalizumab users, those newly starting omalizumab, and those who have established users at study initiation.
  - Interim efficacy results demonstrated that at month 24, the ACT score increased in all 3 patient groups: from 18.4 to 20 in non-omalizumab users, from 15.2 to 19.4 in those newly starting on omalizumab, and from 18.2 to 19.4 in established omalizumab users. For patients newly starting omalizumab treatment, 54% achieved at least a minimally important difference, defined as a ≥ 3 point increase from baseline in ACT. The study demonstrated that established users of omalizumab maintained asthma control during the study period (*Eisner et al 2012*).
  - To investigate the relationship between omalizumab and malignant neoplasms, safety information from the EXCELS trial was analyzed. Similar rates of primary malignancies in omalizumab- and non-omalizumab-treated patients were found. However, study limitations preclude definitively ruling out a malignancy risk with omalizumab (*Long et al 2014*).
  - A higher incidence of overall cardiovascular and cerebrovascular serious adverse events was observed in omalizumab-treated patients compared to non-omalizumab-treated patients (*Iribarren et al 2017*). To further evaluate the risk, a pooled analysis of 25 randomized controlled trials was conducted. An increased risk of cardiovascular and cerebrovascular serious adverse events was not noted, but the low number of events, the young patient population, and the short duration of follow-up prevent a definite conclusion about the absence of a risk (*FDA 2014*).
  - Patients from the EXCELS study were eligible for the XPORT trial, a 52-week, randomized, placebo-controlled trial evaluating the persistence of response to omalizumab in patients who discontinued omalizumab therapy after long-term use. Patients were randomized to continue their omalizumab therapy or to omalizumab discontinuation. More patients who continued omalizumab did not have an exacerbation compared to those who discontinued therapy (67.0% vs 47.7%; absolute difference, 19.3%; 95% CI, 5.0 to 33.6). The authors concluded that continuation of omalizumab after long-term use results in sustained benefit *(Ledford et al 2017)*.

Chronic Idiopathic Urticaria

- The safety and efficacy of omalizumab for the treatment of CIU was assessed in 2 placebo-controlled, multiple-dose clinical studies. Patients received omalizumab 75, 150, or 300 mg or placebo by SC injection every 4 weeks in addition to their baseline level of H_1 antihistamine therapy for 24 or 12 weeks, followed by a 16-week washout observation period. In both studies, patients who received omalizumab 150 mg or 300 mg had greater decreases from baseline in weekly itch severity scores and weekly hive count scores than placebo at week 12. The 75 mg dose did not demonstrate consistent evidence of efficacy and is not approved for use (*Kaplan et al 2013, Maurer et al 2013*).
- Another randomized, double-blind, placebo-controlled study evaluated omalizumab as add-on therapy for 24 weeks in patients with CIU who remained symptomatic despite H_1 antihistamine therapy. Similar to previous studies, patients treated with omalizumab had significantly greater reductions in weekly itch severity score from baseline to week 12 compared to placebo ($p \leq 0.001$) (*Saini et al 2015*).
- A meta-analysis of randomized clinical trials evaluating omalizumab for the treatment of CIU was published in 2016. The analysis included 7 randomized, placebo-controlled studies with 1312 patients with CIU. Patients treated with omalizumab (75 to 600 mg every 4 weeks) had significantly reduced weekly itch and weekly wheal scores compared with the placebo group. The effects of omalizumab were dose-dependent, with the strongest reduction in weekly itch and weekly wheal scores observed with 300 mg. Rates of complete response were significantly higher in the omalizumab group ($p < 0.00001$) and dose-dependent, with the highest rates in the 300 mg group. Rates of patients with adverse events were similar in the omalizumab and placebo groups (*Zhao et al 2016*). Similar results were identified in a 2019 meta-analysis of 6 trials and a 2020 meta-analysis of 9 trials, both comparing omalizumab with placebo (*Jia and He 2020, Rubini et al 2019*).
- A Phase 4 randomized clinical trial evaluated the effect of omalizumab in 205 patients with antihistamine-resistant CIU/chronic spontaneous urticaria. After an initial 24-week period of open-label treatment with omalizumab 300 mg every 4 weeks, patients randomized to continue omalizumab for another 24 weeks of double-blind therapy experienced a significantly lower rate of clinical worsening compared with patients randomized to double-blind placebo (21.0% vs 60.4%; $p < 0.0001$). No new safety signals were detected over the 48-week omalizumab treatment period *(Maurer et al 2018)*.

BENRALIZUMAB

Asthma

- The safety and efficacy of benralizumab were evaluated in a 52-week dose-ranging exacerbation trial, 3 confirmatory trials, and a 12-week lung function trial (*Bleecker et al 2016, Castro et al 2014, Ferguson et al 2017, Fitzgerald et al 2016, Nair et al 2017*).
  - In a randomized, controlled, double-blind, dose-ranging Phase 2b study, 324 adults with uncontrolled eosinophilic asthma were randomly assigned to placebo (n = 80), benralizumab 2 mg (n = 81), benralizumab 20 mg (n = 81), or benralizumab 100 mg (n = 82) and 285 adults with non-eosinophilic asthma were randomized to benralizumab 100 mg (n = 142) or placebo (n = 143) (*Castro et al 2014*). Treatments were given as 2 SC injections every 4 weeks for the first 3 doses, then every 8 weeks, for 1 year. Among adults with eosinophilic asthma, benralizumab 100 mg reduced exacerbation rates as compared to placebo (0.34 vs 0.57; rate reduction, 41%; 80% CI, 11 to 60; p = 0.096). A significant reduction in exacerbation rates was not seen with benralizumab 2 mg or 20 mg as compared to placebo in these patients. In patients with a baseline blood eosinophil count of ≥ 300 cells/µL, exacerbation rates were lower than in the placebo group for the benralizumab 20 mg (0.30 vs 0.68; rate reduction, 57%; 80% CI, 33 to 72; p = 0.015) and 100 mg (0.38 vs 0.68; rate reduction, 43%; 80% CI, 18 to 60; p = 0.049) groups.
  - SIROCCO was a randomized, multicenter, double-blind, placebo-controlled, 48-week, Phase 3 trial (N = 1205) involving patients with severe asthma with eosinophilia uncontrolled with high-dose ICS and LABAs (*Bleecker et al 2016*). Enrolled patients were randomly assigned to placebo (n = 407), benralizumab 30 mg every 4 weeks (n = 400), or benralizumab 30 mg every 8 weeks (n = 398). Compared with placebo, benralizumab reduced the annual asthma exacerbation rate over 48 weeks when administered every 4 weeks (RR, 0.55; 95% CI, 0.42 to 0.71; p < 0.0001) or every 8 weeks (RR, 0.49; 95% CI, 0.37 to 0.64; p < 0.0001). Both doses of benralizumab also significantly improved pre-bronchodilator FEV_1 in patients at week 48 vs placebo. Asthma symptoms were improved with benralizumab every 8 weeks, but not every 4 weeks, as compared to placebo.
  - CALIMA was a randomized, multicenter, double-blind, placebo-controlled, 56-week, Phase 3 trial that assessed benralizumab as add-on therapy (to high-dose ICS and LABA) for patients with severe, uncontrolled asthma and elevated blood eosinophil counts (*Fitzgerald et al 2016*). A total of 1306 patients were randomly assigned to benralizumab 30 mg every 4 weeks (n = 425), benralizumab 30 mg every 8 weeks (n = 441) or placebo (n = 440). When compared to placebo, significant reductions in annual exacerbation rates were seen with benralizumab every 4 weeks (RR, 0.64; 95% CI, 0.49 to 0.85; p = 0.0018) and every 8 weeks (RR, 0.72; 95% CI, 0.54 to 0.95; p = 0.0188). Benralizumab was also associated with significantly improved pre-bronchodilator FEV_1 and total asthma symptom scores vs placebo.
  - Patients enrolled in the SIROCCO and CALIMA trials who completed treatment were eligible for the BORO Phase 3 safety extension trial. This was a randomized, double-blind study that randomized patients to received benralizumab 30 mg every 4 or 8 weeks. Adult patients received treatment for 52 weeks and adolescents (12 to 17 years of age) were treated for 108 weeks. A total of 1576 patients were included in the full-analysis set with safety assessed at 56 weeks. Treatment discontinuation due to any adverse event occurred in approximately 2% of patients in each group. The most common adverse events were viral upper respiratory tract infections and worsening asthma. Serious adverse events included worsening asthma (3% in the every-8-week dosing group and 4% in the every-4-week dosing group), pneumonia (< 1% in both groups) and pneumonia caused by bacterial infection (< 1% in the every-4-week dosing group and 1% in the every-8-week dosing group). New malignancy occurred in 12 (1%) of the 1,576 patients. Hypersensitivity related to treatment occurred in 3 patients. For the secondary efficacy outcome, patients with elevated blood eosinophil levels had similar exacerbation rates to that observed during the first year of treatment in the SIROCCO and CALIMA trials (*Busse et al 2018*).
  - BISE was a randomized, multicenter, double-blind, placebo-controlled, 12-week, Phase 3 trial that evaluated benralizumab therapy for patients with mild to moderate persistent asthma (*Ferguson et al 2017*). Patients (N = 211) had been receiving either low- to medium-dose ICS or low-dose ICS plus LABA therapy and were randomized to benralizumab 30 mg every 4 weeks (n = 106) or placebo (n = 105). Benralizumab resulted in an 80 mL (95% CI, 0 to 150; p = 0.04) greater improvement in pre-bronchodilator FEV_1 after 12 weeks as compared to placebo. Despite this improvement, this lung function result does not warrant the use of benralizumab in mild to moderate asthma because it did not reach the minimum clinically important improvement of 10%.
  - ZONDA was a randomized, multicenter, double-blind, placebo-controlled, 28-week trial that primarily assessed whether or not benralizumab was effective as an oral glucocorticoid-sparing therapy in patients on oral steroids to manage severe asthma associated with eosinophilia (*Nair et al 2017*). Of the enrolled patients, 220 were randomly

assigned to benralizumab 30 mg every 4 weeks (n = 72), benralizumab 30 mg every 8 weeks (n = 73), or placebo (n = 75). Results revealed that the 2 benralizumab dosing regimens significantly reduced the median final oral glucocorticoid doses from baseline by 75% vs a 25% reduction seen with placebo ($p < 0.001$ for both comparisons). Additionally, benralizumab administered every 4 weeks resulted in an annual exacerbation rate that was 55% lower than that seen with placebo (marginal rate, 0.83 vs 1.83; $p = 0.003$) and benralizumab administered every 8 weeks resulted in a 70% lower rate than that seen with placebo (marginal rate, 0.54 to 1.83; $p < 0.001$).

- Fitzgerald et al conducted a study exploring the efficacy of benralizumab for patients with different baseline blood eosinophil thresholds and exacerbation histories. This study was a pooled analysis (n = 2295 patients) of the results from the SIROCCO and CALIMA phase 3 studies. The annual exacerbation rate among patients with baseline blood eosinophil counts of ≥ 0 cells/μL was 1.16 (95% CI, 1.05 to 1.28) in patients who received placebo vs 0.75 (0.66 to 0.84) in patients who received benralizumab every 8 weeks (RR, 0.64; 0.55 to 0.75; $p < 0.0001$). In patients who received benralizumab every 4 weeks who had eosinophil counts of ≥ 0 cells/μL, the annual exacerbation rate was 0.73 (0.65 to 0.82); RR vs placebo was 0.63 (0.54 to 0.74; $p < 0.0001$). The extent to which exacerbation rates were reduced increased with increasing blood eosinophil thresholds and with greater exacerbation history in patients in the every-4-week and every-8-week benralizumab groups. Greater improvements in the annual exacerbation rate were seen with benralizumab compared with placebo for patients with a combination of high blood eosinophil thresholds and a history of more frequent exacerbations *(FitzGerald et al 2018).*
- A 2017 meta-analysis evaluated the therapeutic efficacy and safety of benralizumab in patients with eosinophilic asthma. A total of 7 articles (n = 2321) met the inclusion criteria of the systematic review. The pooled analysis found that benralizumab significantly reduced exacerbations (RR, 0.63; 95% CI, 0.52 to 0.76; $p < 0.00001$) compared to placebo. There was no statistical trend for improvement in FEV_1 or asthma control indices such as Quality of Life Assessment (AQLQ) and Asthma Control Questionnaire score in benralizumab-treated patients. In addition, safety data indicated that benralizumab administration did not result in an increased incidence of adverse events and was well tolerated (RR, 1.00; 95% CI, 0.95 to 1.05; $p = 0.96$) *(Tien et al 2017)*.

MEPOLIZUMAB

Asthma

- The safety and efficacy of mepolizumab were evaluated in 3 double-blind, placebo-controlled, multicenter, randomized controlled trials in adolescent and adult patients with severe refractory asthma and signs of eosinophilic inflammation. Generally, patients were eligible for enrollment in the trials if they had eosinophils ≥ 150 cells/μL in the peripheral blood at screening or ≥ 300 cells/μL at some time during the previous year. Patients also were required to be on a high-dose ICS as well as another controller medication (*Bel et al 2014, Ortega et al 2014, Pavord et al 2012*).
  - DREAM was a dose-ranging, 52-week, Phase 2b/3 study (N = 621) that compared annual asthma exacerbation frequency and improvements in clinical symptoms between patients receiving 75 mg, 250 mg, and 750 mg intravenous (IV) mepolizumab and placebo. Mepolizumab decreased clinically significant exacerbation rates across all doses compared to placebo, at a rate of 2.40 per patient per year in the placebo group, 1.24 in the 75 mg mepolizumab group ($p < 0.0001$), 1.46 in the 250 mg mepolizumab group ($p = 0.0005$), and 1.15 in the 750 mg mepolizumab group ($p < 0.0001$). No significant improvements were found for secondary clinical symptom measures, which included change in pre-bronchodilator FEV_1 from baseline, or change in Asthma Control Questionnaire (ACQ) scores *(Pavord et al 2012)*.
  - MENSA was a 32-week Phase 3 trial (N = 576) that compared annual asthma exacerbation frequency and improvements in clinical symptoms between patients receiving SC and IV mepolizumab vs placebo. Patients were selected on the basis of frequent exacerbations, treatment with high doses of ICS, and a defined blood eosinophil count. Both SC and IV mepolizumab significantly decreased clinically significant exacerbation rates compared to placebo, at a rate of 1.74 per patient per year in the placebo group, 0.93 per patient per year in the IV mepolizumab group ($p < 0.001$), and 0.83 per patient per year in the SC mepolizumab group ($p < 0.001$). In both the SC and IV mepolizumab-treated groups, the ACQ scores met thresholds for minimal clinically important change and were significantly improved compared to placebo ($p < 0.001$) *(Ortega et al 2014)*.
  - SIRIUS was a 24-week Phase 3 trial (N = 135) that compared oral corticosteroid requirements between patients receiving SC mepolizumab and placebo. The likelihood of a reduction in the daily oral glucocorticoid dose was 2.39 times higher in the mepolizumab group (95% CI, 1.25 to 4.56; $p = 0.008$). The median reduction in daily oral corticosteroid dose was 50% (95% CI, 20 to 75) in the mepolizumab-treated group compared to 0% (95% CI, -20 to 33.3) in the placebo group ($p = 0.007$) *(Bel et al 2014)*.

- A post-hoc analysis of data from DREAM and MENSA was conducted to assess the relationship between baseline blood eosinophil counts and efficacy of mepolizumab. Of 1192 patients, 846 received mepolizumab and 346 received placebo. The overall rate of mean exacerbations per person per year was reduced from 1.91 with placebo to 1.01 with mepolizumab (47% reduction; RR, 0.53; 95% CI, 0.44 to 0.62; p < 0.0001). The exacerbation rate reduction with mepolizumab vs placebo increased progressively from 52% (RR, 0.48; 95% CI, 0.39 to 0.58) in patients with a baseline blood eosinophil count of ≥ 150 cells/µL to 70% (RR, 0.30; 95% CI, 0.23 to 0.40) in patients with a baseline count of ≥ 500 cells/µL. At a baseline count < 150 cells/µL, predicted efficacy of mepolizumab was reduced. The authors concluded that the use of a baseline blood eosinophil count will help to select patients who are likely to achieve important asthma outcomes with mepolizumab (*Ortega et al 2016*).
- COSMOS was a 52-week, open-label extension study in patients who received mepolizumab or placebo in MENSA or SIRIUS. Patients received SC mepolizumab regardless of prior treatment allocation and continued to receive appropriate standard-of-care asthma therapy throughout. In total, 558 (86%; previous mepolizumab: 358; previous placebo: 200) and 94 (14%; previous mepolizumab: 58; previous placebo: 36) patients experienced on-treatment adverse events and serious adverse events, respectively. No fatal adverse events or instances of mepolizumab-related anaphylaxis were reported. Mepolizumab treatment was shown to exert a durable response, with patients who previously received mepolizumab in MENSA or SIRIUS maintaining reductions in exacerbation rate and oral corticosteroid dosing throughout COSMOS. Patients who previously received placebo in MENSA or SIRIUS demonstrated improvements in these endpoints following treatment with mepolizumab (*Lugogo et al 2016*).
- COLUMBA was an open-label extension study of patients enrolled in the DREAM trial who received mepolizumab 100 mg every 4 weeks plus standard of care until criterion for discontinuation was met (safety profile not positive for patient, patient withdrawn by their physician, patient withdrew consent, or drug became commercially available). There were 347 patients enrolled who received treatment for a mean of 3.5 years. Adverse events most frequently reported were respiratory tract infection (67%), headache (29%), bronchitis (21%), and worsening asthma (27%). Although 6 deaths occurred, none were considered related to study treatment. No anaphylaxis reactions were reported. Malignancy was reported in 2% (n = 6) of patients. The exacerbation rate for patients on treatment for 156 weeks or longer was 0.74 events/year, which was a 56% reduction from the off-treatment period between the 2 studies (*Khatri et al 2018*).
- A pharmacokinetic study of SC mepolizumab 40 and 100 mg (for bodyweight < 40 and ≥ 40 kg, respectively) every 4 weeks in 36 children 6 to 11 years of age with severe eosinophilic asthma and ≥ 2 exacerbations in the prior year demonstrated reductions in blood eosinophil count by 89% at week 12 *(Gupta et al 2019a)*. A 52-week safety extension study of 30 children demonstrated no safety or immunogenicity concerns, as well as improvements in blood eosinophil counts and asthma control from baseline *(Gupta et al 2019b)*. Findings of these studies supported FDA approval of mepolizumab for the treatment of severe eosinophilic asthma in children (*GlaxoSmithKline 2019*).
- A systematic review and meta-analysis compared hospitalization or hospitalization and/or emergency room visit rates in patients with severe eosinophilic asthma treated with mepolizumab or placebo in addition to standard of care for ≥ 24 weeks. Four studies (N = 1388) were eligible for inclusion. Mepolizumab significantly reduced the rate of exacerbations requiring hospitalization (relative rate, 0.49; 95% CI, 0.30 to 0.80; p = 0.004) and hospitalization/emergency room visit (relative rate, 0.49; 95% CI, 0.33 to 0.73; p < 0.001) vs placebo. Significant reductions of 45% and 38% were also observed for the proportion of patients experiencing 1 or more hospitalization and hospitalization and/or emergency room visit, respectively (*Yancey et al 2017*).

