OPTUMRx®

Silver State Scripts Board Meeting

SEPTEMBER 23, 2021

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Agenda

Steve Sisolak
Governor

Richard Whitley, MS
Director

DEPARTMENT OF HEALTH AND HUMAN SERVICES

DIVISION OF HEALTH CARE FINANCING AND POLICY

Helping people. It's who we are and what we do.

Suzanne Bierman, JD MPH
Administrator

REVISED NOTICE OF PUBLIC MEETING – SILVER STATE SCRIPTS BOARD

Date of Posting: ~~August 18, 2021~~
August 31, 2021

Date of Meeting: Thursday, September 23, 2021, 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: Microsoft Teams

OR

https://tinyurl.com/SSSB092321

The physical location for this meeting which is open to the public is at:

Springs Preserve
333 South Valley View Blvd
Las Vegas, NV 89107
(702) 822-7700

Please check with staff to verify room location.

Space is limited at the physical location and subject to any applicable social distancing or mask wearing requirements as may be in effect at the time of the meeting for the county in which the physical meeting is held.

Note: *If at any time during the meeting an individual who has been named on the agenda or has an item specifically regarding them included on the agenda is unable to participate because of technical or other difficulties, please email rxinfo@dhcfp.nv.gov and note at what time the difficulty started so that matters pertaining specifically to their participation may be continued to a future agenda if needed or otherwise addressed.*

Meeting Audio Information: Phone: (952) 222-7450
Event: 999 587 133#

PLEASE DO NOT PUT THIS NUMBER ON HOLD (*hang up and rejoin if you must take another call***)**

YOU MAY BE UNMUTED BY THE HOST WHEN SEEKING PUBLIC COMMENT, PLEASE HANG UP AND REJOIN IFYOU ARE HAVING SIDE CONVERSATIONS DURING THE MEETING

This meeting will be recorded to facilitate note-taking or other uses. By participating you consent to recording of your participation in this meeting.

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. General Public Comment

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 or the meeting's virtual platform as well as in person opportunities, 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 comment may be limited to three minutes per person. ***Note: this guidance applies for all periods of public comment referenced further in the agenda, such as those related to clinical presentations****.*

Public comments may be related to topics on the agenda or matters related to other topics per NRS 241.020(3)(3)(II).

3. Administrative

a. **For Possible Action:** Review and Approve Meeting Minutes from July 29, 2021.
b. Status Update by 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 - 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 – Antilipemics - 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 Psychotropic Agents - ADHD Agents and Psychostimulants Narcolepsy 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 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.

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

a. **For Possible Action:** Discussion and possible adoption of Cardiovascular Agents – Antilipemics - Bile Acid Sequestrants

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 Anti-infective Agents – Aminoglycosides - Inhaled Aminoglycosides.

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 Biologic Response Modifiers – Targeted Immunomodulators and Multiple Sclerosis Agents, Injectable.

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.~~c. **For Possible Action:** Discussion and possible action of Dermatological Agents – Topical Analgesics.

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.~~d. **For Possible Action:** Discussion and possible adoption of Gastrointestinal Agents – Gastrointestinal Enzymes.

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.~~e. **For Possible Action:** Discussion and possible adoption of Hormones and Hormone Modifiers - Antidiabetic Agents - Incretin Mimetics and 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.

~~e.~~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.

~~f.~~g. **For Possible Action:** Discussion and possible adoption of Neurological Agents - Antiparkinsonian Agents - Dopamine Precursors; Neurological Agents - Anti-Migraine Agents - Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists and Serotonin-Receptor Agonists.

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.~~h. **For Possible Action:** Discussion and possible adoption of Ophthalmic Agents - Ophthalmic Antihistamines.

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.~~i. **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.

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. Antihistamines, Antihistamines, H1 blockers, Non-Sedating H1 Blockers.
iii. Anti-infective Agents, 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.

iv. Autonomic Agents, Sympathomimetics, Self-Injectable Epinephrine.

v. Biologic Response Modifiers, Specific Symptomatic Treatment.

vi. Cardiovascular Agents, Antihypertensive Agents, Angiotensin II Receptor Antagonists; Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors); Beta-Blockers; Calcium-Channel Blockers; Vasodilators, Inhaled; Vasodilators, Oral; Antilipemics, Cholesterol Absorption Inhibitors; Fibric Acid Derivatives; Niacin Agents; Omega-3 Fatty Acid.

vii. Dermatological Agents, Antipsoriatic Agents; ~~Topical Analgesics;~~ Topical Anti-infectives, Topical Impetigo Agents; Topical Antivirals, Topical Scabicides; Topical Anti-inflammatory Agents, Immunomodulators: Topical; Topical Anti-infectives, Acne Agents: Topical, Benzoyl Peroxide, Antibiotics and Combination Products.

viii. Electrolytic and Renal Agents, Phosphate Binding Agents.

ix. Gastrointestinal Agents, Antiemetics, Antiemetics, Pregnancy-induced Nausea and Vomiting Treatment; Serotonin-receptor antagonists/Combo; Antiulcer Agents, H2 blockers; Proton Pump Inhibitors (PPIs); Functional Gastrointestinal Disorder Drugs; Gastrointestinal Anti-inflammatory Agents.

x. Genitourinary Agents, Benign Prostatic Hyperplasia (BPH) Agents, 5-Alpha Reductase Inhibitors; Benign Prostatic Hyperplasia (BPH) Agents Alpha-Blockers; Bladder Antispasmodics.

xi. Hematological Agents, Anticoagulants, Oral; Injectable; Erythropoiesis-Stimulating Agents; Platelet Inhibitors.

xii. Hormones and Hormone Modifiers, Androgens; Antidiabetic Agents, Alpha-Glucosidase Inhibitors/Amylin analogs/Misc.; Biguanides; Dipeptidyl Peptidase-4 Inhibitors; Meglitinides; Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors; Sulfonylureas; Thiazolidinediones; Anti-hypoglycemic Agents; Pituitary Hormones, Growth hormone modifiers; Progestins for Cachexia.

xiii. Monoclonal Antibodies for the treatment of Respiratory Conditions.

xiv. Musculoskeletal Agents, Bone Resorption Inhibitors, Bisphosphonates; Nasal Calcitonins; Restless Leg Syndrome Agents; Skeletal Muscle Relaxants.

xv. Neurological Agents, Neurological Agents, Alzheimers Agents; Anticonvulsants, Anticonvulsants; Barbiturates; Benzodiazepines; Hydantoins; Antiparkinsonian Agents, Non-ergot Dopamine Agonists.

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

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

xviii. 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.

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

xx. Toxicology Agents, Antidotes, Opiate Antagonists; Substance Abuse Agents.

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

9. Closing Discussion

a. Public comments on any subject.
(No action may be taken upon a matter raised under public comment period unless the matter itself has been specifically included on an agenda as an action item. Comments will be limited to three minutes per person. Persons making comment will be asked to begin by stating their name for the record and to spell their last name and provide the secretary with written comments.)

b. **For Possible Action**: Date and location 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 three minutes.

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. Email notice has been made to such individuals as have requested notice of meetings (to request notifications please contact rxinfo@dhcfp.nv.gov, or at 1100 East William Street, Suite 101, Carson City,
Nevada 89701).

If you require a physical copy of supporting material for the public meeting, please contact rxinfo@dhcfp.nv.gov, or at 1100 East William Street, Suite 101, Carson City, Nevada 89701). Limited copies of materials will also be available on site at the meeting's physical location. Supporting material will also be posted online at http://dhcfp.nv.gov/ and https://www.medicaid.nv.gov/providers/rx/sssb/SilverStateScriptsBoard.aspx.

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 rxinfo@dhcfp.nv.gov in writing, at 1100 East William Street, Suite 101, Carson City, Nevada 89701.

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 3 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

Mark Crumby, Pharm.D.

Michael Hautekeet, R.Ph

Sapandeep Khurana, MD

Brian Passalacqua, MD

Aditi Singh, MD

Silver State Scripts Board Meeting scheduled for 2021

Date	Time	South Nevada Location	North Nevada Location
September 23, 2021	1:00 PM	Springs Preserve, Las Vegas	None
December 9, 2021	1:00 PM	Springs Preserve, Las Vegas	None

Web References

Preferred Drug List:

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

Medicaid Services Manual (MSM) Chapter 1200:

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

Silver State Scripts Board Bylaws:

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

The Division of Health Care Financing and Policy Public Notices:

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

Definition of "Therapeutic Alternative"

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

Standard Preferred Drug List Exception Criteria

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

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

Current Preferred Drug List

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® LIDOCAINE PATCH * 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		CAMBIA ® POWDER

Preferred Products	PA Criteria	Non-Preferred Products
FLURBIPROFEN TAB IBUPROFEN SUSP IBUPROFEN TAB INDOMETHACIN CAP KETOROLAC TAB QL ¥ MELOXICAM TAB NABUMETONE TAB NAPROXEN SUSP NAPROXEN TAB NAPROXEN DR TAB PIROXICAM CAP SULINDAC TAB	¥ PA Required	DICLOFENAC SODIUM TAB ER 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 OTC LEVOCETIRIZINE 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® CETIRIZINE D OTC CLARITIN® CLARINEX® DESLORATADINE FEXOFENADINE SEMPREX® XYZAL®
Anti-infective Agents		
Aminoglycosides		
Inhaled Aminoglycosides		
BETHKIS® KITABIS® PAK TOBRAMYCIN NEBULIZER		TOBI PODHALER®
Antivirals		
Alpha Interferons		
PEGASYS® PEGASYS® CONVENIENT PACK		

Preferred Products	PA Criteria	Non-Preferred Products
PEG-INTRON® and REDIPEN		
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	PA Required	CEDAX® CAPS and SUSP CEFDITOREN CEFIXIME CAPS/SUSP OMNICEF® SPECTRACEF® SUPRAX® VANTIN®

Preferred Products	PA Criteria	Non-Preferred Products
Macrolides		
AZITHROMYCIN TABS/SUSP CLARITHROMYCIN TABS/SUSP ERYTHROMYCIN BASE ERYTHROMYCIN ESTOLATE ERYTHROMYCIN ETHYLSUCCINATE ERYTHROMYCIN STEARATE		BIAXIN® DIFICID® ZITHROMAX® ZMAX®
Quinolones		
Quinolones - 2nd Generation		
CIPROFLOXACIN TABS CIPRO® SUSP	PA Required	FLOXIN® OFLOXACIN
Quinolones - 3rd Generation		
LEVOFLOXACIN MOXIFLOXACIN	PA Required	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® AVSOLA® CIMZIA® COSENTYX® ENBREL® HUMIRA® INFLECTRA® KEVZARA® KINERET® OLUMIANT® ORENCIA® OTEZLA® RENFLEXIS® SILIQ® SIMPONI® STELARA®	Prior authorization is required for all drugs in this class https://www.medicaid.nv.gov/Downloads/provider/FA-61.pdf	ILARIS® ENTYVIO® ILUMYA® REMICADE® RINVOQ® SKYRIZI® TREMFYA

Preferred Products	PA Criteria	Non-Preferred Products
TALTZ® XELJANZ®		
Multiple Sclerosis Agents		
Injectable		
AVONEX® AVONEX® ADMIN PACK BETASERON® COPAXONE® QL REBIF® QL TYSABRI®	*Trial of only one agent is required before moving to a non-preferred agent* *PA required*	EXTAVIA® GLATIRAMER GLATOPA® KESIMPTA® LEMTRADA® OCREVUS® PLEGRIDY®
Oral		
AUBAGIO® GILENYA® TECFIDERA®	PA required	BAFIERTAM® DIMETHYL FUMARATE MAVENCLAD® MAYZENT® VUMERITY® ZEPOSIA®
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	£ PREFERRED FOR AGES 10 AND UNDER ǂ NONPREFERRED FOR OVER 10 YEARS OLD	ACCURETIC® EPANED® ǂ FOSINOPRIL MAVIK® MOEXIPRIL

Preferred Products	PA Criteria	Non-Preferred Products
ENALAPRIL HCTZ EPANED® £ LISINOPRIL LISINOPRIL HCTZ RAMIPRIL		PERINDOPRIL QUINAPRIL QUINARETIC® QBRELIS® TRANDOLAPRIL UNIVASC®
Beta-Blockers		
ACEBUTOLOL ATENOLOL ATENOLOL/CHLORTH BISOPROLOL BISOPROLOL/HCTZ BYSTOLIC® CARVEDILOL LABETALOL METOPROLOL (Reg Release and Ext release) PINDOLOL PROPRANOLOL PROPRANOLOL/HCTZ SOTALOL		BETAXOLOL KAPSPARGO® NADOLOL SOTYLIZE® TIMOLOL
Calcium-Channel Blockers		
AFEDITAB CR® AMLODIPINE AMLODIPINE/BENAZEPRIL AMLODIPINE/VALSARTAN AMLODIPINE/VALSARTAN /HCT CARTIA XT® DILTIA XT® DILTIAZEM ER DILTIAZEM HCL FELODIPINE ER NICARDIPINE NIFEDIPINE ER TAZTIA XT® VERAPAMIL VERAPAMIL ER		EXFORGE® EXFORGE HCT® ISRADIPINE KATERZIA® LOTREL® MATZIM TAB LA NISOLDIPINE ER NORVASC® NYMALIZE® SOLN
Vasodilators		
Inhaled		
VENTAVIS® TYVASO®		

Preferred Products	PA Criteria	Non-Preferred Products
Oral		
BOSENTAN ORENITRAM® REVATIO ® TADALAFIL		ADCIRCA® ADEMPAS® ALYQ® AMBRISENTAN LETAIRIS® OPSUMIT® SILDENAFIL TRACLEER® UPTRAVI®
Antilipemics		
Bile Acid Sequestrants		
COLESTIPOL CHOLESTYRAMINE WELCHOL®		QUESTRAN®
Cholesterol Absorption Inhibitors		
EZETIMIBE		ZETIA®
Fibric Acid Derivatives		
FENOFIBRATE FENOFIBRIC GEMFIBROZIL		ANTARA® FENOGLIDE® FIBRICOR® LIPOFEN® LOFIBRA® TRICOR® TRIGLIDE® TRILIPIX®
HMG-CoA Reductase Inhibitors (Statins)		
ATORVASTATIN LOVASTATIN PRAVASTATIN ROSUVASTATIN SIMVASTATIN VYTORIN®		ALTOPREV® AMLODIPINE/ATORVASTATIN CADUET® CRESTOR® QL EZALLOR® EZETIMIBE-SIMVASTATIN FLUVASTATIN FLUVASTATIN XL LESCOL® LESCOL XL® LIPITOR® LIPTRUZET® LIVALO® MEVACOR® PRAVACHOL® SIMCOR® ZOCOR® ZYPITAMAG®