Eosinophilic Granulomatosis with Polyangiitis

- A 52-week, randomized, placebo-controlled, double-blind, parallel-group, multicenter, Phase 3 trial assessed the efficacy and safety of mepolizumab as add-on therapy (to glucocorticoid treatment, with or without immunosuppressive therapy) for patients with relapsing or refractory EGPA (*Wechsler et al 2017*). A total of 136 patients were randomly assigned to mepolizumab 300 mg every 4 weeks (n = 68) or placebo (n = 68). Results demonstrated the following for the mepolizumab and placebo groups, respectively:
  - Percentage of patients with ≥ 24 weeks of accrued remission: 28% vs 3% (OR, 5.91; 95% CI, 2.68 to 13.03; p < 0.001).
  - Percentage of patients in remission at both week 36 and week 48: 32% vs 3% (OR, 16.74; 95% CI, 3.61 to 77.56; p < 0.001).
  - Annualized relapse rate: 1.14 vs 2.27 (RR, 0.50; 95% CI, 0.36 to 0.70; p < 0.001).
  - Percentage of patients able to reduce their daily dose of concomitant prednisone or prednisolone to 4 mg or less (average of weeks 48 to 52): 44% vs 7% (OR, 0.20; 95% CI, 0.09 to 0.41; p < 0.001).

RESLIZUMAB

Asthma

- The safety and efficacy of reslizumab were evaluated in 4 double-blind, placebo-controlled, multicenter, randomized controlled trials. In all 4 studies, patients were required to be on at least a medium-dose ICS with or without additional controller medications (*Bjermer et al 2016, Castro et al 2015, Corren et al* 2016).
  - Studies 3082 and 3083 were 52-week studies (N = 953) in patients with asthma who were required to have a blood eosinophil count ≥ 400 cells/µL, and ≥ 1 asthma exacerbation requiring systemic corticosteroid use over the past 12 months. These studies compared the asthma exacerbation rate and improvements in clinical symptoms between patients receiving reslizumab 3 mg/kg IV administered once every 4 weeks and placebo. In both studies, patients receiving reslizumab had a significant reduction in the frequency of asthma exacerbations (Study 3082: RR, 0.50; 95% CI, 0.37 to 0.67; Study 3083: RR, 0.41; 95% CI, 0.28 to 0.59; both $p < 0.0001$) compared with those receiving placebo. In both trials, an improvement in FEV_1 was evident for reslizumab vs placebo by the first on-treatment assessment at week 4, which was sustained through week 52. Reslizumab treatment also resulted in significant improvements compared with placebo in AQLQ total score, ACQ-7 score, and Asthma Symptom Utility Index (ASUI) score (*Castro et al 2015*).
  - Study 3081 was a 16-week study (N = 315) in patients who were required to have a blood eosinophil count ≥ 400 cells/µL. The study compared the change from baseline in FEV_1 and improvements in clinical symptoms between reslizumab 3 mg/kg vs placebo. Reslizumab 3 mg/kg significantly improved FEV_1 (difference vs placebo: 160 mL; 95% CI, 60 to 259; $p = 0.0018$). Reslizumab also statistically significantly improved ACQ and AQLQ; however, the minimally important difference was only reached for AQLQ (*Bjermer et al 2016*).
    - Study 3084 was a 16-week study in 496 patients unselected for baseline blood eosinophil levels (approximately 80% of patients had a screening blood eosinophil count < 400 cells/µL). Patients were not allowed to be on maintenance oral corticosteroids. The study compared the change from baseline in FEV_1 and improvements in clinical symptoms between reslizumab 3 mg/kg vs placebo. In the subgroup of patients with baseline eosinophils < 400 cells/µL, patients treated with reslizumab showed no significant improvement in FEV_1 compared with placebo. In the subgroup with eosinophils ≥ 400 cells/µL, however, treatment with reslizumab was associated with much larger improvements in FEV_1, ACQ, and rescue SABA use compared with placebo (*Corren et al 2016*).
  - An open-label, non-randomized extension study of these placebo-controlled trials continued treatment of patients with eosinophilic asthma with reslizumab 3 mg/kg every 4 weeks for up to 24 months to assess the drug's safety. Patients initially randomized to placebo also received active drug. A total of 1051 patients were included (n = 480 reslizumab-naive and n = 571 reslizumab-treated patients). Of these, 740 patients received treatment for 12 months or longer, and 249 patients received treatment for 24 months or longer. Worsening asthma and nasopharyngitis were the most common adverse events. Serious adverse events occurred in 7% of patients and treatment discontinuation due to an adverse event occurred in 2% of patients. No deaths (n = 3) were related to treatment. Malignancy occurred in 15 (1%) patients. Patients previously on reslizumab maintained asthma control and those naive to treatment demonstrated improvement in asthma control and lung function. The authors concluded that reslizumab maintained asthma control for up to 2 years in patients with moderate-to-severe eosinophilic asthma (*Murphy et al 2017*).
  - A post hoc analysis of pooled data from 2 randomized, placebo-controlled trials in patients with inadequately controlled asthma and elevated blood eosinophil levels compared the efficacy of reslizumab vs placebo among the subgroup of patients with oral corticosteroid dependent asthma. Reslizumab was associated with a significant improvement in overall asthma exacerbations (RR, 0.32; 95% CI, 0.18 to 0.55) *(Nair et al 2019)*.
- A 2017 meta-analysis of 5 randomized controlled trials comparing reslizumab to placebo (N = 1366) revealed improvements in exacerbations, FEV_1, and ACQ score with reslizumab. Asthma exacerbations occurred less frequently in reslizumab patients vs placebo (OR, 0.46; 95% CI, 0.35 to 0.59; $p < 0.00001$). FEV_1 also improved with reslizumab compared to placebo (mean difference, 0.16; 95% CI, 0.10 to 0.23; $p < 0.00001$). Finally, ACQ score improved with reslizumab compared to placebo (mean difference, -0.26; 95% CI, -0.36 to -0.16; $p < 0.00001$). All studies included in the meta-analysis were of limited duration of 15 or 16 weeks (*Li et al 2017*).
- A 2019 meta-analysis of 6 randomized controlled trials (5 placebo-controlled trials and 1 open-label extension) evaluated the safety of reslizumab (n = 1028) with placebo (n = 730) in adults with uncontrolled asthma. Compared with placebo, reslizumab was associated with lower proportions of patients with ≥ 1 adverse event (67% vs 81%; RR, 0.83; 95% CI, 0.79 to 0.89) and with ≥ 1 serious adverse event (7% vs 10%; RR, 0.65; 95% CI, 0.48 to 0.89) *(Virchow et al 2019)*.

DUPILUMAB

AD

- The efficacy and safety of dupilumab compared to placebo in adults with moderate-to-severe AD was evaluated in two Phase 3 trials, SOLO 1 (n = 671) and SOLO 2 (n = 708). Adults who did not have an adequate response to topical treatments were included. Patients were randomized to either placebo, dupilumab 300 mg SC weekly or every other week for 16 weeks. The proportion of patients with an Investigator's Global Assessment (IGA) score of 0 or 1 (indicating clear or almost clear skin) and a reduction of 2 points or more in the score from baseline at week 16 was the primary outcome. In both studies between 36% and 38% of patients who received either regimen of dupilumab achieved the primary outcome compared to 8% to 10% of patients who received placebo ($p < 0.001$ for all comparisons). Significantly more patients who received dupilumab had ≥ 75% improvement from baseline on the Eczema Area and Severity Index (EASI-75) compared to those who received placebo ($p < 0.001$). Pruritus and quality of life measures were also significantly improved with dupilumab. The most common adverse effects with dupilumab compared to placebo were conjunctivitis and injection-site reactions (*Simpson et al 2016*).
- The long-term efficacy and safety of dupilumab were compared to placebo in 740 patients with moderate to severe AD not adequately controlled with topical corticosteroids in the LIBERTY AD CHRONOS study. Patients received either dupilumab 300 mg once weekly, once every 2 weeks, or placebo for 52 weeks. The co-primary endpoints were proportion of patients achieving an Investigators Global Assessment (IGA) score of 0 or 1 and ≥ 2-point improvement from baseline and EASI-75 at week 16. At week 16, 39% of patients in both dupilumab groups achieved an IGA score of 0 or 1 compared to 12% of patients who received placebo. EASI-75 was achieved in 64% and 69% of the dupilumab groups vs 23% in the placebo group ($p < 0.0001$). Similar efficacy results were reported at week 52. At 1 year, the most common adverse events associated with dupilumab were injection-site reactions and conjunctivitis. Localized herpes simplex infections were more common with dupilumab while herpes zoster and eczema herpeticum were more common in the placebo group (*Blauvelt et al 2017*).
- The efficacy of dupilumab compared to placebo was evaluated in 251 patients 12 to 17 years of age with moderate-to-severe AD in a double-blind, multicenter, randomized controlled trial. Patients < 60 kg received dupilumab 400 mg initially then 200 mg every 2 weeks and patients ≥ 60 kg received 600 mg initially then 300 mg every 2 weeks for 16 weeks. Compared with placebo, dupilumab resulted in significantly higher proportions of patients achieving EASI-75 at week 16 (41.5% vs 8.2%; $p < 0.001$) and IGA score of 0 or 1 with 2 or more points improvement at week 16 (24.4% vs 2.4%; $p < 0.001$) (*Dupixent prescribing information 2020, Simpson et al 2019*).
- The efficacy of dupilumab plus topical corticosteroids was compared to topical corticosteroids alone in 367 patients 6 to 11 years of age with moderate-to-severe AD in a 16-week double-blind, multicenter, randomized controlled trial. Patients < 30 kg received dupilumab 200 mg initially then 100 mg every 2 weeks and patients ≥ 30 kg received 400 mg initially then 200 mg every 2 weeks. Patients in a third group were dosed regardless of weight at 600 mg initially and 300 mg every 4 weeks thereafter. The primary endpoint was the proportion of patients with an IGA score of 0 (clear) or 1 (almost clear) at Week 16. In patients who received dupilumab 300 mg every 4 weeks plus topical corticosteroids, 30% achieved the primary outcome vs 13% with topical corticosteroids alone. In patients who received dupilumab 200 mg every 2 weeks, 39% achieved the primary outcome vs 10% with topical corticosteroids alone (*Dupixent prescribing information 2020, Clinicaltrials.gov Web site*).

Asthma

- A 52-week randomized, double-blind, placebo-controlled study evaluated the efficacy of dupilumab in patients ≥ 12 years of age with moderate-to-severe asthma uncontrolled with a medium-to-high dose ICS plus up to 2 additional controller medications (LABA and/or leukotriene receptor antagonist). Approximately 1900 patients were randomized to add-on therapy with dupilumab (200 mg or 300 mg every 2 weeks) or matching placebo for 52 weeks. The annual rate of severe exacerbations during the 52-week study period and the absolute change in FEV_1 at week 12 were the primary endpoints. A subgroup analysis of patients with an elevated blood eosinophil count of 300/mm^3 was also planned. Both doses of dupilumab resulted in a reduced rate (46% and 47.7%, respectively) of asthma exacerbation compared to placebo ($p < 0.0001$). Patients with higher blood eosinophil levels had greater than 65% reduction in the annual exacerbation rate compared to placebo. The change in FEV_1 was also significantly improved with both doses of dupilumab compared to placebo and even more pronounced in patients with elevated blood eosinophil levels. Adverse events more common with dupilumab compared to placebo included injection-site reactions and eosinophilia (*Castro et al 2018*). In the subgroup of patients with baseline evidence of allergic asthma, dupilumab 200 mg and 300 mg every 2 weeks reduced severe asthma exacerbation rates by 36.9% and 45.5%, respectively (both $p < 0.01$) and improved FEV_1 at week 12 by 0.13 and 0.16 L, respectively (both $p < 0.001$) *(Corren et al 2019)*.

- A total of 210 patients ≥ 12 years of age with oral glucocorticoid-dependent severe asthma were randomized to receive add-on therapy with dupilumab 300 mg or placebo every other week for 24 weeks. Glucocorticoid doses were tapered from week 4 to week 20 and then maintained at a stable dose for 4 weeks. The percentage in glucocorticoid dose reduction at week 24 was the primary outcome. The percentage change in glucocorticoid dose was -70.1% with dupilumab vs -41.9% with placebo ($p < 0.001$). A dose reduction of ≥ 50% was observed in 80% of dupilumab-treated patients compared to 50% of placebo patients. Almost 70% of patients in the dupilumab group achieved a glucocorticoid dose of less than 5 mg compared to 33% in patients who received placebo. The exacerbation rate was 59% lower with dupilumab compared to placebo. Injection site reactions and eosinophilia were more common with dupilumab compared to placebo (*Rabe et al 2018*).
- A meta-analysis and systematic review of 4 RCTs evaluated the safety and efficacy of dupilumab compared to placebo in approximately 3000 patients with uncontrolled asthma. The rate of severe asthma exacerbation was significantly reduced with dupilumab compared to placebo (RR, 0.44; 95% CI, 0.35 to 0.055; $p < 0.01$). FEV_1 was also significantly increased with dupilumab with a mean difference of 0.14 L (95% CI, 0.12 to 0.17; $p < 0.01$). With respect to adverse events, the risk of injection site reactions was higher with dupilumab compared to placebo (RR, 1.91; 95% CI, 1.14 to 2.59; $p < 0.01$) (*Zayed et al 2018*).

Chronic rhinosinusitis with nasal polyposis

- Two randomized, double-blind, placebo-controlled trials evaluated dupilumab added to standard of care in adults with severe bilateral CRSwNP (*Bachert et al 2019*). Patients had experienced symptoms despite receiving intranasal corticosteroids, systemic corticosteroids in the previous 2 years, or sinonasal surgery. In both the 24- and 52-week trials, dupilumab resulted in significant improvement as measured by least-squares mean differences in nasal polyp score (-2.06; 95% CI, -2.43 to -1.69 and -1.80; 95% CI, -2.10 to -1.51, respectively), nasal congestion or obstruction score (-0.89; 95% CI, -1.07 to -0.71 and -0.87; 95% CI, -1.03 to -0.71, respectively), and Lund-Mackay computed tomography score (-7.44; 95% CI, -8.35 to -6.53 and -5.13; 95% CI, -5.80 to -4.46, respectively). The risk of any adverse event, serious adverse events, and adverse events leading to treatment discontinuation were not significantly different between dupilumab and placebo.

COMPARATIVE REVIEWS

Asthma

- In 2017, Cockle et al conducted a systematic review and indirect treatment comparison to assess the comparative effectiveness and tolerability of mepolizumab and omalizumab, as add-on therapy to standard of care, in patients with severe asthma. Studies included in the primary analysis were double-blind, randomized controlled trials, ≥12 weeks' duration enrolling patients with severe asthma with a documented exacerbation history, and receiving a high-dose ICS plus ≥1 additional controller. Two populations were examined: patients potentially eligible for 1) both treatments (overlap population) and 2) either treatment (trial population) (*Cockle et al 2017*).
  - For the overlap population, no difference was found between mepolizumab and omalizumab. However, trends in favor of mepolizumab were observed, with median estimated RRs of 0.66 (95% CI, 0.37 to 1.19) for the rate of clinically significant exacerbations and 0.19 (95% CI, 0.02 to 2.32) for the rate of exacerbations requiring hospitalization.
  - Results of the trial population analysis showed that mepolizumab was associated with an estimated median RR of 0.63 (95% CI, 0.45 to 0.89) corresponding to a reduction of 37% in the rate of clinically significant exacerbations vs omalizumab. No difference between treatments was observed for the rate of exacerbations resulting in hospitalization; however, the median RR of 0.58 (95% CI, 0.16 to 2.13) demonstrated a trend for mepolizumab over omalizumab.
  - Both treatments had broadly comparable effects on lung function and similar tolerability profiles.
- Another 2017 systematic review was unable to detect differences in efficacy when comparing add-on therapy with mepolizumab or omalizumab in asthma patients who were not well controlled on ICS therapy. The analysis included both randomized controlled trials and cohort studies with duration of ≥12 weeks. A total of 18 omalizumab studies (N = 4854) and 4 mepolizumab studies (N = 1620) were included. Network meta-analysis did not find a significant difference in FEV_1 between groups (mean difference, 9.3 mL in favor of mepolizumab; 95% CI, -67.7 to 86.3). Both omalizumab and mepolizumab reduced the annualized rates of asthma exacerbations by approximately 50% compared with placebo. Although the authors were unable to identify significant differences in efficacy, there was high heterogeneity among the clinical trials and major differences in study inclusion criteria *(Nachef et al 2018)*.
- A systematic review of the IL-5 antagonists, mepolizumab, reslizumab, and benralizumab, included 13 studies (N = 6000) conducted in patients with asthma poorly controlled by ICS. The majority of patients had severe eosinophilic

asthma. All of the IL-5 antagonists reduced asthma exacerbations by approximately 50% and improved FEV_1 by 0.08 L to 0.11 L. Overall, there was not an increase in serious adverse events with any IL-5 antagonist; however, more patients discontinued benralizumab (36/1599) than placebo (9/998) due to adverse events *(Farne et al 2017)*.

- A 2019 network meta-analysis of 11 studies aimed to indirectly compare the efficacy (n = 1855) and safety (n = 3462) of reslizumab with benralizumab in patients with eosinophilic asthma. The efficacy analysis compared a benralizumab subgroup with blood eosinophils ≥ 300 cells/µL (n = 1537) to a reslizumab subgroup in GINA step 4/5 with 2 or more previous exacerbations and blood eosinophils ≥ 400 cells/µL. Reslizumab was found to have significantly greater improvement in the ACQ and AQLQ scores compared to benralizumab. No significant difference between the groups was observed in clinical asthma exacerbation, but a sensitivity analysis with the overall study population suggested a significantly greater reduction in exacerbations with reslizumab. There were fewer discontinuations due to adverse events with reslizumab; however, the frequency and types of adverse events were not significantly different between treatment groups (*Casale et al 2019).*
- A 2019 network meta-analysis of 11 studies compared efficacy of licensed doses of mepolizumab, benralizumab, and reslizumab in patients with severe eosinophilic asthma based on eosinophil levels. Mepolizumab reduced clinically significant exacerbations compared to benralizumab for patients with blood eosinophils ≥ 150 cells/µL (RR, 0.66; 95% CI, 0.49 to 0.89), ≥ 300 cells/µL (RR, 0.61; 95% CI, 0.37 to 0.99), and ≥ 400 cells/µL (RR, 0.55; 95% CI, 0.35 to 0.87) and with mepolizumab compared to reslizumab for patients with blood eosinophils ≥ 400 cells/µL (RR, 0.55; 95% CI, 0.36 to 0.85). Additionally, change from baseline in ACQ score was greater with mepolizumab compared to benralizumab in patients with baseline blood eosinophils ≥ 150 cells/µL (difference, -0.33; 95% CI, -0.54 to -0.11), ≥ 300 cells/µL (-0.40; 95% CI, -0.76 to -0.03), and ≥ 400 cells/µL (difference, -0.36; 95% CI, -0.66 to -0.05) and compared to reslizumab with blood eosinophils ≥ 400 cells/µL (difference, -0.39; 95% CI, -0.66 to -0.12). There was no difference between reslizumab and benralizumab in clinically significant exacerbations or ACQ scores in patients with blood eosinophils ≥ 400 cells/µL *(Busse et al 2019)*.
- A 2019 systematic review and network meta-analysis of 30 randomized controlled trials compared biologic therapies for treatment of type 2 (ie, eosinophilic) asthma. Mepolizumab, reslizumab, and benralizumab significantly reduced the risk of exacerbations compared with placebo; however, network meta-analysis showed no superiority of any biologic therapy for this outcome among benralizumab, dupilumab, mepolizumab, reslizumab, and other biologics not available in the US (lebrikizumab, tralokinumab, and tezepelumab) *(Edris et al 2019)*.
- In a 2020 meta-analysis including data from 3 trials (n = 2640), dupilumab and benralizumab were compared in patients with inadequately controlled asthma. While there were no significant differences in the annual exacerbation rates between both drugs in the overall population (RR, 0.83; 95% CI, 0.62 to 1.09) and in the subgroup with the blood eosinophil count <150 cells/µL (RR, 1.57; 95% CI, 0.73 to 2.82), dupilumab was superior to benralizumab for the subgroup with a blood eosinophil count of ≥ 300 cells/µL (RR, 0.58; 95% CI, 0.39 to 0.84) and ≥ 150 but < 300 cells/µL (RR, 0.51; 95% CI, 0.29 to 0.92). The incidence of adverse events was similar between groups (OR, 1.023; 95% CI, 0.688 to 1.526) (*Ando et al 2020*).
- Additional meta-analyses have not found significant differences in asthma exacerbation rates between mepolizumab and reslizumab or between benralizumab and mepolizumab *(Bourdin et al 2018, Henriksen et al 2018, Yan et al 2019).*
- The magnitude of treatment effect of biologic agents (including benralizumab, reslizumab, dupilumab, mepolizumab, lebrikizumab [investigational], and tralokinumab [investigational]) in patients with eosinophilic asthma was evaluated in a network meta-analysis. The outcomes evaluated were change in FEV_1, ACQ score, and AQLQ score. Event rates for asthma exacerbation and associated RRs were determined for each drug. A total of 26 studies were included in the analysis (n = 7 benralizumab, n = 2 dupilumab, n = 4 lebrikizumab, n = 7 mepolizumab, n = 4 reslizumab, n = 2 tralokinumab) with a total of 8444 patients (n = 4406 on active treatment, n = 4038 in control groups). The duration of treatment ranged from 12 to 56 weeks. An increase in FEV_1, reduction in ACQ score, and increase in AQLQ score were observed with all treatments except tralokinumab. Compared to placebo, the greatest FEV_1 increase was with dupilumab (0.16 L; 95% CI, 0.08 to 0.24), followed by reslizumab (0.13 L; 95% CI, 0.10 to 0.17), and benralizumab (0.12 L; 95% CI, 0.08 to 0.17). Mepolizumab and lebrikizumab both had an increase of 0.09 L (95% CI, 0.03 to 0.15 with mepolizumab, 0.04 to 0.15 with lebrikizumab). Reduction in ACQ score (indicating better asthma control) in order of greatest to least reduction was mepolizumab, dupilumab, benralizumab, and reslizumab. The investigational agents had the least impact on the ACQ score. Quality of life scores were similarly increased with the 4 agents while the investigational agents had the least impact on quality of life. Compared to placebo, the calculated RR for annualized asthma exacerbation was significant only for dupilumab (RR, 0.37; 95% CI, 0.17 to 0.80) and reslizumab (RR, 0.64; 95% CI, 0.53 to 0.78). Comparisons between treatments did not show any significant difference for change in FEV_1,

asthma control or quality of life except for superiority of mepolizumab to the 2 investigational agents in ACQ score reduction (*Iftikhar et al 2018*).

- In a 2020 network meta-analysis including 9 studies, treatment rankings estimated that dupilumab was most effective at reducing the risk of asthma exacerbation, followed by mepolizumab, reslizumab, and benralizumab. Similar to other indirect treatment comparisons, there were no within-group differences as related to the risk for asthma exacerbations (*Ramonell et al 2020*).

CLINICAL GUIDELINES

Asthma

- According to guidelines from the NHLBI/National Asthma Education and Prevention Program, pharmacologic therapy is based on a stepwise approach in which medications are increased until asthma is controlled and then decreased when possible to minimize side effects of treatments. The level of asthma control is based on (*NHLBI 2007*):
  - Reported symptoms over the past 2 to 4 weeks
  - Current level of lung function (FEV_1 and FEV_1/forced vital capacity [FVC] values)
  - Number of exacerbations requiring oral corticosteroids per year.
- The NHLBI guidelines state that omalizumab is used as adjunctive therapy in patients 12 years and older who have allergies and severe persistent asthma that is not adequately controlled with the combination of high-dose ICS and LABA therapy (*NHLBI 2007*).
- In 2020, the Global Initiative for Asthma (GINA) published updated guidelines for asthma management and prevention. In April 2019, GINA updated a guideline on diagnosis and management of difficult-to-treat and severe asthma. Criteria for establishing a diagnosis of severe asthma was included, which requires multiple interventions before a diagnosis can be made. For patients with a diagnosis of severe asthma, uncontrolled on Step 4 treatment (eg, 2 or more controllers or taking maintenance oral corticosteroids), phenotyping for Type 2 inflammation into categories such as severe allergic, aspirin-exacerbated, allergic bronchopulmonary aspergillosis, chronic rhinosinusitis, nasal polyposis, atopic dermatitis, or eosinophilic asthma is recommended. Treatment with a biologic agent should be considered in patients who are uncontrolled despite a high-dose ICS/LABA or need maintenance oral corticosteroids. Anti-IgE treatment with omalizumab is recommended for patients ≥ 6 years of age with severe allergic asthma. Similarly, add-on anti-IL-5 therapy (ie, benralizumab, mepolizumab) is recommended for patients ≥ 12 years of age or reslizumab for patients ≥ 18 years of age with severe eosinophilic asthma. Anti-IL4 receptor therapy (ie, dupilumab) is recommended for patients ≥ 12 years of age with severe eosinophilic/Type 2 asthma or patients taking oral corticosteroids. Prior to initiation of these agents, several factors are recommended to consider including cost, insurance eligibility criteria, evaluation of predictors of response, delivery route, dosing frequency and patient preference(*GINA 2019, GINA 2020*).
  - The 2020 GINA report provides interim guidance on the management of asthma in the context of the coronavirus disease 2019 (COVID-19) pandemic. Patients with asthma should continue their prescribed asthma medications, including ICS with or without LABA and add-on therapies, during the pandemic. Use of nebulizers should be avoided when possible to prevent transmission of the virus to other patients or healthcare workers (*GINA 2020*).

Chronic Idiopathic Urticaria

- Guidelines developed by the American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma & Immunology, and the Joint Council of Allergy, Asthma & Immunology recommend a stepwise treatment approach for CIU. Treatment with omalizumab is recommended in patients inadequately controlled with antihistamines and a leukotriene receptor antagonist (*Bernstein et al 2014*).
- Joint guidelines by the European Academy of Allergy and Clinical Immunology, the Global Allergy and Asthma European Network, the European Dermatology Forum, and the World Allergy Organization recommend treatment with omalizumab in patients with symptoms despite treatment with a 4-fold dose of modern second-generation antihistamines. This is a change from previous guidelines in which use of either omalizumab or cyclosporine after failure of high-dose antihistamines was recommended. However, due to adverse effects and the lack of an approved indication, the new recommendation was that cyclosporine should only be considered if omalizumab does not provide an adequate response. (*Zuberbier et al 2018*).
- Recent guidelines published by the British Society for Allergy and Clinical Immunology similarly recommend omalizumab as a potential second-line agent in patients inadequately controlled on a 4-fold dose of a non-sedating antihistamine (*Powell et al 2015*).

Eosinophilic Granulomatosis with Polyangiitis

- Both the EGPA (Churg-Strauss) Consensus Task Force recommendations and the American Society for Apheresis guideline recommend glucocorticoids alone for patients without life- and/or organ-threatening EGPA. For patients with life- and/or organ-threatening EGPA, both glucocorticoids and an immunosuppressant are recommended, as well as maintenance therapy with azathioprine or methotrexate. Guidelines from the American Society for Apheresis recognized mepolizumab as a future treatment option, and the EGPA Consensus Task Force recommendations noted that mepolizumab held promise for this condition based on the pilot studies available at the time of guideline development. IVIG can be considered for refractory EGPA or for treatment during pregnancy (*Groh et al 2015, Padmanabhan et al 2019*).

AD

- According to the American Academy of Dermatology, interventions that provide effective control of AD for a majority of patients include non-pharmacologic interventions with emollients, topical treatment with corticosteroids and calcineurin inhibitors, and avoidance of environmental triggers. Phototherapy is the next option for children and adults with moderate to severe AD not controlled with the first-line interventions. A third-line treatment recommended for patients who fail phototherapy is treatment with systemic immunomodulators, such as cyclosporine and methotrexate. The guidelines did not provide a recommendation on use of biologic agents due to limited data available at the time of publication (*Sidbury et al 2014*)
- 2017 guidance from the International Eczema Council provides clinicians with similar guidance as the American Academy of Dermatology as well as additional steps to be taken before initiation of systemic treatment. These include consideration of an alternative diagnosis, ensuring patient compliance with topical treatment, a trial of intensive topical therapy, treatment of infection, identification and avoidance of all potential triggers, and use of phototherapy if possible. The guidance does not comment on use of biologic agents due to limited data (*Simpson et al 2017*). The International Eczema Council also published a position statement on conjunctivitis in atopic dermatitis with and without dupilumab therapy based on an opinion survey and round table discussion of its members. Based on expert opinion, a consensus was reached that patients should be informed about possible conjunctivitis with dupilumab prior to treatment, patients with new-onset conjunctivitis during dupilumab therapy should be referred to ophthalmologists, and treatment should be continued after referral to an ophthalmologist *(Thyssen et al 2019).*
- A 2018 European consensus guideline from a variety of organizations on treatment of atopic eczema includes dupilumab as a treatment option for patients with moderate-to-severe disease in whom an adequate response is not achieved with topical treatments and for whom other systemic treatments are not available. Concomitant use of emollients is recommended and combination with topical agents may be needed. No specific information on use of pediatrics was provided due to lack of data. (*Wollenberg et al 2018*).

CRSwNP

- Treatment of CRSwNP is addressed in guidelines from the American Academy of Otolaryngology-Head and Neck Surgery; American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma & Immunology, and the Joint Council of Allergy, Asthma & Immunology; the International Forum of Allergy & Rhinology; and the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA).
- Routine treatment recommendations include saline irrigation and/or intranasal glucocorticoids in patients with mild symptoms, and short-term systemic glucocorticoids and surgery in patients with severe or refractory symptoms *(Orlandi et al 2016, Peters et al 2014, Rosenfeld et al 2015)*. While not approved at the time of writing, some guidelines acknowledged the demonstration of benefit with IL-5 antagonists *(Orlandi et al 2016, Peters et al 2014)*.
- In 2019, EUFOREA published an expert consensus focused on the use of biologics for CRSwNP with or without asthma. Per EUFOREA, biologics are indicated in patients with bilateral nasal polyps and previous sinus surgery who also meet 3 of the following criteria: evidence of type 2 inflammation (biological biomarkers); the need for systemic corticosteroids in the past 2 years; significant quality-of-life impairment; significant loss of smell; and diagnosis of comorbid asthma. In patients who have never had surgery, 4 of the aforementioned criteria need to be met before a biologic is indicated. Patients with previous sinus surgery plus severe asthma may also qualify for treatment in consultation with their pulmonologist. Lastly, biologics should not be initiated in the following situations: CRSwNP and lack of signs of type 2 inflammation; cystic fibrosis; unilateral nasal polyps; mucoceles; general contraindications for

biological treatments, such as immunodeficiencies; and patient-related factors such as noncompliance to therapy (*Fokkens et al 2019*).

SAFETY SUMMARY

- All agents are contraindicated in patients with a history of hypersensitivity to the specific agent or excipients in its formulation.
- Abrupt discontinuation of systemic, topical or inhaled corticosteroids is not recommended when treatment with any of these agents are initiated. If appropriate, the corticosteroid dosage should be reduced gradually.

Cinqair:

- Boxed warning: Anaphylaxis has been observed with Cinqair infusion in 0.3% of patients in placebo-controlled clinical studies. Anaphylaxis was reported as early as the second dose of Cinqair. Patients should be observed for an appropriate period of time after Cinqair administration by a healthcare professional prepared to manage anaphylaxis.
- Key warnings and precautions:
  - In placebo-controlled clinical studies, 6/1028 (0.6%) patients receiving 3 mg/kg Cinqair had ≥1 malignant neoplasm reported compared to 2/730 (0.3%) patients in the placebo group. The observed malignancies in Cinqair-treated patients were diverse in nature and without clustering of any particular tissue type.
  - Pre-existing helminth infections should be treated before therapy with Cinqair. If patients become infected while receiving Cinqair and do not respond to anti-helminth treatment, Cinqair should be discontinued until the parasitic infection resolves.
- The most common adverse reaction (≥ 2%) included oropharyngeal pain.

Dupixent:

- Key warnings and precautions:
  - Hypersensitivity reactions (eg, anaphylaxis, erythema nodosum, serum sickness, urticaria, and rash) have occurred after administration of Dupixent. Dupixent should be discontinued in the event of a hypersensitivity reaction.
  - For patients with AD, conjunctivitis and keratitis has occurred more often when compared to placebo in clinical trials evaluating Dupixent. New or worsening eye symptoms should be reported to a healthcare provider.
  - For patients with asthma, cases of eosinophilic pneumonia and vasculitis consistent with EGPA have been reported. Occurrence of vasculitic rash, worsening pulmonary symptoms, and/or neuropathy, especially upon reduction of oral corticosteroids should be monitored.
  - Pre-existing helminth infections should be treated before therapy with Dupixent. If a patient becomes infected while receiving Dupixent and does not respond to anti-helminth treatment, Dupixent should be discontinued until the parasitic infection resolves.
- Most common adverse reactions in patients with AD included injection site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye.
- Most common adverse reactions in patients with asthma included injection site reactions, oropharyngeal pain, and eosinophilia.

Fasenra:

- Key warnings and precautions:
  - Hypersensitivity reactions (eg, anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of Fasenra. Fasenra should be discontinued in the event of a hypersensitivity reaction.
  - Pre-existing helminth infections should be treated before therapy with Fasenra. If patients become infected while receiving Fasenra and do not respond to anti-helminth treatment, Fasenra should be discontinued until the parasitic infection resolves.
- The most common adverse reactions (≥ 5%) included headache and pharyngitis.

Nucala:

- Key warnings and precautions:
  - Hypersensitivity reactions (eg, anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of Nucala.

- Herpes zoster infections have occurred in patients receiving Nucala. Vaccination should be considered if clinically appropriate.
- Pre-existing helminth infections should be treated before therapy with Nucala. If patients become infected while receiving Nucala and do not respond to anti-helminth treatment, Nucala should be discontinued until the parasitic infection resolves.

- The most common adverse reactions (≥ 5%) included headache, injection site reaction, back pain, and fatigue.