Preferred Products	PA Criteria	Non-Preferred Products
Niacin Agents		
NIASPAN® (Brand only) NIACIN ER (ALL GENERICS)		NIACOR®
Omega-3 Fatty Acids		
OMEGA-3-ACID VASCEPA®		LOVAZA®
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® ACZONE GEL® AZELEX® 20% cream BENZOYL PEROXIDE (2.5, 5 and 10% only) CLINDAMYCIN ERYTHROMYCIN/BENZOYL PEROXIDE SODIUM	PA required if over 21 years old	AMZEEQ® FOAM BENZACLIN® BENZOYL PER AEROSOL CLINDAMYCIN AEROSOL CLINDAMYCIN/BENZOYL PEROXIDE GEL DAPSONE GEL DUAC CS® ERYTHROMYCIN ONEXTON GEL® SODIUM SULFACETAMIDE/SULFUR SULFACETAMIDE
Impetigo Agents: Topical		
MUPIROCIN OINT		ALTABAX® CENTANY® MUPIROCIN CREAM

Preferred Products	PA Criteria	Non-Preferred Products
Topical Antivirals		
ABREVA® DENAVIR® XERESE® CREAM ZOVIRAX® CREAM ZOVIRAX®, OINTMENT		ACYCLOVIR OINT ACYCLOVIR CREAM
Topical Scabicides		
LINDANE NATROBA® NIX® PERMETHRIN RID® ULESFIA®		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		
DIFFERIN® RETIN-A TAZORAC® ZIANA®	Payable only for recipients up to age 21.	ADAPALENE GEL AND CREAM ADAPALENE/BENZOYL PEROXIDE ATRALIN® AVITA® EPIDUO® RETIN-A MICRO®(Pump and Tube) TAZAROTENE TRETINOIN TRETIN-X® VELTIN®
Electrolytic and Renal Agents		
Phosphate Binding Agents		
CALCIUM ACETATE CAP CALCIUM ACETATE TAB PHOSLYRA® RENAGEL® RENVELA®		AURYXIA ® FOSRENOL® LANTHANUM CARBONATE PHOSLO® SEVELAMER CARBONATE SEVELAMER HCL VELPHORO®

Preferred Products	PA Criteria	Non-Preferred Products
Gastrointestinal Agents		
Antiemetics		
Pregnancy-induced Nausea and Vomiting Treatment		
BONJESTA® OTC Doxylamine 25mg/Pyridoxine 10mg		DICLEGIS® DOXYLAMINE-PYRIDOXINE TAB 10-10
Serotonin-receptor antagonists/Combo		
GRANISETRON QL ONDANSETRON QL	PA required for all medication in this class	AKYNZEO® ANZEMET® QL SANCUSO® ZOFRAN® QL ZUPLENZ® QL BARHEMSYS®
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	MOTEGRITY® MOVANTIK® RELISTOR® SYMPROIC® TRULANCE® ZELNORM®
Gastrointestinal Anti-inflammatory Agents		
APRISO® ASACOL®SUPP CANASA® COLAZAL® DELZICOL® PENTASA® SULFASALAZINE DR SULFASALAZINE IR		BALSALAZIDE® ASACOL HD® LIALDA ® MESALAMINE (GEN APRISO) MESALAMINE (GEN ASACOL HD) MESALAMINE (GEN DELZICOL) MESALAMINE (GEN LIALDA) MESALAMINE ENEMA SUSP MESALAMINE SUPP

Preferred Products	PA Criteria	Non-Preferred Products
Gastrointestinal Enzymes		
CREON® ZENPEP®		PANCREAZE® PANCRELIPASE PERTZYE® ULTRESA® VIOKACE®
Genitourinary Agents		
Benign Prostatic Hyperplasia (BPH) Agents		
5-Alpha Reductase Inhibitors		
DUTASTERIDE FINASTERIDE		AVODART® DUTASTERIDE/TAMSULOSIN JALYN® PROSCAR®
Alpha-Blockers		
ALFUZOSIN DOXAZOSIN TAMSULOSIN TERAZOSIN		CARDURA® FLOMAX® MINIPRESS® PRAZOSIN RAPAFLO® SILODOSIN UROXATRAL®
Bladder Antispasmodics		
BETHANECHOL OXYBUTYNIN TABS/SYRUP/ER SOLIFENACIN TOVIAZ®		DARIFENACIN DETROL® DETROL LA® DITROPAN XL® ENABLEX® FLAVOXATE GELNIQUE® MYRBETRIQ® OXYTROL® SANCTURA® TOLTERODINE TROSPIUM VESICARE® VESICARE® LS
Hematological Agents		
Anticoagulants		
Oral		
COUMADIN® ELIQUIS® * JANTOVEN® PRADAXA® * QL	* No PA required if approved diagnosis code transmitted on claim	SAVAYSA®*

Preferred Products	PA Criteria	Non-Preferred Products
WARFARIN XARELTO ® *		
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® ASPIRIN BRILINTA® * QL CILOSTAZOL® CLOPIDOGREL DIPYRIDAMOLE PRASUGREL	* PA required	ANAGRELIDE ASPIRIN/DIPYRIDAMOLE DURLAZA® EFFIENT® * QL PLAVIX® YOSPRALA® ZONTIVITY®
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)		GLUCOPHAGE® GLUCOPHAGE XR® GLUMETZA® METFORMIN (GEN FORTAMET)

Preferred Products	PA Criteria	Non-Preferred Products
RIOMET®		
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® OZEMPIC® TRULICITY® VICTOZA®	No PA required if Dx of Type 2 Diabetes transmitted on claim	ADLYXIN® BYDUREON® BCISE RYBELSUS® SOLIQUA® TANZEUM® XULTOPHY®
Insulins (Vials, Pens and Inhaled)		
APIDRA® HUMALOG® HUMULIN® 70/30 HUMULIN® U-500 INSULIN LISPRO INJ 100U/ML LANTUS® LEVEMIR ® NOVOLIN® N NOVOLIN® R NOVOLIN® 70/30 NOVOLOG® INSULIN ASPART TOUJEO SOLO® 300 IU/ML TRESIBA FLEX INJ		ADMELOG® AFREZZA® BASAGLAR® FIASP® HUMULIN ® N HUMULIN® R HUMALOG® U-200 INSULIN ASPART MIX INSULIN LISPRO MIX LYUMJEV® NOVOLIN® 70/30 SEMGLEE®
Meglitinides		
REPAGLINIDE		NATEGLINIDE (Starlix®) PRANDIN® STARLIX®
Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors		
FARXIGA® GLYXAMBI® INVOKANA® INVOKAMET® JARDIANCE® SYNJARDY® SYNJARDY® XR XIGDUO XR®		INVOKAMET® XR QTERN® SEGLUROMET® STEGLATRO® STEGLUJAN™ TRIJARDY® XR

Preferred Products	PA Criteria	Non-Preferred Products
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® AVANDARYL® AVANDIA® DUETACT® PIOGLITAZONE/METFORMIN PIOGLITAZONE/GLIMEPR
Anti-Hypoglycemic Agents		
GLUCAGON EMERGENCY KIT		BAQSIMI® GVOKE®
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® FASENRA®	PA Required	CINQAIR®

Preferred Products	PA Criteria	Non-Preferred Products
NUCALA® XOLAIR®		
Musculoskeletal Agents		
Antigout Agents		
ALLOPURINOL COLCRYS® TAB PROBENECID PROBENECID/COLCHICINE ULORIC®		COLCHICINE TAB/CAP FEBUXOSTAT 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®
Restless Leg Syndrome Agents		
PRAMIPEXOLE ROPINIROLE		HORIZANT® MIRAPEX® MIRAPEX® ER REQUIP XL REQUIP
Skeletal Muscle Relaxants		
BACLOFEN CHLORZOXAZONE CYCLOBENZAPRINE DANTROLENE METHOCARBAMOL METHOCARBAMOL/ASPIRIN ORPHENADRINE CITRATE ORPHENADRINE COMPOUND TIZANIDINE		
Neurological Agents		
Alzheimers Agents		
DONEPEZIL DONEPEZIL ODT		ARICEPT® 23mg ARICEPT®

Preferred Products	PA Criteria	Non-Preferred Products
EXELON® PATCH EXELON® SOLN MEMANTINE TABS		GALANTAMINE GALANTAMINE ER MEMANTINE SOL MEMANTINE XR NAMENDA® TABS NAMENDA® XR TABS NAMZARIC® RAZADYNE® RAZADYNE® ER RIVASTIGMINE CAPS RIVASTIGMINE TRANSDERMAL
Anticonvulsants		
CARBAMAZEPINE CARBAMAZEPINE XR CARBATROL ER® CELONTIN® DEPAKENE® DEPAKOTE ER® DEPAKOTE® DIVALPROEX SODIUM DIVALPROEX SODIUM ER EPIDIOLEX® EPITOL® ETHOSUXIMIDE FELBATOL® FINTEPLA® * FYCOMPA® GABAPENTIN GABITRIL® LAMACTAL ODT® LAMACTAL XR® LAMICTAL® LAMOTRIGINE LEVETIRACETAM LYRICA® NEURONTIN® OXCARBAZEPINE QUDEXY XR® STAVZOR® DR TEGRETOL® TEGRETOL XR® TOPAMAX® TOPIRAGEN® TOPIRAMATE IR	PA required for members under 18 years old *PA Required for all ages	APTIOM® BANZEL® BRIVIACT® DIACOMIT® KEPPRA XR® KEPPRA® OXTELLAR XR® POTIGA® SABRIL® SPRITAM® TOPIRAMATE ER TROKENDI XR® VIGABATRIN XCOPRI®

Preferred Products	PA Criteria	Non-Preferred Products
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 DIASTAT® DIAZEPAM NAYZILAM® SPRAY* TRANXENE T-TAB® VALIUM® VALTOCO® SPRAY*	*PA Required for all ages	DIAZEPAM rectal soln KLONOPIN® ONFI® SYMPAZAN® FILM
Hydantoins		
CEREBYX® DILANTIN® ETHOTOIN FOSPHENYTOIN PEGANONE® PHENYTEK® PHENYTOIN PRODUCTS		
Anti-Migraine Agents		
Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists		
AJOVY® EMGALITY® NURTEC® ODT UBRELVY®	PA required for all products	AIMOVIG®
Serotonin-Receptor Agonists		
RIZATRIPTAN ODT SUMATRIPTAN TABLET ZOLMITRIPTAN ODT ZOMIG® SPRAY	PA required for exceeding Quantity Limit	ALMOTRIPTAN AMERGE® AXERT® FROVA® ELETRIPTAN

Preferred Products	PA Criteria	Non-Preferred Products
		FROVATRIPTAN SUCCINATE IMITREX® MAXALT® TABS MAXALT® MLT NARATRIPTAN ONZETRA XSAIL® RELPAX® REYVOW® RIZATRIPTAN BENZOATE SUMATRIPTAN INJECTION SUMATRIPTAN NASAL SPRAY SUMATRIPTAN/NAPROXEN SUMAVEL® TOSYMRA® TREXIMET® ZEMBRACE SYMTOUCH ZOLMITRIPTAN ZOMIG® TAB ZOMIG® ZMT
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®		ALPHAGAN® BETAGAN® BETOPTIC ® BIMATOPROST COSOPT PF® COSOPT® DORZOL/TIMOL SOL PF

Preferred Products	PA Criteria	Non-Preferred Products
DORZOLAM DORZOLAM / TIMOLOL LATANOPROST LEVOBUNOLOL LUMIGAN® METIPRANOLOL RHOPRESSA® ROCKLATAN® SIMBRINZA® TIMOLOL DROPS/ GEL SOLN TRAVATAN Z® TRAVATAN®		OCUPRESS® OPTIPRANOLOL® TIMOPTIC XE® TIMOPTIC® TRAVOPROST BAK Free TRUSOPT® VYZULTA® XALATAN® XELPROS® ZIOPTAN®
Ophthalmic Antihistamines		
BEPREVE® KETOTIFEN PAZEO® ZADITOR OTC®		ALAWAY® AZELASTINE ALOMIDE ALOCRIL ELESTAT® EMADINE® EPINASTINE LASTACRAFT® OLOPATADINE (drop/sol) OPTIVAR® PATADAY® PATANOL® ZERVIATE®
Ophthalmic Anti-infectives		
Ophthalmic Macrolides		
ERYTHROMYCIN OINTMENT		
Ophthalmic Quinolones		
BESIVANCE® CIPROFLOXACIN VIGAMOX® ZYMAXID®		CILOXAN® GATIFLOXACIN LEVOFLOXACIN MOXEZA® MOXIFLOXACIN OFLOXACIN®
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

Preferred Products	PA Criteria	Non-Preferred Products
		TOBRADEX ST SUS
Ophthalmic Anti-inflammatory Agents		
Ophthalmic Corticosteroids		
ALREX® DUREZOL® FLAREX® FML® FML FORTE® MAXIDEX® PRED FORTE®		DEXAMETHASONE FLUOROMETHOLONE INVELTYS® LOTEMAX® LOTEPREDNOL OMNIPRED® PREDNISOLONE PRED MILD® VEXOL®
Ophthalmic Nonsteroidal Anti-inflammatory Drugs (NSAIDs)		
DICLOFENAC FLURBIPROFEN ILEVRO® KETOROLAC NEVANAC®		ACULAR® ACULAR LS® ACUVAIL® BROMDAY® BROMFENAC® PROLENSA®
Ophthalmics for Dry Eye Disease		
ARTIFICIAL TEARS RESTASIS®		CEQUA® 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		
ADDERALL XR® AMPHETAMINE SALT COMBO IR CONCERTA® DAYTRANA® DESOXYN® DEXMETHYLPHENIDATE DEXTROAMPHETAMINE SA TAB DEXTROAMPHETAMINE TAB FOCALIN XR®	PA required for entire class	ADDERALL® ADHANSIA® XR ADZENYS® AMPHETAMINE ER SUSP AMPHETAMINE SALT COMBO XR APTENSIO XR® ATOMOXETINE CLONIDINE HCL ER COTEMPLA XR®-ODT

Preferred Products	PA Criteria	Non-Preferred Products
GUANFACINE ER JORNAY PM® METADATE CD® METHYLIN® METHYLPHENIDATE METHYLPHENIDATE ER (All forms generic extended release) METHYLPHENIDATE SOL RITALIN LA® STRATTERA® VYVANSE®	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	DEXEDRINE® DEXTROAMPHETAMINE SOLUTION DYANAVEL® EVEKEO® EVEKEO® ODT FOCALIN® INTUNIV® METADATE ER® METHYLPHENIDATE TAB ER (RELEXXII) METHYLPHENIDATE CHEW MYDAYIS® PROCENTRA® QUILLICHEW® QUILLIVANT® XR SUSP RELEXXII® RITALIN® ZENZEDI®
Antidepressants		
Other		
BUPROPION BUPROPION SR BUPROPION XL DULOXETINE MIRTAZAPINE MIRTAZAPINE RAPID TABS PRISTIQ® TRAZODONE VENLAFAXINE (ALL FORMS)	PA required for members under 18 years old *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®