Xolair:

- Boxed warning: Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported. Patients should be observed closely for an appropriate period of time after Xolair administration. Health care providers administering Xolair should be prepared to manage anaphylaxis that can be life-threatening.
  - Patients with a prior history of anaphylactic reactions to other causes may be at an increased risk for anaphylaxis. The frequency of anaphylaxis is reported to be between 0.1 to 0.2% and may occur immediately or up to a year post-treatment.
- Key warnings and precautions:
  - Malignant neoplasms were observed in a higher rate of Xolair-treated patients (0.5%) than control patients (0.2%) in clinical trials. A subsequent 5-year observational cohort study found similar rates of primary malignancies in Xolair- and non-Xolair-treated patients. However, study limitations preclude definitively ruling out a malignancy risk with Xolair (*Long et al 2014*).
  - Rarely, patients on therapy with Xolair may present with serious systemic eosinophilia, which may present with features of vasculitis consistent with Churg-Strauss syndrome. These events usually have been associated with the reduction of oral corticosteroid therapy.
  - Some patients have reported signs and symptoms similar to serum sickness, including arthritis/arthralgia, rash, fever, and lymphadenopathy.
- Adverse reactions in asthma studies: In patients ≥ 12 years of age, the most commonly observed adverse reactions in clinical studies (≥ 1% in Xolair-treated patients and more frequently than reported with placebo) were arthralgia, pain (general), leg pain, fatigue, dizziness, fracture, arm pain, pruritus, dermatitis, and earache. In clinical studies with pediatric patients 6 to < 12 years of age, the most common adverse reactions were nasopharyngitis, headache, pyrexia, upper abdominal pain, streptococcal pharyngitis, otitis media, viral gastroenteritis, arthropod bites, and epistaxis.
- Adverse reactions in CIU studies: Adverse reactions from 3 placebo-controlled, multiple-dose CIU studies that occurred in ≥ 2% of patients receiving Xolair and more frequently than in those receiving placebo included arthralgia, cough, headache, nasopharyngitis, nausea, sinusitis, upper respiratory tract infection, and viral upper respiratory tract infection.
- Cardiovascular and cerebrovascular events in asthma studies: In a 5-year observational cohort study, a higher incidence of overall cardiovascular and cerebrovascular serious adverse events was observed in Xolair-treated patients compared to non-Xolair-treated patients. To further evaluate the risk, a pooled analysis of 25 randomized, controlled, clinical trials was conducted. An increased risk of cardiovascular and cerebrovascular serious adverse events was not noted, but the low number of events, the young patient population, and the short duration of follow-up prevent a definite conclusion about the absence of a risk (*FDA 2014*).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Route	Usual Recommended Frequency	Comments
Cinqair (reslizumab)	IV	Every 4 weeks	• Administered by IV infusion over 20 to 50 minutes. • Safety and effectiveness in pediatric patients ≤ 17 years of age have not been established. • Cinqair should be administered by a healthcare professional.
Dupixent (dupilumab)	SC	AD: every other week (children 15 to 29 kg,	• AD: Safety and efficacy in pediatric patients < 6 years of age have not been established.

Drug	Route	Usual Recommended Frequency	Comments
		every 4 weeks) Asthma: every other week Chronic rhinosinusitis with nasal polyposis: every other week	• Asthma: Safety and efficacy in pediatric patients < 12 years of age have not been established. • Chronic rhinosinusitis with nasal polyposis: Safety and efficacy in pediatric patients < 18 years of age have not been established. • Dupixent may be administered by a healthcare professional or self-administered via an autoinjector.
Fasenra (benralizumab)	SC	Every 4 weeks for first 3 doses, followed by every 8 weeks	• Safety and efficacy in pediatric patients < 12 years of age have not been established. • Fasenra may be administered by a healthcare professional or self-administered via an autoinjector.
Nucala (mepolizumab)	SC	Asthma: every 4 weeks EGPA: every 4 weeks	• Safety and efficacy in pediatric patients < 6 years of age have not been established. • Nucala may be administered by a healthcare professional or self-administered via an autoinjector.
Xolair (omalizumab)	SC	Allergic asthma: Every 2 or 4 weeks CIU: Every 4 weeks	• Xolair should be administered by a healthcare professional. Allergic asthma: • The dose and frequency is determined by serum total IgE level (IU/mL), measured before the start of treatment, and body weight. • Safety and efficacy in pediatric patients with asthma < 6 years of age have not been established. CIU: • Dosing in CIU is not dependent on serum IgE level or body weight. • Safety and efficacy in pediatric patients with CIU < 12 years of age have not been established.

See the current prescribing information for full details.

CONCLUSION

- Xolair is a humanized monoclonal antibody that is FDA-approved for patients 6 years of age and older with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with an ICS. Xolair has been shown to decrease the incidence of asthma exacerbations in these patients.
- Although clinical trial results have been mixed and several trials had an open-label design, there is some evidence to indicate that Xolair may decrease asthma-related emergency visits and hospitalizations, as well as decreasing the dose of ICS and rescue medication and increasing symptom-free days (*Buhl et al 2002, Busse et al 2011, Holgate et al 2004, Lanier et al 2003, Solèr et al 2011*).
- Xolair is administered SC in a physician's office every 2 to 4 weeks in a dose that is determined by body weight and the levels of serum IgE. Xolair carries a boxed warning due to the risk of anaphylaxis, and thus must be administered under medical supervision.

- Although Xolair therapy is generally safe, analysis of a 5-year, observational cohort, epidemiological study (EXCELS) showed an increased number of cardiovascular and cerebrovascular adverse events in patients receiving Xolair compared to placebo (*Iribarren et al 2017*). However, a pooled analysis of 25 randomized, double-blind, placebo-controlled clinical trials did not find notable imbalances in the rates of cardiovascular and cerebrovascular serious adverse events (*FDA 2014*).
- Asthma guidelines generally recommend Xolair therapy in patients with severe allergic asthma that is inadequately controlled with a combination of high-dose ICS and LABA (*GINA 2019, GINA 2020, NHLBI 2007*). Based on a limited place in therapy and the need for administration under medical supervision, Xolair is appropriate for a small percentage of patients with asthma.
- Xolair received FDA approval for the treatment of adults and adolescents (12 years of age and above) with CIU who remain symptomatic despite H_1-antihistamine treatment. Two randomized, placebo-controlled trials demonstrated its efficacy in reducing weekly itch severity scores and weekly hive count scores significantly greater than placebo at week 12. Xolair was well-tolerated, with a safety profile similar to that observed in asthma patients. In patients with CIU, Xolair is dosed at 150 or 300 mg SC every 4 weeks in a physician's office. Guidelines for the treatment of CIU recommend treatment with Xolair in patients who are inadequately controlled with a 4-fold dose of modern second-generation antihistamines. Although previous guidelines suggested the use of omalizumab after a leukotriene receptor antagonist, the most recent guideline from the European Academy of Allergy and Clinical Immunology, the Global Allergy and Asthma European Network, the European Dermatology Forum, and the World Allergy Organization state that a recommendation regarding use of a leukotriene receptor antagonist cannot be made due to a low level of evidence. Additionally, use of Xolair is recommended before treatment with cyclosporine (*Bernstein et al 2014, Zuberbier et al 2018, Powell et al 2015*).
- Cinqair, Fasenra, and Nucala are IL-5 antagonists approved as add-on treatment options for patients with severe eosinophilic asthma, and have demonstrated effectiveness in reducing asthma exacerbations (*Bel et al 2014, Bjermer et al 2016, Castro et al 2015, Corren et al 2016, Pavord et al 2012, Ortega et al 2014, Bleecker et al 2016, Fitzgerald et al 2016*). The mechanism of action of Fasenra is slightly different, in that it binds to the IL-5 receptor on immune effector cells, whereas Cinqair and Nucala bind to the IL-5 cytokine. All of these agents provide a more targeted treatment option for patients with severe, refractory asthma and should be considered in those with an eosinophilic phenotype uncontrolled on conventional asthma therapy after confirmation of severe disease, along with individual patient factors (*GINA 2019, GINA 2020*).
- Dupixent is an IL-4/IL-13 antagonist with 3 FDA-approved indications: treatment of patients ≥ 6 years of age with moderate-to-severe AD, treatment of patients ≥ 12 years of age with severe asthma of the eosinophilic type or dependent on oral corticosteroids, and add-on treatment in adults with inadequately controlled CRSwNP. Its use in AD should be determined by its approved indication and clinician judgment. According to the most recent GINA guideline on treatment of severe asthma, the use of Dupixent for severe asthma with an eosinophilic phenotype can be considered for patients with severe eosinophilic/Type 2 asthma or patients taking oral corticosteroids. The approval of Dupixent in CRSwNP occurred after publication of several guidelines, although some acknowledged the potential role for biologic therapies *(Orlandi et al 2016, Peters et al 2014).* In a 2019 EUFOREA expert consensus publication focused on the use of biologics for CRSwNP with or without asthma, biologics were indicated in patients with bilateral nasal polyps and previous sinus surgery who also meet 3 of the following criteria: evidence of type 2 inflammation (biological biomarkers); need for systemic corticosteroids in the past 2 years; significant quality-of-life impairment; significant loss of smell; and diagnosis of comorbid asthma. In patients who have never had surgery, 4 of the aforementioned criteria need to be met before a biologic is indicated. Patients with previous sinus surgery plus severe asthma may also qualify for treatment in consultation with their pulmonologist. Lastly, biologics should not be initiated in the following situations: CRSwNP and lack of signs of type 2 inflammation; cystic fibrosis; unilateral nasal polyps; mucoceles; general contraindications for biological treatments, such as immunodeficiencies; and patient-related factors such as noncompliance to therapy (*Fokkens et al 2019*).
- Nucala is the only antiasthmatic monoclonal antibody approved for the treatment of adult patients with EGPA.
- There are no head-to-head trials comparing Cinqair, Fasenra, Dupixent and Nucala. However, a systematic review of the IL-5 antagonists conducted in patients with asthma poorly controlled by ICS revealed that all of the IL-5 antagonists reduced asthma exacerbations by approximately 50% and improved FEV_1 by 0.08 L to 0.11 L. Overall, there was not an increase in serious adverse events with any IL-5 antagonist; however, more patients discontinued benralizumab (36/1599) than placebo (9/998) due to adverse events *(Farne et al 2017).* One network meta-analysis of IL-4, IL-5 and IL-13 antagonists demonstrated that all agents reduced FEV_1 and improved ACQ and AQLQ scores, except for the

investigational agent, tralokinumab; other analyses found that dupilumab, mepolizumab, reslizumab, and benralizumab significantly reduced the risk of exacerbations compared with placebo (*Iftikhar et al 2018, Edris et al 2019, Ando et al 2020, Ramonell et al 2020*). Treatment rankings in a 2020 network meta-analysis estimate that dupilumab is most effective at reducing the risk of asthma exacerbation, followed by mepolizumab, reslizumab, and benralizumab (*Ramonell et al 2020*)

- Compared to Nucala and Fasenra, Cinqair does have several limitations, including: an indication for patients ≥ 18 years of age (vs ≥ 6 and 12 years of age with Nucala and Fasenra, respectively), IV administration (SC for Nucala and Fasenra), and a boxed warning for anaphylaxis. Dupixent is indicated for treatment of patients ≥ 12 years of age with severe asthma and patients ≥ 6 years of age with AD.
- Subcutaneous autoinjector formulations are available for Dupixent, Fasenra, and Nucala.

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Publication Date: June 18, 2020

Therapeutic Class Overview
Neuropathic Pain and Fibromyalgia Agents

INTRODUCTION

- Neuropathic pain is commonly described by patients as burning or electrical in nature and results from injury or damage to the nervous system (*Herndon et al 2017*). Management of neuropathic pain may prove challenging due to unpredictable patient response to drug therapy (*Attal et al 2010*).
- Fibromyalgia is characterized by chronic musculoskeletal pain with unknown etiology and pathophysiology. Patients typically complain of widespread musculoskeletal pain, fatigue, cognitive disturbance, psychiatric symptoms, and multiple somatic symptoms (*Goldenberg 2019*). Fibromyalgia is often difficult to treat and requires a multidisciplinary, individualized treatment program (*Goldenberg 2018*).
- This review focuses on medications that are approved by the Food and Drug Administration (FDA) for the treatment of fibromyalgia, neuropathic pain, and/or post-herpetic neuralgia (PHN). The products in this review include Cymbalta (duloxetine), Gralise (gabapentin ER), Horizant (gabapentin enacarbil ER), Lidoderm (lidocaine 5% patch), Lyrica (pregabalin), Lyrica CR (pregabalin ER), Neurontin (gabapentin), Nucynta ER (tapentadol ER), Qutenza (capsaicin), Savella (milnacipran), and ZTlido (lidocaine 1.8% topical system). These agents represent a variety of pharmacologic classes, including anticonvulsants, serotonin-norepinephrine reuptake inhibitors (SNRIs), extended-release (ER) opioids, and topical analgesics. As such, these agents hold additional FDA-approved indications that are outlined in Table 2; however, clinical information included within this review will not address the use of these agents for these additional indications (*Prescribing information: Cymbalta 2019, Gralise 2015, Horizant 2016, Lidoderm 2018, Lyrica 2019, Lyrica CR 2019, Neurontin 2019, Nucynta ER 2019, Qutenza 2013, Savella 2017, ZTLido 2018*).
- Medispan classes: Anticonvulsants - Misc.; Fibromyalgia Agents; Local Anesthetics – Topical; Opioid Agonists; Postherpetic Neuralgia (PHN) Agents; Restless Leg Syndrome (RLS) Agents; Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Diabetic Neuropathy

- Approximately 50% of patients with diabetes will eventually develop neuropathy. The high rate of diabetic neuropathy results in substantial patient morbidity, which includes recurrent lower extremity infections, ulcerations, and subsequent amputations (*Feldman 2018*).
- The condition is categorized into distinct syndromes based on the neurologic distribution, although syndromes may overlap in some patients. The most frequently encountered diabetic neuropathies include distal symmetric polyneuropathy, autonomic neuropathy, polyradiculopathies, and mononeuropathies (*Feldman et al 2019*).
- The 3 main components to the management of diabetic neuropathy are glycemic control, foot care, and pain management (*Feldman et al 2019*).
  - Optimal glucose control is important for the prevention of diabetic neuropathy. Clinical trial evidence demonstrates that rigorous blood glucose control in patients with type 1 diabetes reduces the occurrence of diabetic neuropathy. In contrast, the role of glycemic control in established diabetic neuropathy is uncertain. Limited evidence suggests that neuropathic symptoms may improve with intensive antidiabetic therapy (*Feldman et al 2019*).
  - Patients with diabetes should be counseled on the importance of daily foot care, including the inspection of feet for the presence of dry or cracking skin, fissures, and plantar callus formation. Regular foot examinations by a healthcare provider are also important (*Feldman et al 2019*).
  - A small proportion of patients with diabetic neuropathy will experience painful symptoms, and in some instances the condition is self-limited. When treatment is necessary, options include antidepressants, anticonvulsants, capsaicin cream, lidocaine patches, alpha-lipoic acid, isosorbide dinitrate topical spray, and transcutaneous electrical nerve stimulation (*Feldman et al 2019*).

Fibromyalgia

- Fibromyalgia is a chronic functional illness marked by widespread musculoskeletal pain for which no alternative cause can be identified. Fibromyalgia patients often experience neuropsychological symptoms of fatigue, unrefreshing sleep, cognitive dysfunction, anxiety, and depression (*Clauw et al 2009*).

- Patients with fibromyalgia have pain that is typically above and below the waist on both sides of the body and involves the axial skeleton (neck, back, or chest). The pain attributable to fibromyalgia is poorly localized, difficult to ignore, severe in its intensity, and associated with a reduced functional capacity (*Crofford 2015*).

- The prevalence of fibromyalgia in the general U.S. population is estimated to be 2 to 3% and increases with age *(Goldenberg 2019)*. It is more common in women than in men, with a ratio of approximately 9:1 (*Crofford 2015*).
- There is an increased prevalence of other syndromes associated with pain and fatigue, including chronic fatigue syndrome, temporomandibular disorder, chronic headaches, irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, and other pelvic pain syndromes in fibromyalgia patients (*Clauw et al 2009, Crofford 2015*).

PHN

- PHN refers to the persistence of the pain of herpes zoster beyond 4 months from the initial onset of the rash. Among patients with acute herpes zoster infection, the major risk factors for PNH are older age, greater acute pain, and greater rash severity. The duration of PHN is highly variable among individuals and may persist for months, years, or life (*Bajwa et al 2019*).
- PHN, as well as acute herpetic neuralgia, can be a severe condition associated with profound psychological dysfunction, including impaired sleep, decreased appetite, and decreased libido (*Bajwa et al 2019*).
- Prevention of PHN involves either treatment of acute herpes zoster infection or use of a vaccine (*Bajwa et al 2019*). Although evidence suggests that antiviral therapy hastens resolution of lesions and acute neuritis of herpes zoster, it is unclear if it decreases the risk of PHN *(Albrecht 2018).*
- A number of treatment modalities have been evaluated in the management of PHN and include tricyclic antidepressants, anticonvulsants, opioids, capsaicin, topical lidocaine, intrathecal glucocorticoids, N-methyl-D-aspartate receptor antagonists, botulinum toxin, cryotherapy, and surgery (*Bajwa et al 2019*).

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Cymbalta (duloxetine delayed-release)	✔
Gralise (gabapentin ER)*	-
Horizant (gabapentin enacarbil ER)*	-
Lidoderm (lidocaine transdermal patch)	✔
Lyrica (pregabalin)	✔
Lyrica CR (pregabalin ER)	-
Neurontin (gabapentin)	✔
Nucynta ER (tapentadol ER)	-
Qutenza (capsaicin transdermal patch)	-
Savella (milnacipran)	-
ZTlido (lidocaine topical system)	-

* Medication is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration.

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. FDA-Approved Indications

Indication	Cymbalta (duloxetine)	Gralise (gabapentin ER)	Horizant (gabapentin enacarbil ER)	Lidoderm, ZTlido (lidocaine)	Lyrica (pregabalin)	Lyrica CR (pregabalin ER)	Neurontin (gabapentin)	Nucynta ER (tapentadol)	Qutenza (capsaicin)	Savella (milnacipran)
Adjunctive therapy for adult patients with partial onset seizures					✔					
Adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients > 3 years of age with epilepsy							✔			
Adjunctive therapy for patients 1 month of age and older with partial onset seizures					✔					
Management of chronic musculoskeletal pain	✔ †									
Management of fibromyalgia	✔				✔					✔
Management of neuropathic pain associated with diabetic peripheral neuropathy	✔				✔	✔		✔ §		
Management of neuropathic pain associated with spinal cord injury					✔					
Management of PHN		✔	✔		✔	✔	✔			
Relief of pain associated with PHN				✔					✔	
Moderate-to-severe primary restless legs syndrome			✔ ‡							
Treatment of generalized anxiety disorder	✔									
Treatment of major depressive disorder	✔									
Management of moderate to severe chronic pain in adults								✔ §		

† This has been established in studies of patients with chronic low back pain and chronic pain due to osteoarthritis.
‡ Gabapentin enacarbil is not indicated for patients who are required to sleep during the day and remain awake at night.
§ Indicated when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. Medication is not for: use as an as-needed analgesic; pain that is mild or not expected to persist for an extended period of time; acute pain; or postoperative pain, unless the patient is already receiving chronic opioid therapy prior to surgery, or if the postoperative pain is expected to be moderate to severe and persist for an extended period of time.