Preferred Products	PA Criteria	Non-Preferred Products
Antipsychotics		
Atypical Antipsychotics - Oral		
ARIPIPRAZOLE		ABILIFY®
CLOZAPINE	PA required for Ages under 18 years old	ABILIFY MYCITE ®
FANAPT®		CAPLYTA®
LATUDA®		CLOZARIL®
NUPLAZID®*	PA Forms: https://www.medicaid.nv.gov/Downloads/provider/FA-70A.pdf (ages 0-5)	FAZACLO®
OLANZAPINE		GEODON®
QUETIAPINE	https://www.medicaid.nv.gov/Downloads/provider/FA-70B.pdf (ages 6-18)	INVEGA®
QUETIAPINE XR		PALIPERIDONE
REXULTI®	*(No PA required Parkinson's related psychosis ICD code on claim)	RISPERDAL®
RISPERIDONE		SECUADO®
SAPHRIS®		SEROQUEL®
VRAYLAR®		SEROQUEL XR®
ZIPRASIDONE		ZYPREXA®
Atypical Antipsychotics – Long Acting Injectable		
ABILIFY® MAINTENA	*****PA Required	
ARISTADA®		
ARISTADA® INITIO		
INVEGA® SUSTENNA		
INVEGA® TRINZA*		
RISPERDAL® CONSTA		
PERSERIS®		
ZYPREXA® RELPREVV		
Anxiolytics, Sedatives, and Hypnotics		
ESTAZOLAM	No PA required if approved diagnosis code transmitted on claim (All agents in this class)	AMBIEN®
FLURAZEPAM		AMBIEN CR®
ROZEREM®		BELSOMRA®
TEMAZEPAM		DORAL®
TRIAZOLAM		ESZOPICLONE
ZALEPLON		EDLUAR®
ZOLPIDEM		HETLIOZ®
		INTERMEZZO®
		LUNESTA®
		SILENOR®
		SOMNOTE®

Preferred Products	PA Criteria	Non-Preferred Products
	PA required for members under 18 years old	SONATA® ZOLPIDEM CR ZOLPIMIST®
Psychostimulants		
Narcolepsy Agents		
ARMODAFINIL * NUVIGIL® * PROVIGIL® * WAKIX® **	* (No PA required for ICD-10 code G47.4) **PA Required for all ages	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® VERAMYST® XHANCE™ ZETONNA®
Phosphodiesterase Type 4 Inhibitors		
DALIRESP® QL	PA required	
Long-acting/Maintenance Therapy		
ADVAIR® DISKUS ADVAIR HFA® ANORO ELLIPTA® ASMANEX® BEVESPI® BREO ELLIPTA® BUDESONIDE NEBS* DULERA®		AEROSPAN HFA® AIRDUO® ALVESCO® ARCAPTA NEOHALER® ARMONAIR® ARNUITY ELLIPTA® BREZTRI® BROVANA®

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

Meeting Minutes

Silver State Script Board

Draft Meeting Minutes

Date of Meeting: Thursday, July 29, 2021, 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.

Agenda Item	Record	Notes
Closed Executive Session		
Financial Review of Drug Classes with Proposed Changes	Chairman Decerbo called the meeting to order at 1:05 PM on July 29, 2021. Roll was taken by Chairman Decerbo. Decerbo, Mark, Pharm.D. – Chair: Present ☒ Absent ☐ Adashek, Joseph, MD: Present ☒ Absent ☐ Chu, Evelyn, Pharm.D.: Present ☒ Absent ☐ Crumby, Mark, Pharm.D.: Present ☒ Absent ☐ Hautekeet, Mike, R.Ph: Present ☒ Absent ☐ Khurana, Sapandeep, MD: Present ☐ Absent ☒ Passalacqua, Brian, MD: Present ☐ Absent ☒ Singh, Aditi, MD: Present ☐ Absent ☒ Ward, Kate, Pharm.D.: Present ☒ Absent ☐	**The DHCFP Staff Present were as follows:** Olsen, David, Social Services Chief III Gudino, Antonio, Social Services Program Specialist III Berntson, Kindra, Social Services Program Specialist II Flowers, Ellen, Program Officer I Lither, Gabriel, DAG Capurro, Antonina, Deputy Administrator

Agenda Item	Record	Notes
	A quorum was present. Chairman Decerbo directed Kevin Whittington to proceed with the Financial Review of Drugs classes with proposed changes up for review during the Second Quarter 2021 Silver State Scripts Board meeting. Mr. Whittington reminded the board members that the financial material presented is confidential and should not be discussed or disclosed outside of this closed session of the Silver States Script Board meeting. Mr. Whittington informed the board the recommendation for the Proposed new class Cardiovascular Agents - Antilipemics - PCSK9 Inhibitors was to defer action at this time; as such, no financial review was presented. Mr. Whittington presented the Financial Review of the Neurological Agents - Anti-Migraine Agents - Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists class noting the products with proposed changes in PDL status. Mr. Whittington presented the Financial Review of the Gastrointestinal Agents - Functional Gastrointestinal Disorder Drugs class noting the products with proposed changes in PDL status. Mr. Whittington presented the Financial Review of the Analgesics Opiate Agonists - Abuse-Deterrent class noting the products with proposed changes in PDL status. Mr. Whittington presented the Financial Review of the Analgesics Opiate Agonists class noting the products with proposed changes in PDL status. Mr. Whittington presented the Financial Review of the Ophthalmic Agents - Antiglaucoma Agent class noting the products with proposed changes in PDL status. Mr. Whittington presented the Financial Review of the Psychotropic Agents - Antipsychotics - Atypical Antipsychotics - Oral class noting the products with proposed changes in PDL status.	**Gainwell Technology Staff Present were as follows**: Leid, Jovanna, Pharm.D. **OptumRx Staff Present were as follows:** Whittington, Kevin, R.Ph. Kiriakopoulos, Amanda, Pharm.D. LeCheminant, Jill, Pharm.D Chien, Michael, Pharm.D. Piccirilli, Annette Medina, Daniel

Agenda Item	Record	Notes
	Mr. Whittington presented the Financial Review of the Dermatological Agents - Topical Anti-infectives - Topical Scabicides class noting the products with proposed changes in PDL status. Mr. Whittington concluded the financial reviews and Chairman Decerbo directed the Board members to transition to the open session of the Silver States Script Board Meeting.	
Open Public Meeting		
1. Call to Order and Roll Call	Chairman Decerbo called the meeting to order at 1:35 PM on July 29, 2021. Roll was taken by Chairman Decerbo. Decerbo, Mark, Pharm.D. – Chair: Present ☒ Absent ☐ Adashek, Joseph, MD: Present ☒ Absent ☐ Chu, Evelyn, Pharm.D.: Present ☒ Absent ☐ Crumby, Mark, Pharm.D.: Present ☒ Absent ☐ Hautekeet, Mike, R.Ph: Present ☒ Absent ☐ Khurana, Sapandeep, MD: Present ☐ Absent ☒ Passalacqua, Brian, MD: Present ☐ Absent ☒ Singh, Aditi, MD: Present ☐ Absent ☒ Ward, Kate, Pharm.D.: Present ☒ Absent ☐ A quorum was present.	**The DHCFP Staff Present were as follows:** Olsen, David, Social Services Chief III Gudino, Antonio, Social Services Program Specialist III Berntson, Kindra, Social Services Program Specialist II Flowers, Ellen, Program Officer I Lither, Gabriel, DAG Capurro, Antonina, Deputy Administrator **Gainwell Technology Staff Present were as follows**: Leid, Jovanna, Pharm.D. **OptumRx Staff Present were as follows:** Kiriakopoulos, Amanda, Pharm.D. LeCheminant, Jill, Pharm.D. Whittington, Kevin, R.Ph. Piccirilli, Annette Medina, Daniel