(*Prescribing information: Cymbalta 2019, Gralise 2015, Horizant 2016, Lidoderm 2018, Lyrica 2019, Lyrica CR 2019, Neurontin 2019, Nucynta ER 2019, Qutenza 2013, Savella 2017, ZTlido 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

Neuropathic Pain

- Pregabalin demonstrated significant improvements in pain relief, functional outcomes, and quality of life compared to placebo for the treatment of diabetic peripheral neuropathic pain. Commonly reported adverse events (AEs) in patients receiving pregabalin include dizziness, somnolence, infection, headache, dry mouth, weight gain, and peripheral edema (*Dworkin et al 2003, Freynhagen et al 2005, Guan et al 2011, Lesser et al 2004, Moon et al 2010, Rosenstock et al 2004, Roth et al 2010, Sabatowski et al 2004, Semel et al 2010, Sharma et al 2010, Skvarc et al 2010*).
- Tapentadol ER demonstrated superiority over placebo in alleviating pain and improving quality of life in patients with diabetic peripheral neuropathy. Tapentadol ER is associated with significant improvements in pain intensity scores, responder rates, and Patient Global Impression of Change (PGIC). Commonly reported AEs in patients receiving tapentadol ER include nausea, vomiting, and constipation (*Schwartz et al 2011*).
- Duloxetine demonstrated consistent superiority over placebo in alleviating pain, improving functional outcomes, and improving quality of life in patients with diabetic peripheral neuropathic pain. Specifically, duloxetine is associated with significant improvements in Brief Pain Inventory, Clinician and Patient Global Impression of Improvement and Severity, Short Form-36 Health Survey (SF-36), Pain-Related Sleep Interference, and Euro Quality of Life assessment (EQ-5D) scores. Commonly reported AEs in patients receiving duloxetine include nausea, somnolence, anorexia, and dysuria (*Armstrong et al 2007, Kajdasz et al 2007, Lunn et al 2014, Parsons et al 2016, Yan et al 2010*).
- Head-to-head trials among the neuropathic pain and fibromyalgia agents are rare. In a 52-week, open-label trial comparing duloxetine to routine care (gabapentin, amitriptyline, and venlafaxine) for the treatment of diabetic peripheral neuropathic pain, there were no significant differences observed between groups in EQ-5D questionnaire scores; however, results differed with regards to SF-36 subscale scores. In another trial, there were no significant between-group differences in SF-36 subscale scores; however, other subscale scores for physical functioning, bodily pain, mental health, and vitality favored duloxetine (*Raskin et al 2006, Wernicke et al 2007[b]*). A second head-to-head trial demonstrated duloxetine to be noninferior to pregabalin for the treatment of pain in patients with diabetic peripheral neuropathy who had an inadequate pain response to gabapentin (*Tanenberg et al 2011*). A post-hoc analysis of study patients who were taking concomitant antidepressants and those who were not taking antidepressants found duloxetine may provide better pain reduction in those patients who were not taking concomitant antidepressants (*Tanenberg et al 2014*). Another head-to-head trial found no significant differences between high-dose duloxetine or pregabalin monotherapy and combination duloxetine/pregabalin therapy, as measured by Brief Pain Inventory Modified Short Form (BPI-MSF) average pain (*Tesfaye et al 2013*).
- Several large meta-analyses and systematic reviews have been conducted evaluating the neuropathic pain and fibromyalgia agents, which further support the safety and efficacy of these agents in FDA-approved indications (*Chou et al 2009, Derry et al 2019, Edelsberg et al 2011, Lunn et al 2014, Meng et al 2014, Quilici et al 2009, Wernicke et al 2007[a], Wiffen et al 2017*). In a meta-analysis by Quilici et al, limited available clinical trial data suitable for indirect comparison demonstrated that duloxetine provides comparable efficacy and tolerability to that of gabapentin and pregabalin for the treatment of diabetic peripheral neuropathic pain (*Quilici et al 2009*).
- The efficacy of pregabalin in patients with neuropathic pain associated with spinal cord injury was established in 2 placebo-controlled trials, 1 of 12 weeks duration and the other of 16 weeks duration. Patients had neuropathic pain associated with spinal cord injury for at least 3 months or with relapses and remissions for at least 6 months. Patients were allowed to take opioids, non-opioid analgesics, antiepileptic drugs, muscle relaxants, and antidepressant drugs if doses were stable for 30 days prior to screening. Patients were also allowed to take acetaminophen and nonsteroidal anti-inflammatory drugs during the trial. In both trials, pregabalin (150 to 600 mg/day) significantly improved weekly pain scores compared to placebo, and increased the proportion of patients with at least a 30 or 50% reduction from baseline in pain score (*Lyrica prescribing information 2019*, *Siddall et al 2006, Vranken et al 2008*).

Fibromyalgia

- From the agents included in this review, the agents that have several randomized controlled trials (RCTs) and meta-analyses demonstrating their efficacy in the treatment of fibromyalgia include duloxetine, pregabalin, and milnacipran (*Arnold et al 2007, Arnold et al 2008, Arnold et al 2009, Clauw et al 2008, Crofford et al 2005, Hauser et al 2009[a], Hauser et al 2009[b], Hauser et al 2010, Lunn et al 2014, Mease et al 2009, Mease et al 2010, Russell et al 2008, Vitton et al 2004, Welsch et al 2018*).
  - A 2009 meta-analysis on the treatment of fibromyalgia syndrome with antidepressants found that antidepressants were associated with improved health-related quality of life. The largest effect size for pain reduction was seen with

the tricyclic antidepressant, amitriptyline, followed by monoamine oxidase inhibitors, moclobemide and pirlindole (medium effect size). Small effect sizes were observed with the selective serotonin reuptake inhibitors (SSRIs), fluoxetine and paroxetine, and the SNRIs, duloxetine and milnacipran. The authors concluded that short-term treatment with amitriptyline and duloxetine could be considered for fibromyalgia-associated pain and sleep disturbances (*Hauser et al 2009[a]*).

- In a meta-analysis of 5 RCTs, gabapentin and pregabalin reduced pain and improved sleep in patients with fibromyalgia. The pooled number-needed-to-treat to achieve ≥ 30% reduction in pain was 8.5. Anxiety, depressed mood, and fatigue were not improved with gabapentin or pregabalin treatment (*Hauser et al 2009[b]*).
- Results from another 2010 meta-analysis noted that duloxetine, milnacipran, and pregabalin have short-term (up to 6-month) efficacy data. The authors concluded that the choice of medication may be dependent on the occurrence of key symptoms of fibromyalgia syndrome and the specific AEs that are associated with each drug (*Hauser et al 2010*).
- A systematic review of 6 randomized trials involving 2249 patients concluded that for the treatment of fibromyalgia, duloxetine 60 and 120 mg/day are effective with a similar magnitude of effect (low quality evidence). The effect in fibromyalgia may be achieved through a greater improvement in mental symptoms than somatic physical pain (*Lunn et al 2014*).
- A 2016 network meta-analysis of 9 RCTs (N = 5140) indirectly compared duloxetine, pregabalin, and milnacipran in the treatment of fibromyalgia. The probability of achieving > 30% improvement in pain scores was numerically highest with duloxetine 60 mg, followed by pregabalin 300 mg, milnacipran 100 mg, and milnacipran 200 mg. While the aforementioned treatment groups each demonstrated superiority over placebo, differences between active treatments did not achieve statistical significance (*Lee et al 2016*).
- A systematic review and meta-analysis of 18 randomized trials involving 7903 patients concluded that duloxetine and milnacipran provided a small incremental benefit over placebo in pain reduction and provided no clinically relevant benefit over placebo in improving health-related quality of life or in reducing fatigue. Dropout rates for duloxetine and milnacipran due to AEs were higher than placebo (*Welsch et al 2018*).

PHN

- In patients with PHN, treatment with lidocaine 5% resulted in significant pain relief compared to placebo (*Galer et al 1999, Galer et al 2002, Meier et al 2003*). In addition, treatment with lidocaine 5% was associated with higher rates of patient preference, less use of rescue medication, and decreases in allodynia and neuropathic symptoms compared to placebo (*Galer et al 1999, Meier et al 2003*). An open-label trial evaluating lidocaine 5% for the management of PHN supports the findings of placebo-controlled trials (*Katz et al 2002*).
- Lidocaine 1.8% was approved via the 505(b)(2) pathway with no new efficacy trials. However, in a single-dose, crossover study conducted in 53 healthy volunteers, lidocaine 1.8% topical system demonstrated equivalent exposure (AUC) and peak concentration (C_{max}) of lidocaine to lidocaine 5% patch. In addition, based on a clinical study in 54 subjects, 47 subjects (87%) had adhesion scores of 0 (≥ 90% adhered) for all evaluations performed every 3 hours during the 12 hours of lidocaine 1.8% administration, 7 subjects (13%) had adhesion scores of 1 (≥ 75% to < 90% adhered) for at least 1 evaluation, and no subjects had scores of 2 or greater (< 75% adhered) *(ZTlido prescribing information 2018)*.
- In patients with PHN, treatment with capsaicin resulted in significant pain relief compared to low dose capsaicin 0.04% (*Backonja et al 2008, Derry et al 2017, Irving et al 2012*). Treatment with capsaicin was associated with improvement in PGIC, reduction in numeric pain rating scale (NPRS) scores, and reduction in neuropathic symptoms compared to low-dose capsaicin for up to 12 weeks of treatment (*Backonja et al 2008, Derry et al 2017, Irving et al 2012*). The long-term tolerability and safety of capsaicin was also demonstrated in a 52-week study, which found that repeat treatment with capsaicin (30 and 60 minutes) in addition to the standard of care therapies (antidepressants, antiepileptics, and/or opioids) was well tolerated with no negative functional or neurological effects when compared to standard of care therapies alone (*Vinik et al 2016*).
- Gabapentin also demonstrated superiority over placebo in alleviating pain, improving functional outcomes, and improving quality of life in patients with PHN. Treatment with gabapentin significantly improved average daily pain and sleep, short-form McGill Pain Questionnaire (SF-MPQ), Patient and Clinician Global Impression of Change, SF-36, and Prolife of Mood States (POMS) scores in RCTs. Commonly reported AEs in patients receiving gabapentin included somnolence, drowsiness, dizziness, ataxia, peripheral edema, and infection (*Rice et al 2001, Rowbotham et al 1998*). In a trial comparing placebo, gabapentin monotherapy, morphine sustained-release monotherapy, and gabapentin and morphine sustained-release combination therapy, combination therapy achieved better analgesia at lower doses of each

agent compared to monotherapy with either agent in patients with PHN. Combination therapy was most commonly associated with constipation, sedation, and dry mouth (*Gilron et al 2005*). Within these clinical trials, doses of gabapentin of up to 3,600 mg/day were evaluated (*Gilron et al 2005, Rice et al 2001, Rowbotham et al 1998*).

- In 2 placebo-controlled trials, gabapentin ER achieved significant improvements in average daily pain and sleep interference scores (*Irving et al 2009, Wallace et al 2010*). In one of these trials, a larger proportion of patients receiving gabapentin ER reported ≥ 50% reduction from baseline in average daily pain scores compared to placebo (*Irving et al 2009*). In general, treatment with gabapentin ER was well tolerated; dizziness, headache, somnolence, and peripheral edema were the most commonly reported AEs (*Irving et al 2009, Wallace et al 2010*). Another placebo-controlled trial concluded that gabapentin ER may be particularly effective in patients with PHN presenting with sharp, dull, sensitive, or itchy pain (*Jensen et al 2009*). Within these clinical trials, doses of gabapentin ER of up to 1,800 mg/day were evaluated (*Irving et al 2009, Jensen et al 2009, Wallace et al 2010*).
- The efficacy of gabapentin enacarbil ER (1200, 2400, and 3600 mg/day) was established in a randomized, placebo-controlled, 12-week trial in adult patients with a documented medical diagnosis of PHN for ≥ 3 months (n = 371) and significant pain, as demonstrated by a minimum baseline 24-hour average Pain Intensity Numerical Rating Scale score ≥ 4 on the 11-point scale. Treatment with gabapentin enacarbil ER significantly improved the mean pain score and increased the proportion of patients with ≥ 50% reduction in pain score from baseline at all doses evaluated. A benefit over placebo was observed for all 3 doses of gabapentin enacarbil ER as early as Week 1 and was maintained at Week 12. Additional benefit of using doses of gabapentin enacarbil ER > 1200 mg/day was not demonstrated (*Zhang et al 2013*). Results of a second, published, placebo-controlled trial confirms these findings. Reported AEs were similar to those of gabapentin and gabapentin ER (ie, dizziness, headache, and nausea) (*Backonja et al 2011*).
- A meta-analysis of 7 trials evaluating gabapentin, gabapentin enacarbil ER, and gabapentin ER was conducted to determine the efficacy and safety of all gabapentin formulations for management of PHN. Although gabapentin was found to be superior to placebo in terms of pain reduction, global impression of change, and sleep quality, patients taking gabapentin were significantly more likely to experience AEs such as dizziness, somnolence, peripheral edema, ataxia, and diarrhea (*Meng et al 2014*).
- Pregabalin demonstrated consistent superiority over placebo in alleviating diabetic peripheral neuropathic pain and PHN-related pain. Two noncomparative, open-label trials evaluating pregabalin for the management of PHN support the findings of placebo-controlled trials (*Ogawa et al 2010, Xochilcal-Morales et al 2010*). In one of these noncomparative trials, long-term treatment of PHN with pregabalin (52 weeks) was found to be safe and effective (*Ogawa et al 2010*). Patients with PHN who were transitioned to pregabalin from gabapentin demonstrated no significant difference in pain scores, based on a visual analog scale, with pregabalin compared to gabapentin. However, in a subset of patients who required an increase in the dosage of pregabalin to improve the analgesic effect after the transition, significant improvement in pain scores was observed (*Ifuku et al 2011*).
- Support for efficacy of pregabalin ER in PHN and diabetic peripheral neuropathy was based on the efficacy of pregabalin in these indications and 1 clinical trial in PHN (*Lyrica CR prescribing information 2019*). In this trial, pregabalin ER demonstrated a significantly longer time to loss of therapeutic response compared with placebo over a 13-week randomized withdrawal phase in a phase 3, double-blind, randomized trial *(Huffman et al 2017).*

CLINICAL GUIDELINES

Diabetic Neuropathy

- The 2011 American Academy of Neurology (AAN) guidelines, which were reaffirmed in 2016 [update in progress 2020], recommend the following:
  - If clinically appropriate, pregabalin should be offered for treatment. Gabapentin and sodium valproate are other anticonvulsants that should be considered for treatment (*Bril et al 2011*).
  - Amitriptyline, venlafaxine, and duloxetine should be considered for treatment; there is insufficient evidence available to recommend one of these agents over another. Combination therapy with venlafaxine and gabapentin may be utilized for a better response.
  - Dextromethorphan, morphine sulfate, tramadol, and oxycodone should be considered for treatment; there is insufficient evidence available to recommend one of these agents over another.
  - With regards to other pharmacologic options, capsaicin and isosorbide dinitrate spray should be considered for treatment, while lidocaine patch may be considered.
- The 2020 American Diabetes Association (ADA) guideline acknowledges the lack of quality of life outcomes and recommends that treatment decisions follow a trial-and-error approach (*ADA 2020*).

- Pregabalin, duloxetine, and tapentadol ER have been approved for relief of diabetic peripheral neuropathy; however, none of these agents affords complete relief, even when used in combination.
- Either pregabalin or duloxetine is recommended as initial pharmacologic therapy for neuropathic pain in diabetes. The use of tapentadol ER is generally not recommended as a first or second-line therapy due to safety concerns such as high-risk for addiction, and the evidence for its use is considered weaker.
- Tricyclic antidepressants, venlafaxine, carbamazepine, and topical capsaicin are not approved for the treatment of painful diabetic peripheral neuropathy, but may be effective and can be considered as treatment options.

- In general, other published guidelines support recommendations from the AAN and ADA concerning the use of the neuropathic pain and fibromyalgia agents in the management of diabetic neuropathy (*Dworkin et al 2007, Handelsman et al 2015, Pop-Busui et al 2017*).

PHN

- According to the 2010 European Federation of Neurological Societies guideline on the pharmacological treatment of neuropathic pain, tricyclic antidepressants or gabapentin/pregabalin are recommended as first-line treatment for PHN. Topical lidocaine may be considered first line in the elderly, especially if there are concerns regarding AEs of oral medications. Capsaicin cream and opioids may be considered a second-line choice; capsaicin patches are promising, but the long-term effects of repeated applications on sensation are unclear *(Attal et al 2010).*

Fibromyalgia

- According to the evidence-based recommendations for the management of fibromyalgia syndrome from the European League Against Rheumatism, non-pharmacologic interventions should be considered first-line therapy for the management of fibromyalgia symptoms. Pharmacologic therapy should only be initiated if there is a lack of effect with non-pharmacologic therapies, and should be tailored to meet the patient's needs. Recommended pharmacologic agents include low-dose amitriptyline, cyclobenzaprine, duloxetine, milnacipran, pregabalin, and tramadol (*Macfarlane 2017*).
- According to the 2012 Canadian guidelines for the diagnosis and management of fibromyalgia syndrome, all classes of antidepressants are options for treatment of pain and other symptoms of fibromyalgia. Anticonvulsants are also options, though the guideline does not recommend specific agents (*Fitzcharles et al 2013*).

SAFETY SUMMARY

- The following key contraindications are included in the prescribing information:
  - Concomitant use or use within the last 14 days of monoamine oxidase inhibitors (MAOIs) is contraindicated with duloxetine, milnacipran, and tapentadol ER.
  - Tapentadol ER is contraindicated in significant respiratory depression, acute or severe bronchial asthmas, or hypercarbia in an unmonitored setting or in the absence of resuscitative equipment, and in known or suspected paralytic ileus.
- Duloxetine and milnacipran carry a boxed warning for clinical worsening, suicidality, and unusual changes in behavior. There is an increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants. All SNRIs are not approved for use in pediatric populations. All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely, especially during the initial few months of a course of drug therapy and following changes in dosage.
- Duloxetine may increase the risk of bleeding events due to interference with serotonin reuptake. Concomitant use with aspirin and other antithrombotics may increase risk of bleeding.
- Tapentadol ER has a boxed warning for the potential for abuse, life-threatening respiratory depression, accidental exposure, risk of neonatal opioid withdrawal syndrome with prolonged use, and interactions with alcohol, benzodiazepines, or other central nervous system depressants that can cause profound sedation, respiratory depression, coma, and death.
- The FDA requires a Risk Evaluation and Mitigation Strategy (REMS) program for opioid analgesics, including tapentadol ER, to assure safe use of these medications.
- Tapentadol ER should not be abruptly discontinued in patients who may be physically dependent on opioids. Rapid discontinuation in these patients may result in withdrawal symptoms, uncontrolled pain, and suicide. Mixed agonist/antagonist or partial agonist analgesics should not be used concomitantly with tapentadol ER.
- Gabapentin, pregabalin, and pregabalin ER carry warnings regarding the risk of anaphylaxis and/or angioedema after the first dose or during therapy.

- Topical lidocaine products have a warning for excessive dosing/overexposure, increased absorption on non-intact skin, risk of overexposure with external heat sources, and hypersensitivity reactions. Methemoglobinemia has been reported in association with local anesthetic use.
- The following monitoring parameters are recommended with treatment:
  - Monitor for clinical worsening of depression, suicidality, or unusual changes in behavior with duloxetine, milnacipran, gabapentin ER, gabapentin enacarbil ER, pregabalin, pregabalin ER, and gabapentin.
  - Patients receiving tapentadol ER, duloxetine, or milnacipran should be monitored for signs of serotonin syndrome when used concurrently with other serotonergic agents (eg, SSRIs, SNRIs, tricyclic antidepressants, triptans, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort). Tapentadol ER, duloxetine or milnacipran should not be used with drugs that impair metabolism of serotonin (eg, MAOIs, linezolid, and methylene blue).
  - Monitor for signs of misuse, abuse, and addiction during tapentadol ER therapy. Patients should also be closely monitored for 72 hours after initiating tapentadol ER treatment and monitored throughout treatment due to an increased risk of respiratory depression.
  - Patients receiving tapentadol ER, duloxetine, capsaicin, or milnacipran should have their blood pressure monitored prior to initiating treatment and periodically throughout treatment.
  - Monitor for worsened seizure control in patients with a history of seizure disorder with the treatment of tapentadol ER, duloxetine, or milnacipran.
  - Patients receiving tapentadol ER should be monitored for signs and symptoms of worsening biliary tract disease, including acute pancreatitis.
- In general, oral neuropathic pain and fibromyalgia agents are commonly associated with central nervous system-related AEs (eg, dizziness, drowsiness, somnolence). Peripheral edema and weight gain may also occur with use of these agents.
  - Caution is advised when prescribing pregabalin concomitantly with opioids due to risk of CNS depression.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Cymbalta (duloxetine delayed-release)	Capsule	Oral	Once daily	Not recommended in ESRD, severe renal impairment (CrCl < 30 mL/min), or hepatic insufficiency
Gralise (gabapentin ER)	Tablet	Oral	Once daily	Administer with evening meal Reduce dose in CrCl of 30 to 60 mL/min; not recommended in CrCl < 30 mL/min or hemodialysis
Horizant (gabapentin enacarbil ER)	Tablet	Oral	Twice daily	Administer with food Reduce dose in CrCl < 60 mL/min or hemodialysis
Lidoderm, ZTlido (lidocaine)	Patch, topical system	Transdermal	Once daily	Apply for up to 12 hours within a 24-hour period Caution in patients with severe hepatic disease
Lyrica (pregabalin)	Capsule, oral solution	Oral	2 or 3 times daily	Schedule V controlled substance Reduce dose in CrCl < 60 mL/min
Lyrica CR (pregabalin ER)	Tablet	Oral	Once daily	Schedule V controlled substance Reduce dose in CrCl < 60 mL/min Administer after evening meal
Neurontin (gabapentin)	Capsule, oral solution, tablet	Oral	3 times daily	Reduce dose in CrCl < 60 mL/min
Nucynta ER (tapentadol ER)	Tablet	Oral	Twice daily	Schedule II controlled substance

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Do not use in severe renal impairment (CrCl < 30 mL/min) or severe hepatic impairment Reduce dose in moderate hepatic impairment
Qutenza (capsaicin)	Patch	Transdermal	60-minute application of up to 4 patches every 3 months	Only administered by physicians or health care professionals
Savella (milnacipran)	Tablet	Oral	Twice daily	Reduce dose in CrCl < 30 mL/min Caution in patients with moderate renal impairment or severe hepatic impairment

Abbreviations: CrCl = creatinine clearance; ESRD = end-stage renal impairment
See the current prescribing information for full details

CONCLUSION

- Included in this review are the neuropathic pain and fibromyalgia agents, duloxetine, gabapentin ER, gabapentin enacarbil ER, lidocaine, pregabalin, pregabalin ER, gabapentin, tapentadol ER, capsaicin, and milnacipran. In general, these agents are FDA-approved for the treatment of diabetic peripheral neuropathic pain, PHN, and/or fibromyalgia.
- Clinical trials support the use of the neuropathic pain and fibromyalgia agents for their FDA-approved indications. Available data demonstrate that neuropathic pain and fibromyalgia agents provide relief from pain; some studies have demonstrated improvement in functional outcomes and quality of life. Direct comparisons among the various agents are rare, and consistent benefit of one agent over another has not been demonstrated.
- According to the available literature, tricyclic antidepressants and duloxetine demonstrate an ability to provide pain relief in patients with painful diabetic neuropathy. While pregabalin and valproate have both demonstrated usefulness in the management of diabetic neuropathy, available literature suggests that the utility of gabapentin is less certain. There is minimal evidence evaluating the use of topical lidocaine for the management of painful diabetic neuropathy. Strong opioids have demonstrated efficacy compared to placebo; however, prescribers may consider this as last line therapy due to concerns regarding long-term safety, including addiction potential and misuse (*Attal et al 2010, Feldman et al 2019, Schwartz et al 2011*).
  - Of the neuropathic pain and fibromyalgia agents included in the review, duloxetine, pregabalin, pregabalin ER, and tapentadol ER are approved for the management of diabetic neuropathy.
- For the management of PHN, available literature demonstrates that tricyclic antidepressants, gabapentin, pregabalin, opioids, topical capsaicin, botulinum toxin, and topical lidocaine are more effective compared to placebo (*Bajwa et al 2019*).
  - Of the neuropathic pain and fibromyalgia agents included in this review, gabapentin ER, gabapentin enacarbil ER, lidocaine, pregabalin, pregabalin ER, gabapentin, and capsaicin are approved for the management or relief of pain associated with PHN.
- For the management of fibromyalgia, available literature demonstrates that amitriptyline, cyclobenzaprine, duloxetine, gabapentin, milnacipran, and pregabalin are all appropriate treatment options. The choice of therapy is guided by specific symptoms, comorbidities, and patient preference (*Goldenberg 2018*).

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Publication Date: March 23, 2020

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 2020b*).
  - 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 2020a*).
- 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).
- 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)	-
Adhansia XR (methylphenidate HCl ER)	-
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)	✔

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020, Facts & Comparisons 2020*)

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)	Adhansia XR, 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 2020*, *Adderall XR 2019*, *Adhansia XR 2019*, *Adzenys ER 2017*, *Adzenys XR-ODT 2018*, *Aptensio XR 2019*, *Concerta 2017*, *Cotempla 2017*, *Daytrana 2019, Desoxyn 2019, Dexedrine Spansule 2019*, *Dyanavel XR 2019*, *Evekeo 2019*, *Evekeo ODT 2019*, *Focalin 2019*, *Focalin XR 2019*, *Intuniv 2019, Jornay PM 2019, Kapvay 2020, Mydayis 2019, Methylin Oral Solution 2017, methylphenidate chewable tablets 2019, methylphenidate ER 2019, methylphenidate ER (CD) 2018, ProCentra 2017*, *QuilliChew ER 2018*, *Quillivant XR 2018*, *Ritalin 2019*, *Ritalin LA 2019*, *Strattera 2020*, *Vyvanse 2018, Zenzedi 2019*)

* Adderall, Evekeo, ProCentra, and Zenzedi are approved for use in children 3 years of age and older. Adhansia XR, 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 (amphetamine sulfate) was approved based on a randomized, double-blind (DB), multicenter (MC), placebo-controlled (PC) laboratory classroom study that was conducted in 107 children between the ages of 6 and 12 years (*Childress et al 2015*). The study found Evekeo to be associated with significant improvements in the average Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) combined score compared to placebo (least squares [LS] mean difference -7.9; 95% CI, -10.1 to -5.6; $p < 0.0001$).
    - 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 (*Childress et al 2015*).
  - Cotempla XR-ODT, a new methylphenidate ER orally disintegrating tablet formulation, was approved based on a randomized, DB, MC, PC laboratory classroom study (*Childress et al 2017*) (N = 87) which found that the average SKAMP-combined score was significantly better for Cotempla XR-ODT than for placebo (LS mean 14.3 [95% CI, 12.2 to 16.4] vs 25.3 [9% CI, 23.0 to 27.6], respectively, $p < 0.0001$).
  - Adhansia XR, a recently approved methylphenidate ER capsule, was approved via the 505(b)(2) regulatory pathway, and its efficacy was supported by 4 clinical studies in patients with ADHD including 2 studies conducted in adults, 1 study in adolescents 12 to 17 years of age, and 1 study in pediatric patients 6 to 12 years of age (*Adhansia XR FDA Clinical Review 2019):*
    - One randomized, DB, MC, PC 4-week study conducted in 368 adult patients with ADHD evaluated the safety and efficacy of 4 doses of Adhansia XR (25 mg, 45 mg, 70 mg, and 100 mg) compared to placebo. The primary

endpoint, change in the ADHD-Rating Scale (ADHD-RS)-5 total score from baseline to Week 5, was significantly improved compared to placebo in the Adhansia XR 45 mg group (LS mean difference, -6.9; 95% CI, -11.5 to -2.2; p = 0.0013), 100 mg group (LS mean difference, -8.1; 95% CI, -12.9 to -3.2; p = 0.0002), and when combining all dosage groups compared to placebo (LS mean difference, -4.7; 95% CI, -7.7 to -1.6; p = 0.0026). No significant difference was seen in the 25 mg or 70 mg groups compared to placebo.

- A second randomized, DB, crossover, PC study was conducted in 45 adults in an adult workplace environment. The study aimed to assess efficacy parameters for Adhansia XR vs placebo over 16 hours post-dose. Patients were titrated to an optimal dose of Adhansia XR (either 25, 35, 45, 55, 70, 85, or 100 mg) during an open-label (OL) treatment period between 2 and 7 weeks, then entered into a 1-week PC, DB treatment phase prior to the adult workplace environment session, followed by a 7-day washout period between crossover periods, then another 1-week treatment phase followed by another adult workplace environment session. The primary endpoint was the average Permanent Product Measure of Performance (PERMP) score for various time points up to 16 hours post-dose. When combining data from all time points, patients treated with Adhansia XR had significant improvements in the PERMP score compared to placebo (LS mean difference, 13.05; 95% CI, 3.88 to 22.23; p = 0.0064).
- A 4-week randomized, DB, PC trial assessed efficacy of Adhansia XR in 354 adolescent patients 12 to 17 years of age. The study compared Adhansia XR 25, 45, 70, and 85 mg to placebo and found significant improvements in the ADHD-5-RS score from baseline to Week 5 in adolescents treated with Adhansia XR 45 mg (LS mean difference, -5.4; 95% CI, -9.2 to -1.6; p = 0.0052), 70 mg (LS mean difference, -5.2; 95% CI, -9.0 to -1.4; p = 0.0069), and when combining all dosage groups compared to placebo (LS mean difference, -4.3; 95% CI, -7.3 to -1.3; p = 0.0049). Adolescents treated with Adhansia XR 25 or 85 mg did not achieve significant improvements in the ADHD-5-RS score compared to placebo.
- A fourth study, which included a 6 week OL dose optimization period (majority of patients received between 45 and 55 mg of Adhansia XR) followed by a 1- week DB PC study, was conducted to assess the efficacy of Adhansia XR in 147 children 6 to 12 years of age in an analog classroom setting. The primary endpoint, average SKAMP-C score (taken at various time points up to 13 hours post-dose), was significantly improved in children treated with Adhansia XR compared to placebo (LS mean difference, -8.6; 95% CI, -10.6 to -6.6).

- 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 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 2019*). 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 (LS mean difference -5.9; 95% CI, -9.1 to -2.7).
  - A randomized, DB, MC, PC, parallel group, forced-dose titration trial was 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 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-RS score, PERMP score) (*Mydayis Prescribing Information 2019, Weisler et al 2017, Wigal et al 2018a, Wigal et al 2018b, Wigal et al 2019*) (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 2020a*, *AAP 2019).*
  - 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 (2019), 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 (2020) 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 to 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.
  - 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:
  - Patients should be treated with a structured behavioral/lifestyle program, combined with CBT or other psychological interventions
  - 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.
    - Adhansia XR capsules contain FD&C yellow No. 5 dye (tartrazine), which may cause allergic-type reactions in susceptible patients.
- 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 a 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)	10 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)	10 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

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
					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 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

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
					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	
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

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
					thoroughly before swallowing. A single dose should not be divided.
Desoxyn (methamphetamine)	3 to 5 h	Tablets	Oral	Daily to twice daily	
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. The ER tablets must be swallowed whole and never crushed or chewed.
Methylphenidate ER	3 to 8 h	Tablets			
Adhansia XR (methylphenidate ER)	13 to 16 h	Capsules	Oral	Daily in the morning	The capsules may be taken whole or they can be opened and sprinkled onto applesauce or yogurt; the entire contents of the mixture should be consumed within 10 minutes, and should not be chewed. The dose of a single capsule should not be divided.
Aptensio XR (methylphenidate ER)	12 h	Capsules	Oral	Daily in the morning	The capsules may be taken whole or they can be opened and

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
					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 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*).
Methylphenidate ER					
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

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
					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 capsule 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.
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.

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
					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 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.

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
					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 2020, Pharmacist's Letter 2016, Krull 2020a*

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 2019*).
- 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 2020a*).
- 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 2020*).
- 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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Publication Date: June 17, 2020

OPTUMRx

Therapeutic Class Overview
Respiratory Beta-Agonists

INTRODUCTION

- Respiratory beta$_2$-agonists are primarily used to treat reversible airway disease. They are Food and Drug Administration (FDA)-approved for the treatment of asthma, chronic obstructive pulmonary disease (COPD), exercise-induced asthma/bronchospasm, and/or reversible bronchospasm.
- Asthma is a chronic lung disease that inflames and narrows the airways, making it difficult to breathe. 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 2018, asthma affected an estimated 19.2 million adults and 5.5 million children in the United States (U.S.). The exact cause(s) of asthma are unknown. A combination of factors such as genetics, certain respiratory infections during childhood, and contact with airborne allergens can contribute to its development. Most patients with asthma have allergies (*Centers for Disease Control and Prevention [CDC] 2020, National Heart, Lung, and Blood Institute [NHLBI] Web site*).
- Current pharmacologic options for asthma management are categorized as: (1) control medications to achieve and maintain control of persistent asthma or prevent exacerbations, and (2) quick-relief medications used to treat acute symptoms and exacerbations (*NHLBI 2007, Global Initiative for Asthma [GINA] 2020*).
  - Control medications include:
    - Corticosteroids (inhaled corticosteroids [ICSs], or oral corticosteroids for severe exacerbations)
    - Long-acting beta$_2$-agonists (LABAs)
    - Leukotriene receptor antagonists (LTRAs)
    - Methylxanthines (ie, theophylline)
    - Cromolyn sodium and nedocromil
    - Add-on immunomodulators (ie, omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab) in patients with severe asthma
    - Add-on tiotropium in patients whose asthma is not well-controlled with ICS/LABA
    - Add-on azithromycin in patients whose asthma is not well-controlled with moderate-high dose ICS/LABA
  - Quick-relief/reliever medications include:
    - Short-acting beta$_2$-agonists (SABAs) for relief of acute symptoms and prevention of exercise-induced bronchospasm
    - ICS-formoterol (per GINA recommendations on the basis of the safety concerns about SABA-only treatment and the fact that ICS and ICS/LABA already have an effective safety record)
    - Anticholinergics (ie, ipratropium bromide) as an alternative bronchodilator for those not tolerating a SABA
    - Systemic corticosteroids, although not short-acting, are used for moderate and severe exacerbations as part of initial treatment.
  - In recent years, additional medications have been made available for select subsets of patients with asthma, including the interleukin-5 (IL-5) antagonists benralizumab, mepolizumab, and reslizumab, and the interleukin-4 (IL-4) antagonist dupilumab, for the management of severe asthma with an eosinophilic phenotype (*Prescribing information: Cinqair 2020, Dupixent 2019, Fasenra 2019, Nucala 2019*). Additionally, tiotropium, long used for COPD, has been FDA-approved for the treatment of asthma (*Spiriva Respimat prescribing information 2019*).
  - ICSs are the most effective and most commonly recommended long-term control medications used for the treatment of asthma. The updated 2020 GINA Report on Global Strategy for Asthma Management and Prevention recommends initial treatment based on a patient's presenting symptoms. Step 1 therapy (for patients with infrequent asthma symptoms) includes preferred controller therapy with low dose ICS-formoterol, with adjustments to the dose of ICS based on control of asthma symptoms (*GINA 2020*).
  - LABAs should not be used as monotherapy for the management of asthma due to increased risk for serious adverse events, including death; however, they can be used as adjunctive therapy in patients who are not adequately controlled with an ICS alone (*GINA 2020, NHLBI 2007*).
  - SABA-only treatment (without an ICS) is no longer recommended by GINA; a low dose ICS should be taken whenever a SABA is taken. In adults and adolescents, low dose ICS-formoterol is the preferred reliever medication, while as-needed SABAs are the only option for reliever medications in children (*GINA 2020*).

- Theophylline and mast-cell stabilizers have weak to low efficacy in asthma. Theophylline has an unfavorable side-effect profile and may be life-threatening at high doses. Mast-cell stabilizers have a more favorable safety profile. Tiotropium is an option for add-on therapy in patients ≥ 6 years of age with a history of exacerbations. Azithromycin may be added in patients experiencing symptomatic asthma despite using ICS and LABA. An IL-5, IL-4, or immunoglobulin E (IgE) antagonist may be added if patients require a higher level of care. Omalizumab, an IgE antagonist, is used in patients with moderate to severe allergic asthma while IL-5 antagonists are used for severe eosinophilic asthma (*GINA 2020, NHLBI 2007*).