Agenda Item	Record	Notes
		Hansen, Sean Lee, Cara, Pharm.D. Chien, Michael, Pharm.D. **The public attendee list is included as Attachment A.** **Note**: Participants may not have chosen to reveal their identity, and in the absence of a sign-in sheet the accuracy of the attendee list is not assured.
2. Public Comment on Any Matter on the Agenda.	Telephonic and web comment was called for and the phone lines were opened. No public comment was offered.	
3. Administrative		
a. For Possible Action: Review and Approve Meeting Minutes from March 25, 2021.	No corrections were offered. The minutes were approved by unanimous consent.	
b. Status Update by the DHCFP.	Chief David Olsen announced Dr. Antonina Capurro as the new Deputy Director. Dr. Capurro introduced herself. Chief Olsen discussed Senate Bill 190 and Senate Bill 325 passed legislation, which allows for the creation of a new pharmacist provider type to increase access to self-administered hormonal contraceptives, HIV prevention medication, and laboratory tests. Chief Olsen stated that pharmacists will have the ability to prescribe and dispense these medications and regulations for this process will be developed by the board of pharmacy. Chief Olsen announced Senate Bill 380 passed, which addresses increased drug transparency in Nevada. Chief Olsen updated the Board that the onboarding process began with the new	Referenced web addresses: The Nevada Department of Health and Human Services, Division of Health Care Financing and Policy Provider Portal. https://www.medicaid.nv.gov/

Agenda Item	Record	Notes
	pharmacy benefit manager, Magellan. Chief Olsen expressed appreciation to Dr. Carl Jeffery for his service to the State of Nevada and informed the Board that he is no longer supporting Nevada Medicaid with OptumRx. Chief Olsen announced DuAne Young's, the former Deputy Administrator, role as the Director of Policy. Mr. Antonio Gudino and Chairman Decerbo thanked Dr. Chu for her service and extended best wishes, as this is her last meeting as a board member. Roll call was taken of meeting participants.	The Division of Health Care Financing and Policy http://dhcfp.nv.gov/
4. Proposed New Drug Classes		
a. For Possible Action: Discussion and possible adoption of Cardiovascular Agents - Antilipemics - PCSK9 Inhibitors.		
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened. Comment was made by Ben Droese with Amgen Medical Affairs, thanking the committee for adding Repatha to the PDL.	
ii. Drug class review presentation by OptumRx.	Dr. Kiriakopoulos discussed the administration of class agents via subcutaneous injection and efficacy in LDL reduction. Dr. Kiriakopoulos highlighted clinical guidelines recommendation of maximally tolerated statins as first-line therapy, and ezetimibe or the PSK9 inhibitors are recommended as potential second-line agents. Dr. Kiriakopoulos recommended the board consider the class clinically and therapeutically equivalent	
iii. Discussion by Board and action by Board to approve	Board Member Adashek moved to accept the class as clinically and therapeutically equivalent. Board Member Chu seconded the motion.	

Agenda Item	Record	Notes
clinical/therapeutic equivalency of agents in class.	A vote was held: Yes / No / Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Adashek, Joseph, MD ☒ ☐ ☐ Chu, Evelyn, Pharm.D. ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. Kiriakopoulos recommended adding Praluent and Repatha as preferred.	
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Board Member Crumby moved to accept the recommendations. Board Member Adashek seconded the motion. A vote was held: Yes / No / Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Adashek, Joseph, MD ☒ ☐ ☐ Chu, Evelyn, Pharm.D. ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
5. Established Drug Classes Being Reviewed Due to the Release of New Drugs		
a. For Possible Action: Discussion and possible adoption of Neurological		

Agenda Item	Record	Notes
Agents - Anti-Migraine Agents - Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists.		
i. Public comment.	The following written public comment is attached hereto: 1) Aimovig package insert from Droese, Ben of Amgen medical administration 2) Letter dated June 16, 2021, from Nguyen, Quang, DO of Las Vegas Endocrinology 3) Letter dated June 17, 2021, from Lee, Katrina, APRN 4) Letter dated June 14, 2021, from Thai, Danny of 986 Specialty Pharmacy The public comments referenced above were highlighted on the record for members of the Board by Dr. Kiriakopoulos. Telephonic and web comment was called for, and the phone lines were opened. Comment was made by Ben Droese of Amgen medical administration providing information for Aimovig. Mr. Droese reviewed package insert information for Aimovig. Mr. Droese discussed the American Headache Society's updated consensus statement on integrating new migraine treatments into clinical practice and an update to new preventative CGRP inhibitors. Trials demonstrating the safety and efficacy of Aimovig were presented. Mr. Droese requests that Aimovig is added to the PDL. Comment was made from Jennifer Shear of Teva pharmaceutical providing information on Ajovy. Ms. Shear reviewed package insert information for Ajovy. Trials demonstrating the safety and efficacy of Ajovy were presented. Ms. Shear requests Aimovig be added to the PDL.	

Agenda Item		Record	Notes
		Comment was made from Jenna Gianninoto of AbbVie medical affairs noting her availability to answer questions regarding Ubrelvy.	
ii.	Drug class review presentation by OptumRx.	Dr. Kiriakopoulos discussed the new product, Vyepti, the mechanism of action, indication, administration, and two trials demonstrating efficacy. Dr. Kiriakopoulos discussed the classification of CGRP agents and showed various classification models. Dr. Kiriakopoulos recommended the Board consider the class clinically and therapeutically equivalent.	
iii.	Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Board Member Hautekeet moved to accept the class as clinically and therapeutically equivalent. Board Member Adashek seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Adashek, Joseph, MD: Yes ☒ No ☐ Abst. ☐ Chu, Evelyn, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
iv.	Presentation of recommendations for PDL inclusion by OptumRx.	Dr. Kiriakopoulos recommended adding Vytepi as non-preferred.	
v.	Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Board Member Adashek moved to accept the proposed changes. Board Member Chu seconded the motion. A vote was held: Yes No Abst.	

Agenda Item	Record				Notes
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
	Adashek, Joseph, MD	☒	☐	☐	
	Chu, Evelyn, Pharm.D.	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
6. Established Drug Classes					
a. For Possible Action: Discussion and possible adoption of Gastrointestinal Agents - Functional Gastrointestinal Disorder Drug.					
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened. Comment was made from Jenna Gianninoto of AbbVie medical affairs noting her availability to answer questions regarding Linzess.				
ii. Drug class review presentation by OptumRx.	Dr. Kiriakopoulos briefly discussed the indications for the agents in the functional gastrointestinal disorder class. Dr. Kiriakopoulos recommended the Board consider the class clinically and therapeutically equivalent.				
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Board Member Chu moved to accept that the list is clinically and therapeutically equivalent. Board Member Adashek seconded the motion. A vote was held:				
		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	

Agenda Item		Record				Notes
		Adashek, Joseph, MD	☒	☐	☐	
		Chu, Evelyn, Pharm.D.	☒	☐	☐	
		Crumby, Mark, Pharm.D.	☒	☐	☐	
		Hautekeet, Mike, R.Ph	☒	☐	☐	
		Ward, Kate, Pharm.D.	☒	☐	☐	
iv.	Presentation of recommendations for PDL inclusion by OptumRx.	Dr. Kiriakopoulos recommended the Board add the lubiprostone to non-preferred and maintaining Amitiza as preferred.				
v.	Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Board Member Adashek moved to accept the proposed updates as presented. Board Member Hautekeet seconded the motion. A vote was held:				
			Yes	No	Abst.	
		Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
		Adashek, Joseph, MD	☒	☐	☐	
		Chu, Evelyn, Pharm.D.	☒	☐	☐	
		Crumby, Mark, Pharm.D.	☒	☐	☐	
		Hautekeet, Mike, R.Ph	☒	☐	☐	
		Ward, Kate, Pharm.D.	☒	☐	☐	
b.	For Possible Action: Discussion and possible adoption of Analgesics - Opiate Agonists - Abuse-Deterrent.					
i.	Public comment.	The following written public comment is attached hereto: 1) Sublocade package insert from submitted				