- 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. Airflow limitation is caused by a combination of small airway disease (eg, obstructive bronchiolitis) and parenchymal destruction (emphysema); the relative contributions of each component vary between patients. The most common symptoms of COPD include dyspnea, cough, and sputum production (*Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2020a*).
  - COPD affects 6.4% of the U.S. population and is a major contributor to mortality from chronic lower respiratory diseases, the fourth leading cause of death in the U.S. (*CDC 2019*). Globally, COPD is responsible for 3 million deaths annually and is expected to cause 5.4 million annual deaths by 2060; the burden of COPD continues to increase due to continued exposure to risk factors and aging of the population (*GOLD 2020a*).
  - Cigarette smoking is the main risk factor for COPD; other risk factors include biomass fuel exposure (such as from cooking and heating in poorly ventilated dwellings) and air pollution. Host factors such as genetic abnormalities, abnormal lung development, and accelerated aging can predispose individuals to COPD development (*GOLD 2020a*).
  - Patients with COPD may experience exacerbations, which are periods of acute worsening of respiratory symptoms (*GOLD 2020a*).
  - Pharmacologic therapy for COPD can reduce symptoms, reduce the frequency and severity of exacerbations, and improve patients' health status and exercise tolerance. There is no conclusive evidence that COPD medications modify the long-term decline in lung function characteristics of COPD (*GOLD 2020a*).
  - Pharmacologic options for COPD treatment comprise several classes, including beta$_2$-agonists, anticholinergics, methylxanthines, ICSs, various combination products, antibiotics, mucolytic agents, and the phosphodiesterase (PDE)-4 inhibitor, roflumilast. Pharmacologic treatments should be individualized based on symptom severity, risk of exacerbations, side effects, comorbidities, drug availability, and cost, as well as the patient's response, preference, and ability to use various drug delivery devices (*GOLD 2020a*).
  - Inhaled bronchodilators are central to COPD symptom management and are usually administered on a regular basis to prevent or reduce symptoms. Several short-acting and long-acting inhaled bronchodilators are available. Long-acting muscarinic antagonists (LAMAs) and LABAs are preferred over short-acting agents except for patients with only occasional dyspnea, and for immediate relief of symptoms in patients already receiving long-acting bronchodilators for maintenance therapy (*GOLD 2020a*).
  - Beta$_2$-agonists differ in their dosing requirements, pharmacokinetic parameters, and potential adverse effects. Several of the SABAs are available generically in at least 1 strength or formulation; however, there are no generic formulations for the LABAs.
- This review includes the single-agent inhaled and oral beta$_2$-agonists. Although several agents are also available in combination inhalers along with an ICS or an anticholinergic, the combination products are not included in this review.
  - Tables in this review are organized by whether the drug product is short- or long-acting. Note that extended-release albuterol is categorized as short-acting for the purposes of this review, along with the other albuterol products.
- Medispan class/subclass: Respiratory sympathomimetics/beta adrenergics

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Short-acting beta$_2$-agonists (SABAs) (oral and inhaled)	
albuterol inhalation aerosols and powder (ProAir HFA, ProAir Digihaler dry powder inhaler*, ProAir RespiClick dry powder inhaler, Proventil HFA, Ventolin HFA)	-†
albuterol solution for nebulization	✔
albuterol, oral tablets, extended-release tablets, and syrup	✔
levalbuterol inhalation aerosol (Xopenex HFA and generic)	-‡
levalbuterol solution for nebulization (Xopenex and generics)	✔

Drug	Generic Availability
metaproterenol syrup	✔
terbutaline, oral tablets and injection	✔
Long-acting beta$_2$-agonists (LABAs) (inhaled)§	
Arcapta Neohaler (indacaterol) inhalation powder	-
Brovana (arformoterol) solution for nebulization	-
Perforomist (formoterol) solution for nebulization‖	-
Serevent Diskus (salmeterol) inhalation powder	-
Striverdi Respimat (olodaterol) inhalation spray	-

Abbreviation: HFA = hydrofluoroalkane
*ProAir Digihaler is a digital dry powder inhaler with built-in sensors to detect when it is used and to measure inspiratory flow, and is designed to be used with a companion mobile app. It has not yet launched at the time of this review but is expected to become commercially available in 2020.
†No A-rated generics have been approved by the FDA for Proventil HFA or Ventolin HFA; however, authorized generics are available for these products. Two A-rated generics for ProAir HFA were approved in early 2020. No generics are available for ProAir Digihaler or ProAir RespiClick.
‡No A-rated generics are approved by the FDA for Xopenex-HFA; however, a generic product is available for this product.
§The inhaled LABA, Arcapta Neohaler (indacaterol), was discontinued by the manufacturer effective April 1, 2020 for business reasons (*OINDP news 2020*). At the time of this review, Arcapta Neohaler was active in Medispan.
‖Formoterol was previously available as a dry powder inhaler (Foradil Aerolizer); however, this formulation is no longer marketed.

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Generic Name	Treatment and/or prevention of bronchospasm in patients with asthma/reversible obstructive airway disease	Prevention of exercise-induced bronchospasm	Maintenance treatment of bronchoconstriction/ airflow obstruction in patients with COPD	Treatment of reversible bronchospasm occurring in association with emphysema and bronchitis
Short-acting beta$_2$-agonists				
albuterol	✔ *	✔ *†		
levalbuterol	✔ ‡			
metaproterenol	✔			✔
terbutaline	✔ §			✔ §
Long-acting beta$_2$-agonists				
arformoterol			✔	
formoterol			✔	
indacaterol			✔ **	
olodaterol			✔ **	
salmeterol	✔ ‖ ¶	✔ ¶	✔	

Abbreviations: COPD = chronic obstructive pulmonary disease; HFA = hydrofluoroalkane
*Age ≥ 4 years (HFA inhalation aerosols and dry powder inhaler); age ≥ 2 (solution for nebulization); age ≥ 2 years (syrup); age ≥ 6 years (tablets and extended-release tablets)
†Inhalation aerosols and dry powder inhalers only
‡Age ≥ 4 years (Xopenex HFA); age ≥ 6 years (Xopenex inhalation solution)
§Age ≥ 12 years
‖Only as a concomitant therapy with a long-term asthma control medication, such as an ICS
¶Age ≥ 4 years
**Indicated for long-term, once-daily maintenance treatment

(*Prescribing information: albuterol solution 2017, albuterol syrup 2016, albuterol tablets 2019, albuterol extended-release tablets 2015, Arcapta Neohaler 2019, Brovana 2019, metaproterenol syrup 2019, Perforomist 2019, ProAir HFA 2019, ProAir Digihaler 2019, ProAir RespiClick 2018, Proventil HFA 2018, Serevent Diskus 2020, Striverdi Respimat 2019, terbutaline injection 2011, terbutaline tablets 2018, Ventolin HFA 2019, Xopenex HFA 2017, Xopenex inhalation solution 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

- Clinical trials have demonstrated the efficacy of SABAs and LABAs in providing relief from asthma exacerbations, COPD exacerbations and exercise-induced asthma (EIA).

SABAs: Asthma and COPD

- In the clinical trials that evaluated SABAs for the treatment of mild asthma, all SABAs have been shown to be efficacious in improving forced expiratory volume in 1 second (FEV_1). In the clinical trials that compared albuterol to levalbuterol, inconsistent results were found (*Carl et al 2003, Gawchik et al 1999, Milgrom et al 2001, Nelson et al 1998, Nowak et al 2004, Nowak et al 2006, Qureshi et al 2005, Schreck et al 2005, Sepracor Trial 1, Sepracor Trial 2, Skoner et al 2001*).
  - In 2 studies (1 retrospective, 1 prospective), levalbuterol resulted in a significantly lower hospitalization rate compared to albuterol (*Carl et al 2003, Schreck et al 2005*).
  - In another trial, when the 2 agents were given in the emergency department, there was no significant difference in the time to discharge (*Skoner et al 2001*).
  - *Nowak et al* also reported that there was no difference in the time to discharge from the emergency room with albuterol compared to levalbuterol (76 and 78.5 minutes; p = 0.74) (*Nowak et al 2006*).
  - Overall, studies have shown no significant differences between the 2 agents in the peak change in FEV_1 and the number and incidence of adverse events experienced (*Carl et al 2003, Gawchik et al 1999, Milgrom et al 2001, Nelson et al 1998, Nowak et al 2004, Nowak et al 2006, Qureshi et al 2005, Schreck et al 2005, Sepracor Trial 1, Sepracor Trial 2, Skoner et al 2001*).
    - In an unpublished study, the difference in peak FEV_1 was statistically significant for albuterol hydrofluoroalkanes (HFA) compared to levalbuterol HFA (p = 0.018) (*Sepracor Trial 2*).
- Albuterol dry powder inhaler (ProAir RespiClick) was compared to placebo dry powder inhaler in patients with asthma maintained on ICS treatment (*Raphael et al 2014*). Patients treated with albuterol dry powder inhaler had significantly improved FEV_1 area under the curve compared to placebo. In patients with exercise-induced bronchoconstriction undergoing treadmill exercise challenge, placebo-treated patients had a greater decrease in FEV_1 compared with albuterol dry powder inhaler-treated patients (*Ostrom et al 2014*). In a cumulative-dose, crossover study, albuterol dry powder inhaler (ProAir RespiClick) was compared with albuterol HFA with similar between-group improvements in FEV_1 at 30 minutes (*Miller et al 2014*). Additionally, albuterol dry power inhaler (ProAir RespiClick) demonstrated favorable FEV_1 improvement in EIA compared to placebo in a crossover study (*Ostrom et al 2015*). Approval of ProAir Digihaler was based on efficacy data from studies with ProAir RespiClick (*ProAir Digihaler prescribing information 2019*).

LABAs: Asthma

- The LABAs salmeterol and formoterol have been found to improve FEV_1 in patients with mild to moderate asthma who require persistent use of SABAs. However, the SMART trial found that salmeterol had significant occurrences of combined respiratory-related deaths or respiratory-related life-threatening experiences compared to placebo ($p < 0.05$) (*Nelson et al 2006*). In a meta-analysis, salmeterol and formoterol both demonstrated an increase in severe exacerbations that required hospitalization, life-threatening exacerbations and asthma-related deaths in adults and children alike when compared to placebo (*Salpeter et al 2006*). Due to the results of these studies, all LABAs have a boxed warning stating that these agents may increase the risk of asthma-related death.

LABAs: COPD

- A systematic review concluded that in patients with COPD, there was no difference in the rate of mild exacerbations between patients treated with an ICS or LABA (odds ratio, 1.63; 95% confidence interval [CI], 0.49 to 5.39) or in the rate of moderate or severe COPD exacerbations (rate ratio, 0.96; 95% CI, 0.89 to 1.02) (*Spencer et al 2011*).
- The safety and efficacy of indacaterol were evaluated in randomized controlled trials that compared it to placebo and other agents used in the management of COPD (*Balint et al 2010, Buhl et al 2011, Chapman et al 2011, Dahl et al 2010, Donohue et al 2010, Feldman et al 2010, Korn et al 2011, Kornmann et al 2011, Magnussen et al 2010, Vogelmeier et al 2010*). Notably, most of these trials evaluated indacaterol in doses of 150, 300 and 600 mcg once daily, rather than the FDA-approved dosing of 75 mcg once daily (*Balint et al 2010, Buhl et al 2011, Chapman et al 2011, Dahl et al 2010, Donohue et al 2010, Feldman et al 2010, Korn et al 2011, Kornmann et al 2011, Magnussen et al 2010, Vogelmeier et al*

2010). However, results from placebo-controlled trials of indacaterol 75 mcg have also been published, lending support to the use of the 75 mcg dose (*Gotfried et al 2012, Kerwin et al 2011*).

- Overall, data from published clinical trials demonstrated that treatment with indacaterol consistently results in significantly higher mean trough FEV_1 after 12 weeks of treatment compared to placebo, formoterol, salmeterol and tiotropium. Patients treated with indacaterol also achieved significant improvements in COPD symptoms, as well as health-related quality of life compared to those treated with placebo. Compared to placebo, indacaterol significantly reduces the use of rescue medications, increases the days of no rescue medication use, and improves diary card-derived symptom variables (eg, nights with no awakenings, days with no daytime symptoms, days able to perform usual activities). In general, treatment with indacaterol is favored over other long-acting bronchodilators for these outcomes, but statistical superiority is not consistently achieved (*Balint et al 2010, Buhl et al 2011, Chapman et al 2011, Dahl et al 2010, Donohue et al 2010, Feldman et al 2010, Gotfried et al 2012, Kerwin et al 2011, Korn et al 2011, Kornmann et al 2011, Magnussen et al 2010, Vogelmeier et al 2010*). Recent meta-analyses comparing indacaterol to tiotropium and to twice-daily LABAs (salmeterol or formoterol) demonstrated that patients treated with indacaterol had higher trough FEV_1 and greater improvements in the use of rescue medications and achieving improvements in dyspnea and health status compared to the alternative treatments. However, the trials included in this meta-analysis used indacaterol doses higher than FDA-approved daily doses of 75 mcg (*Cope et al 2013, Rodrigo et al 2012*).
- Placebo-controlled trials demonstrate that within 5 minutes after administration of indacaterol, significant improvements in bronchodilation are achieved (*Balint et al 2010, Donohue et al 2010, Gotfried et al 2012, Kerwin et al 2011, Magnussen et al 2010, Vogelmeier et al 2010*). These results have also been observed when comparing indacaterol to salmeterol, salmeterol/fluticasone, and tiotropium (*Buhl et al 2011, Korn et al 2011, Vogelmeier et al 2010*).
- In 2 studies, patients diagnosed with COPD were treated with arformoterol, salmeterol, or placebo. These studies found that both arformoterol and salmeterol significantly improved morning trough FEV_1 throughout the 12 weeks of daily treatment compared to placebo ($p < 0.001$ in both trials) (*Baumgartner et al 2007, Sepracor, 2005*). In a head-to-head study against salmeterol, formoterol was associated with a greater change from baseline in FEV_1 at 5 minutes post-dose on day 28 ($p = 0.022$) (*Cote et al 2009*). Currently, there is a lack of head-to-head randomized, double-blind clinical trials to determine a preferential status of one agent over another for the treatment of COPD.
- Two replicate, multicenter, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 studies investigated the long-term efficacy and safety of once-daily olodaterol via Respimat soft-mist inhaler vs placebo and formoterol over 48 weeks in patients with moderate to very severe COPD receiving usual-care background therapy. Patients were randomized to receive once-daily olodaterol 5 or 10 mcg, twice-daily formoterol 12 mcg, or placebo. Co-primary endpoints were FEV_1 area under the curve from 0 to 3 hours (AUC_{0-3}), trough FEV_1, and Mahler transition dyspnea index (TDI) total score after 24 weeks. Overall, in Study 1222.13 (N = 904) and Study 1222.14 (N = 934), patients who received treatment with olodaterol had significantly improved FEV_1 AUC_{0-3} vs placebo in both studies ($p < 0.0001$ for all comparisons) and trough FEV_1 vs placebo ($p < 0.01$). Formoterol also showed statistically significant differences in both Study 1222.13 ($p < 0.01$) and Study 1222.14 ($p < 0.05$) (*Koch et al 2014*).
- Two replicate, randomized, double-blind, placebo-controlled, parallel-group, Phase 3 trials investigated the long-term safety and efficacy of olodaterol in patients with moderate to very severe COPD receiving usual-care background therapy. Patients received olodaterol 5 mcg or 10 mcg or placebo once daily for 48 weeks. Co-primary endpoints were FEV_1 AUC_{0-3} (change from baseline) and trough FEV_1 at 12 weeks. Overall, Study 1222.11 (N = 624) and Study 1222.12 (N = 642) showed that olodaterol 5 mcg and 10 mcg significantly improved the FEV_1 AUC_{0-3} response ($p < 0.0001$) and trough FEV_1 (Study 1222.11, $p < 0.0001$; Study 1222.12, $p < 0.05$, post hoc) at week 12. The incidence of adverse events was comparable with that of placebo (*Ferguson et al 2014*).
- Two replicate, multicenter, randomized, double-blind, double-dummy, placebo-controlled, 4-way cross-over group, Phase 3 studies investigated the long-term efficacy and safety of once-daily olodaterol via Respimat soft-mist inhaler vs placebo and formoterol over 6 weeks in patients with moderate to very severe COPD receiving usual-care background therapy. Patients were randomized to receive once-daily olodaterol 5 or 10 mcg, twice-daily formoterol 12 mcg, or placebo. Co-primary endpoints were FEV_1 area under the curve from 0 to 12 hours (AUC_{0-12}) and FEV_1 area under the curve from 12 to 24 hours (AUC_{12-24}) after 6 weeks. Overall, in Study 1222.24 (N = 99) and Study 1222.25 (N = 100), patients who received treatment with both doses of olodaterol and formoterol had significantly improved FEV_1 profiles (co-primary endpoints of FEV_1 AUC_{0-12} and FEV_1 AUC_{12-24} and the key secondary endpoint [FEV_1 AUC_{0-24}]) vs placebo in both studies (for all comparisons $p < 0.0001$). No statistically significant differences were reported between the 3 active comparators (*Feldman et al 2014*).

- A meta-analysis that compared LABAs (salmeterol, formoterol, and indacaterol) to tiotropium demonstrated that tiotropium was more effective than LABAs as a group in preventing COPD exacerbations and disease-related hospitalizations. However, overall hospitalization rates, mortality, symptom improvement, and changes in lung function were similar among groups (*Chong et al 2012*). Another meta-analysis compared the use of LABAs plus tiotropium to the use of either LABAs alone or tiotropium alone. The analysis demonstrated that there was a significant improvement in FEV_1 with combination therapy compared to tiotropium alone. There was also a small mean improvement in health-related quality of life for patients receiving a LABA plus tiotropium compared to tiotropium alone, but the clinical significance of this small difference is unclear. Hospital admissions and mortality were not significantly different between groups. Data comparing LABA plus tiotropium to LABA alone were somewhat limited, but demonstrated a significant improvement in health-related quality of life, FEV_1 and exacerbations (*Farne et al 2015*).

EIA

- For the treatment of EIA, albuterol, metaproterenol, and formoterol have demonstrated an improvement in FEV_1 compared to placebo (*Berkowitz et al 1986, Bonini et al 2013, Edelman et al 2000, Richter et al 2002, Shapiro et al 2002, Storms et al 2004*).
  - In 1 study, albuterol- and metaproterenol-treated patients had a lower incidence of exercise-induced bronchospasm compared to placebo (*Cote et al 2009*).
  - In another study comparing albuterol, formoterol and placebo for EIA, both active treatment groups provided a statistically significant decrease in mean maximum percent of FEV_1 compared to placebo ($p < 0.01$) (*Shapiro et al 2002*).