Agenda Item		Record	Notes
		The public comment referenced above was highlighted on the record for members of the Board by Dr. Kiriakopoulos. Chairman Decerbo questioned if Sublocade will be reviewed at an upcoming meeting. Dr. Kiriakopoulos stated that she will research when Sublocade will be reviewed. Telephonic and web comment was called for, and the phone lines were opened. No public comment was offered.	
ii.	Drug class review presentation by OptumRx.	Dr. Kiriakopoulos discussed Hysingla ER. Generic hydrocodone bitartrate is available. Dr. Kiriakopoulos recommended the Board consider the class clinically and therapeutically equivalent.	
iii.	Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Board Member Adashek moved to accept the class as clinically and therapeutically equivalent. Board Member Crumby seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Adashek, Joseph, MD: Yes ☒ No ☐ Abst. ☐ Chu, Evelyn, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
iv.	Presentation of recommendations	Dr. Kiriakopoulos recommended removing Embeda and Morphabond as preferred and Arymo ER as non-preferred as these products are no longer	

Agenda Item	Record	Notes
for PDL inclusion by OptumRx.	manufactured. Dr. Kiriakopoulos recommended adding hydrocodone bitartrate as non-preferred.	
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Board Member Adashek moved to accept the recommendation. Board Member Crumby seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Adashek, Joseph, MD: Yes ☒ No ☐ Abst. ☐ Chu, Evelyn, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
c. For Possible Action: Discussion and possible adoption of Analgesics - Opiate Agonists		
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened. No public comment was offered.	
ii. Drug class review presentation by OptumRx.	Dr. Kiriakopoulos discussed Zohydro ER. Generic hydrocodone bitartrate is available. Dr. Kiriakopoulos recommended the Board consider the class clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to approve clinical/therapeutic	Board Member Adashek moved to accept the class as clinically and therapeutically equivalent. Board Member Crumby seconded the motion.	

Agenda Item	Record	Notes
equivalency of agents in class.	A vote was held: Decerbo, Mark, Pharm.D. – Chair ☒ Yes ☐ No ☐ Abst. Adashek, Joseph, MD ☒ Yes ☐ No ☐ Abst. Chu, Evelyn, Pharm.D. ☒ Yes ☐ No ☐ Abst. Crumby, Mark, Pharm.D. ☒ Yes ☐ No ☐ Abst. Hautekeet, Mike, R.Ph ☒ Yes ☐ No ☐ Abst. Ward, Kate, Pharm.D. ☒ Yes ☐ No ☐ Abst.	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. Kiriakopoulos recommended adding hydrocodone bitartrate to non-preferred.	
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Board Member Adashek moved to accept the recommendation. Board Member Crumby seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair ☒ Yes ☐ No ☐ Abst. Adashek, Joseph, MD ☒ Yes ☐ No ☐ Abst. Chu, Evelyn, Pharm.D. ☒ Yes ☐ No ☐ Abst. Crumby, Mark, Pharm.D. ☒ Yes ☐ No ☐ Abst. Hautekeet, Mike, R.Ph ☒ Yes ☐ No ☐ Abst. Ward, Kate, Pharm.D. ☒ Yes ☐ No ☐ Abst.	
d. For Possible Action: Discussion and possible adoption of Ophthalmic Agents – Antiglaucoma Agents.		
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened.	

Agenda Item	Record	Notes
	No public comment was offered.	
ii. Drug class review presentation by OptumRx.	Dr. Kiriakopoulos discussed Brimonidine and Brinzolamide. Generic products brimonidine tartrate ophthalmic solutions 0.2% and 1% are available. Dr. Kiriakopoulos recommended the Board consider the class clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Board Member Crumby moved to accept the class as clinically and therapeutically equivalent. Board Member Chu seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Adashek, Joseph, MD: Yes ☒ No ☐ Abst. ☐ Chu, Evelyn, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. Kiriakopoulos recommended moving Brimonidine to non-preferred and adding Brinzolamide to non-preferred. Alphagan P and Azopt to remain preferred.	
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Board Member Adashek moved to accept the recommendation. Board Member Crumby seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐	

Agenda Item	Record				Notes
	Adashek, Joseph, MD	☒	☐	☐	
	Chu, Evelyn, Pharm.D.	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
e. For Possible Action: Discussion and possible adoption of Psychotropic Agents – Antipsychotics - Atypical Antipsychotics – Oral.					
i. Public comment.	The following written public comment is attached hereto: 1) Letter dated June 7, 2021, from Mahakian, Charles, MD 2) Letter dated June 7, 2021, from Raini, Francis, APRN 3) Letter dated June 8, 2021, from Anooshian, John, MD 4) Letter dated June 2, 2021, from Tan, Rhigel, APRN 5) Letter dated June 2, 2021, from Ramirez, Ruth, APRN 6) Letter dated June 9, 2021, from Zafar, Uzma MD 7) Letter dated May 25, 2021, from Duncan, Cameron, DNP 8) Letter dated June 4, 2021, from Lynch, M. 9) Letter dated June 4, 2021, from Stoll, Kathi 10) Letter dated June 4, 2021, from Steinagel, Gerri, MD 11) Letter dated June 4, 2021, from Luback-Neves, Marie, DNP 12) Letter dated June 4, 2021, from Price, Charles, MD 13) Letter dated June 9, 2021, from Dr. Vuppalapati 14) Letter dated June 10, 2021, from Evans, Jennifer, PMHNP 15) Letter dated May 25, 2021, from Stolzner, Pauline, APRN 16) Letter dated June 8, 2021, from Nguyen, Paul, MD 17) Letter dated June 7, 2021, from Ortega, Luis Carlos, MD 18) Letter dated May 28, 2021, from Cruey, Karen, MD				

Agenda Item	Record	Notes
	19) Letter dated June 7, 2021, from Horne, Robert Lynn, MD 20) Package insert for Perseris The public comments referenced above were highlighted on the record for members of the Board by Dr. Kiriakopoulos. Telephonic and web comment was called for, and the phone lines were opened. Comment was made by Ruth Ramirez of Psychiatrist Solutions Clinic requesting Caplyta as a preferred drug. Information was provided on favorable outcomes for patients on Caplyta treatment. Comment was made by Paul Nguyen requesting Caplyta be a preferred drug. Concern was expressed on patient relapse after hospitalization if Caplyta is not accessible. Information was provided on favorable outcomes for patients on Caplyta treatment. Comment was made from Jenna Gianninoto of AbbVie medical affairs noting her availability to answer questions regarding Vraylar. Comment was made by Robin Reedy of NAMI Nevada. NAMI supports open access to all safe and effective medications for mental health conditions as prescribed by qualified health care professionals. Open access allows patients to receive the medication that works best for that individual patient. Ms. Reedy discussed Nevada's last-place ranking in mental health services due to restricted access to medications, number of providers, and lack of pediatric services. Comment was made by Micah Lands, MSL. Caplyta package insert information was reviewed. Trials demonstrating safety and efficacy of Caplyta were presented. Ms. Lands requests Caplyta be considered when making formulary decisions.	

Agenda Item		Record	Notes
ii.	Drug class review presentation by OptumRx.	Dr. Kiriakopoulos discussed indications of Invega, Saphris, and Secuado. Generic options for these products are available. Asenapine patch and ODT formulations were reviewed. Dr. Kiriakopoulos recommended the Board consider the class clinically and therapeutically equivalent.	
iii.	Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Board Member Adashek moved to accept the class as clinically and therapeutically equivalent. Board Member Ward seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Adashek, Joseph, MD: Yes ☒ No ☐ Abst. ☐ Chu, Evelyn, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
iv.	Presentation of recommendations for PDL inclusion by OptumRx.	Dr. Kiriakopoulos recommended including “topical” in the title for this class for clarification purposes. Recommendation made to move Invega to preferred and add asenapine to non-preferred.	