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 ICSs, 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. ICSs 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 ICSs 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 2020 GINA report also provides a stepwise approach to asthma management. It recommends as-needed low-dose ICS-formoterol as a preferred controller to prevent exacerbations and control asthma symptoms in adult or adolescent patients with infrequent asthma symptoms (eg, < twice a month). If patients remain uncontrolled, an ICS or ICS/LABA is the next preferred controller options. The choice of a specific dose and combination depends on the age of the patient and step within the therapy. As-needed ICS-formoterol is also the preferred reliever medication for adults and adolescents, while as-needed SABAs are the only option for reliever medications in children; of note, a low dose ICS should be taken whenever a SABA is taken. At the highest step, the patient should be referred for add-on treatment (eg, tiotropium, azithromycin, omalizumab, mepolizumab, benralizumab, reslizumab, dupilumab) (*GINA 2019, GINA 2020*).
- The 2020 GINA report provides interim guidance on the management of asthma in the context of the coronavirus disease 2019 (COVID-19) pandemic. Patients with asthma should continue their prescribed asthma medications, including ICS with or without LABA and add-on therapies, during the pandemic. Use of nebulizers should be avoided when possible to prevent transmission of the virus to other patients or healthcare workers (*GINA 2020*).
- In 2019, recommendations were published in the Annals of Allergy, Asthma, and Immunology (AAAI) for stepping down asthma controller therapy in patients whose asthma has been well-controlled, based on the stepwise approach to asthma treatment. For steps 2 through 5, the authors provided specific recommendations for stepping down therapy to a step below the patient's current level of care. In general, step-down strategies at each level recommend lowering the

dose of the ICS as an initial strategy; however, implementation of a step-down in treatment will vary, and patient-specific factors must be considered (*Chipps et al 2019*).

- A European Respiratory Society/American Thoracic Society guideline on the management of severe asthma recommends the addition of tiotropium for patients with uncontrolled asthma despite GINA step 4 or 5 or NAEPP step 5 therapy, and a trial of chronic macrolide therapy to reduce exacerbations in patients who require additional control despite GINA step 5 or NAEPP step 5 therapy (*Holguin et al 2020*).

COPD

- The 2020 GOLD guidelines state that the management strategy for stable COPD should be predominantly based on an assessment of the patient's symptoms and future risk of exacerbations; the risk of exacerbations is based on a patient's exacerbation history. Of note, the 2020 GOLD guidelines no longer recognize the phrase "asthma-COPD overlap," instead, emphasize that asthma and COPD are unique disease states with some similar signs and symptoms. Key recommendations from the GOLD guidelines are as follows (*GOLD 2020a*):
  - 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, and for immediate relief of symptoms in patients already receiving long-acting bronchodilators for maintenance therapy.
  - 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.
  - 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 ICSs is not recommended. Long-term treatment with ICSs may be considered in association with LABAs for patients with a history of exacerbations despite treatment with long-acting bronchodilators. Long-term treatment with ICS may cause pneumonia in patients with severe disease.
- Treatment recommendations are given for patients with COPD based on their GOLD patient group (see Table 3).
  - 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.
  - 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.
  - Follow-up treatments: The follow-up treatments apply to any patients receiving maintenance treatment irrespective of the patient GOLD group.
    - For persistent dyspnea: The use of 2 bronchodilators is recommended in patients receiving 1 long-acting bronchodilator and experiencing persistent breathlessness or exercise limitation. Patients with persistent dyspnea symptoms on LABA + ICS may benefit from LAMA + LABA + ICS.
    - For exacerbations: Patients with persistent exacerbations on long-acting bronchodilator monotherapy 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 or blood eosinophil count ≥ 300 cells/µL, ICS + LABA is preferred. In patients who develop further exacerbations on LAMA + LABA therapy, alternative pathways include escalation to a LAMA + LABA + ICS if eosinophil count ≥ 100 cells/µL or addition of roflumilast or azithromycin if eosinophil count < 100 cells/µL. In patients with additional exacerbations on LABA + ICS, patients should try LAMA + LABA + ICS therapy. 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.

- Patients with COPD should continue their usual therapy, including inhaled or oral corticosteroids during the coronavirus disease 2019 (COVID-19) pandemic (*GOLD 2020b*).

Table 3. Assessment of symptoms and risk of exacerbations to determine GOLD patient group

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 Medical Research Council questionnaire

- Guidelines for the prevention of acute exacerbations of COPD from the American College of Chest Physicians and the Canadian Thoracic Society state that a LAMA is recommended over either a short-acting muscarinic antagonist or a LABA. The guidelines state that certain combination bronchodilators or bronchodilator/ICS combinations may reduce exacerbations, but does not state that any combination is superior to LAMA monotherapy in patients with stable COPD (*Criner et al 2015*).

Exercise-induced bronchoconstriction

- For exercise-induced bronchoconstriction, guidelines from the American Thoracic Society recommend administration of an inhaled SABA 15 minutes prior to exercise. The guidelines also recommend a controller agent added whenever SABA therapy is used at least once daily. Additional guidelines are set forth for patients with symptoms despite using an inhaled SABA before exercise (*Parsons et al 2013*). Joint guidelines from the American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma & Immunology, and the Joint Council of Allergy, Asthma & Immunology state that beta$_2$-agonists (SABAs or LABAs) are most effective at short-term protection against exercise-induced bronchoconstriction and for accelerating recovery from exercise-induced bronchoconstriction. However, daily use of a SABA or LABA will lead to tolerance. Additional or adjunctive options include daily use of leukotriene inhibitors or ICSs, cromolyn sodium before exercise, or ipratropium for patients who have not responded to other agents (*Weiler et al 2016*).

SAFETY SUMMARY

- Contraindications:
  - Serevent Diskus, ProAir Digihaler, and ProAir RespiClick, are contraindicated in patients with a severe hypersensitivity to milk proteins.
  - LABAs should generally not be used as a primary treatment of status asthmaticus or other acute episodes of asthma or COPD that require intensive measures; this is listed as a contraindication for Serevent Diskus.
  - All LABAs are contraindicated for use in patients with asthma without concomitant use of a long-term asthma control medication.
- Key warnings and precautions:
  - Salmeterol has a boxed warning for asthma-related deaths and should be prescribed only as an additional therapy to ICS.
  - All LABAs have a warning describing the increased risk of asthma-related deaths and asthma-related hospitalizations (mainly in pediatric and adolescent patients) when used as monotherapy. The fixed-dose combinations of LABA and ICS do not increase serious asthma-related events compared with ICS alone. The use of a LABA without an ICS is contraindicated in patients with asthma. Patients with COPD do not experience increased mortality with the use of LABAs.
  - Beta$_2$-agonists may also lead to:
    - paradoxical bronchospasm
    - fatalities with excessive use
    - cardiovascular effects such as increased heart rate, blood pressure, and/or electrocardiogram changes
    - central nervous system effects and/or seizures

- LABAs should not be used to treat acute symptoms or initiated in the setting of acutely deteriorating asthma or COPD.

- Adverse events
  - Commonly-reported adverse events (≥ 5% for at least 1 medication in the class) include chest pain, palpitations, tachycardia, dizziness, excitement, fatigue, headache, nervousness, shakiness, somnolence, tremor, rash, diarrhea, nausea, vomiting, pain, asthma exacerbation, bronchitis, cough, influenza, nasal congestion, nasopharyngitis/pharyngitis, respiratory disorder, rhinitis, throat irritation, upper respiratory tract infection, viral respiratory infection, accidental injury, fever, and viral infection.
- Albuterol solution, syrup, tablets, and extended-release tablets, metaproterenol, terbutaline injection, and indacaterol are Pregnancy Category C; arformoterol, levalbuterol, ProAir HFA, Proventil HFA, ProAir Digihaler, ProAir HFA, ProAir RespiClick, Ventolin HFA, formoterol, olodaterol, salmeterol, and terbutaline tablets are not assigned a Pregnancy Category.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Generic Name	Available Formulations	Route	Usual Recommended Frequency	Comments
Short-acting beta$_2$-agonists				
albuterol	Inhalation: metered dose aerosol inhaler (HFA), metered dose dry powder inhaler, solution for nebulization Oral: extended-release tablets, syrup, tablets	Inhalation, oral	Treatment or prevention of bronchospasm in patients with asthma: • Aerosol/dry powder inhaler: 1 to 2 inhalations every 4 to 6 hours • Solution for nebulization: 3 to 4 times daily • Extended-release tablets: twice daily • Syrup, tablets: 3 to 4 times daily Exercise-induced bronchospasm: • Aerosol/dry powder inhaler: 2 inhalations 15 to 30 minutes before exercise	
levalbuterol	Metered dose aerosol inhaler (HFA), solution for nebulization	Inhalation	Treatment or prevention of bronchospasm in patients with asthma: • Aerosol inhaler: 1 to 2 inhalations every 4 to 6 hours • Solution for nebulization: 3 times daily	
metaproterenol	Syrup	Oral	3 to 4 times daily	
terbutaline	Injection, tablets	Subcutaneous injection, oral	• Injection: 1 subcutaneous injection, may repeat in 15 to 30 minutes if improvement does not occur; maximum, 0.5 mg in 4 hours • Tablets: 3 times daily, 6 hours apart	Injection: Safety and efficacy in children < 12 years of age have not been established.
Long-acting beta$_2$-agonists				
arformoterol	Solution for nebulization	Inhalation	Twice daily	Safety and efficacy in children have not been established.

Generic Name	Available Formulations	Route	Usual Recommended Frequency	Comments
formoterol	Solution for nebulization	Inhalation	Twice daily	Safety and efficacy in children have not been established.
indacaterol	Capsule for inhalation	Inhalation	Once daily	Safety and efficacy in children have not been established.
olodaterol	Inhalation spray	Inhalation	Once daily	Safety and efficacy in children have not been established.
salmeterol	Dry powder inhaler	Inhalation	Treatment or prevention of bronchospasm in patients with asthma/maintenance treatment of bronchoconstriction in COPD 1 inhalation twice daily Exercise-induced bronchospasm: 1 inhalation at least 30 minutes before exercise; at least 12 hours should elapse between doses	

Abbreviations: COPD = chronic obstructive pulmonary disease; HFA = hydrofluoroalkane

See the current prescribing information for full details.

CONCLUSION

- Single-entity respiratory beta$_2$-agonist agents are FDA-approved for the treatment of asthma, COPD, reversible airway obstruction and/or exercise-induced bronchospasm.
  - Beta$_2$-agonists are classified as short- or long-acting based on their onset and duration of action, and are available in various dosage forms, including solution for nebulization, aerosol inhaler, dry powder inhaler, oral solution, immediate- and extended-release tablets, and solution for injection.
  - SABAs are generally dosed multiple times per day for the treatment or prevention of symptoms.
  - LABAs are typically administered twice daily for COPD, with the exception of indacaterol and olodaterol, which are administered once daily.
- Overall, SABAs have demonstrated similar efficacy and safety. Similarly, for LABAs, head-to-head clinical trials have not determined the superiority of any one agent.
- All LABAs (salmeterol also has a boxed warning) have a warning describing the increased risk of asthma-related deaths and asthma-related hospitalizations (mainly in pediatric and adolescent patients) when used as monotherapy.
  - In the treatment of asthma, LABAs should not be used as monotherapy, but rather added on to another long-acting controller medication such as an ICS.
- According to GINA and NHLBI guidelines, as-needed SABAs may provide symptomatic relief in patients with asthma, including children, adolescents, and adults. The GINA guideline advises against the use of SABAs without ICS; a low dose ICS should be taken whenever a SABA is taken. In adults and adolescents, low dose ICS-formoterol is the preferred reliever medication. For chronic management of asthma, the preferred controller options consist of ICS-formoterol (on as-needed basis), ICS, or ICS/LABA depending on the age of a patient and severity of symptoms.
- GOLD guidelines state that inhaled bronchodilators are a key component of COPD treatment, and long-acting agents are generally preferred over short-acting agents for maintenance therapy.
  - Depending on the COPD patient subtype, initial COPD management may include use of a beta$_2$-agonist and/or an anticholinergic agent.

- The majority of the current asthma or COPD treatment guidelines do not recommend the use of one specific inhaled beta$_2$-agonist product over another, except for the GINA guideline which lists low-dose ICS-formoterol as the preferred controller and reliever medication in adults and adolescents.
  - Administration instructions and inhalation devices vary among products and should be considered in product selection.

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Publication Date: June 22, 2020

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 2020*).
  - 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 (SAMHSA) 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 (DATA) 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 [CSAT] 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 2020*).
- 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) SC 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 due to patent infringement claims made by the manufacturer of Suboxone. The current estimated launch date of Cassipa is unknown, and the FDA shows that the product has been discontinued (*Drugs@FDA.gov 2020*).
- 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; Agents for Chemical Dependency

Table 1. Medications for Treatment of Opioid Dependence Included Within Class Review

Drug	Generic Availability
Single-Entity Agents	
Lucemyra (lofexidine) tablet	-
naltrexone hydrochloride (HCl)* tablet	✔
Sublocade (buprenorphine) subcutaneous (SC) injection	-
Subutex (buprenorphine)* sublingual tablet	✔
Vivitrol (naltrexone) intramuscular (IM) 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.
†Generic version not anticipated until 2032.

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

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 (*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, most 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 2019*).
- 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 IM or 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 2020*).
- 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 HCl) auto-injector	-
naloxone HCl* injection	✔
Narcan (naloxone HCl) nasal spray	- †

*Brand name product was discontinued; however, generic formulations are available
†Generic product approved by the FDA, but not yet launched

(*Drugs@FDA 2020, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020*)

INDICATIONS

Table 3. FDA-Approved Indications for Buprenorphine and Buprenorphine/Naloxone Products

Indication	Single-Entity Agents		Combination Products			
	Sublocade (buprenorphine) SC 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 2019, buprenorphine/naloxone sublingual tablets 2019, Bunavail 2019, Sublocade 2019, Suboxone film 2019, Zubsolv 2019*)

Table 4. FDA-Approved Indications for Naltrexone Agents Used in Opioid Dependence

Indication	naltrexone HCl 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 2019*)

Table 5. FDA-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. FDA-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, Weiss 2011, Woody et al 2008*).
- 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. Most studies have demonstrated that buprenorphine-based therapy was as effective as methadone in the management of opioid dependence; however, some newer data suggest that buprenorphine may be superior in this regard (*Bahji et al 2019, Dalton et al 2019*, *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 2015, Petitjean et al 2001, Soyka et al 2008, Strain et al 2011).* In a 2019 meta-analysis (N = 150,235 patients across 32 cohort studies), overall mortality rates were higher with methadone vs buprenorphine; however, when comparing time in-treatment to time out-of-treatment, methadone significantly reduced mortality vs buprenorphine (*Bahji et al 2019*). In another meta-analysis that same year (N = 370,611 patients across 30 studies), buprenorphine demonstrated lower all-cause mortality post-medication assisted therapy (MAT) vs methadone or naltrexone. However, all-cause mortality during MAT was lowest with naltrexone, followed by buprenorphine and methadone (*Ma et al 2019*).
- 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 another 2019 meta-analysis (N = 847 overdose events across 4 studies), there was no statistically significant difference for retention in treatment between patients who received buprenorphine/naloxone vs buprenorphine or methadone alone (*Dalton et al 2019*).
- In a 24-week, Phase 3, double-blind, placebo-controlled, randomized controlled trial (n = 504), the efficacy and safety of multiple SC 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 to 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 negative self-reports 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% [300 mg/100 mg], 29% [300 mg/300mg], and 2% [placebo]) ($p < 0.0001$) *(FDA Advisory Committee Briefing Document, Haight et al 2019)*.
- Extended-release IM 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 IM naltrexone; as a result, in the intention-to-treat analysis, relapse-free survival was lower with extended-release IM naltrexone compared to sublingual buprenorphine/naloxone. However, among patients who were able to successfully initiate treatment, extended-release IM 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 IM 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*). A small, randomized, open-label study (n = 60) found that patients receiving extended-release IM naltrexone were twice as likely to remain in treatment for 6 months compared to patients receiving oral naltrexone (*Sullivan et al 2019*).
- 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 results were found in another placebo-controlled trial *(Fishman et al 2019)*. 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 prescribing 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*).
- A retrospective cohort study including 3,085 patients found that of out-of-hospital naloxone administration improved outcomes for approximately 73% of patients with presumed opioid overdose (*Ashburn et al 2020*).

CLINICAL GUIDELINES

- The American Academy of Pediatrics (AAP), APA, ASAM, CSAT/U.S., 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 [update pending Spring 2020], Kleber et al 2006, Kraus et al 2011, SAMHSA 2019 [update pending], 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 [update pending Spring 2020], VHA 2015).*
  - Use of tapered 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 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 (*Kampman 2015 [update pending Spring 2020], WHO 2014*).
  - 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 with 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 SC injection also has several unique warnings and precautions, including serious harm or death if administered IV (boxed warning); risks associated with treatment of emergent acute pain; and 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 2020*).

- 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 IM 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 IM 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 IM naltrexone has a REMS program due to the risk of severe injection site reactions (*REMS@FDA 2020*).

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 (including adverse cardiovascular events).
- 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)	SC 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)	IM 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;	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	• 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
	generics equivalent to Suboxone tablet)		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 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	• 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

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			respiratory functions are not obtained. *Children:* • The usual initial dose in children is given IV; a subsequent dose may be administered if the desired degree of clinical improvement is not obtained.	intoxication since absorption may be erratic or delayed.
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) SC 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 moderate-to-severe 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 2020*).
- 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*).
- Most studies have demonstrated that buprenorphine-based therapy was as effective as methadone in the management of opioid dependence; however, some newer data suggest that buprenorphine may be superior in this regard (*Bahji et al 2019, Dalton et al 2019, 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 IM 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 IM 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*). Retention rates with extended-release IM naltrexone are better than those seen with oral naltrexone (*Sullivan et al 2019*).
- 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 IM naltrexone include hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache. Extended-release IM 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 [update pending Spring 2020], Kleber et al 2006, Kraus et al 2011, SAMHSA 2019 [update pending], 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 [update pending Spring 2020], 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 approvals 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 [update pending Spring 2020]*).
  - 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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Publication Date: March 17, 2020