Agenda Item	Record	Notes
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Board member Adashek moves to accept the proposed changes and move Caplyta to preferred due to the number of providers that have taken the time to make this request. Board Member Ward seconded the motion. Chairman Decerbo expressed appreciation for the Medicaid providers in general and for taking the time to speak with the Board to optimize the formulary. Dr. Kiriakopoulos reviewed the PDL categories, noting non-preferred agents are part of the PDL and are available through the PA process if there is a medically justifiable reason a non-preferred product is needed over a preferred product. Dr. Kiriakopoulos discussed Medicaid formularies that have open access to mental health medications still have criteria around safety and other edits, and commented on the large number of preferred products on the Nevada Medicaid formulary. Board member Adashek discussed the difficulties and concerns with this class of medications and the requirement for members to try and fail preferred agents before accessing the non-preferred agents. Dr. Kiriakopoulos agreed with the concern and notes that finding an agent that works for the patient is often done through trial and error. Chairman Decerbo discussed pharmacogenomics and the future potential to eliminate the need for trial and error. The increased coverage provided with the addition of Invega to preferred products is noted. Board member Chu asks for clarification on the advantage of Caplyta as a first-line agent. Paul Nguyen responds that, in his clinical experience, patients using Caplyta have a good response to the medication because Caplyta negates metabolic	

Agenda Item	Record	Notes
	side effects seen with other agents. Dr. Nguyen notes member medication compliance is better with Caplyta. Ruth Ramirez comments that patients experience less weight gain with Caplyta and notes members who gain weight due to medication often stop therapy without informing their provider. Dr. Ramirez states there is a less cardiovascular risk with Caplyta, making it a safer option. Gabriel Lither asked if the motion from board member Adashek was seconded. Chairman Decerbo confirms the motion was seconded by board member Ward. Gabriel Lither requests clarification from Board member Adashek on the intention of the motion. Board member Adashek commented he intended to recommend Caplyta as preferred. Board member Adashek amends the motion to move Caplyta to preferred. Board member Ward second the motion. A vote was held: Yes / No / Abst. Decerbo, Mark, Pharm.D. – Chair ☐ ☒ ☐ Adashek, Joseph, MD ☒ ☐ ☐ Chu, Evelyn, Pharm.D. ☐ ☒ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☐ ☒ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐ Board Member Hautekeet moved to accept the changes as presented: to add “topical” to the drug class name, add Invega to preferred, and add asenapine to non-preferred.	

Agenda Item	Record	Notes
	Board Member Chu seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Adashek, Joseph, MD: Yes ☒ No ☐ Abst. ☐ Chu, Evelyn, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☐ No ☒ Abst. ☐	
f. For Possible Action: Discussion and possible adoption of Dermatological Agents – Topical Anti-Infectives – Topical Scabicides.		
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened. No public comment was offered.	
ii. Drug class review presentation by OptumRx.	Dr. Kiriakopoulos discussed Sklice. Generic ivermectin is available. Dr. Kiriakopoulos recommended the Board consider the class clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to approve	Board Member Ward moved to accept the class as clinically and therapeutically equivalent.	

Agenda Item	Record	Notes
clinical/therapeutic equivalency of agents in class.	Board Member Crumby seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair ☒ Yes ☐ No ☐ Abst. Adashek, Joseph, MD ☒ Yes ☐ No ☐ Abst. Chu, Evelyn, Pharm.D. ☒ Yes ☐ No ☐ Abst. Crumby, Mark, Pharm.D. ☒ Yes ☐ No ☐ Abst. Hautekeet, Mike, R.Ph ☒ Yes ☐ No ☐ Abst. Ward, Kate, Pharm.D. ☒ Yes ☐ No ☐ Abst.	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. Kiriakopoulos recommended adding ivermectin to non-preferred.	
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Board Member Adashek moved to accept the recommendation. Board Member Hautekeet seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair ☒ Yes ☐ No ☐ Abst. Adashek, Joseph, MD ☒ Yes ☐ No ☐ Abst. Chu, Evelyn, Pharm.D. ☒ Yes ☐ No ☐ Abst. Crumby, Mark, Pharm.D. ☒ Yes ☐ No ☐ Abst. Hautekeet, Mike, R.Ph ☒ Yes ☐ No ☐ Abst. Ward, Kate, Pharm.D. ☒ Yes ☐ No ☐ Abst.	
7. OptumRx Reports: New Drugs to Market and New Line Extensions	Dr. Kiriakopoulos reviewed teplizumab, a new treatment being launched for the delay of type 1 diabetes. Atogepant, a migraine prophylaxis agent, was noted. Dr. Kiriakopoulos discussed new treatments coming out for atopic dermatitis, including abrocitinib, tralokinumab, and ruxolitinib, and their respective expected indications and mechanisms of action. Dr.	

	Kiriakopoulos highlighted a new treatment for plaque psoriasis, bimekizumab. Dr. Kiriakopoulos identified generic pipeline medications with their expected availability, including Bepreve, Daliresp, Restasis, Byetta, Chantix, Forteo, intranasal Narcan, and Bystolic.	
8. Closing Discussion		
a. Public comments on any subject.	Telephonic and web comment was called for, and the phone lines were opened. No public comment was offered.	
b. Date and location of the next meeting.	Chairman Decerbo confirmed the next meeting is scheduled for September 23, 2021, and will be a hybrid meeting.	
c. Adjournment.	Chairman Decerbo adjourned the meeting at 3:02 PM.	

Attachment A – Members of the Public in Attendance

Ashton, Elisa, Johnson and Johnson
Balen, Valerie, Belz Case
Berry, Kenneth
Booth, Robert, AbbVie
Droese, Ben, Amgen
Duerre, Mark, Itci-Inc
Duke, Michelle
Ferroli, Joseph, Takeda
Germain, Joe, Biogen
Gianninoto, Jenna, AbbVie
Isaki, Steven, Lundbeck
Kniffin, Jason, Novo Nordisk
Lands, Micah, Itci-Inc
Large, David
Lau, Jimmy
Leroue, Chelsea, Biohaven Pharma
Lovan, Charlie, AbbVie
Nassif, Leila, Amgen
Robinson, Lovell, AbbVie
Nguyen, Paul
Oliver, Carmen, Biohaven Pharma
Ramirez, Ruth
Reedy, Robin, NAMI
Ritter, Jean, Zealand Pharma
Roy, Melissa, Otsuka-Us
Shear, Jennifer, Teva Pharm
Sullivan, Mike, Amgen
Wright, Matthew, Artia Solutions
Zarob, Michael
Attendee with no last name available: Mark

Attachment B – Submitted Written Comment

- Ajovy SSSB July 2021 Request for Public Comment
- Caplyta - RxInfo
- Caplyta - Scan Jun 15 2021
- Caplyta - signed caplyta letter. june 2021 doc08336720210609130332
- Caplyta - SSSB Caplyta
- caplyta (002)
- Caplyta Agenda Item 6d
- Caplyta email 2 2021 06
- Caplyta email 3 2021 06
- Caplyta email 4 2021 06
- Caplyta email 5 2021 06
- Caplyta email 6 2021 06
- Caplyta email 7 2021 06
- Caplyta email 8 2021 06
- Caplyta email 9 2021 06
- Caplyta email 2021 06
- Caplyta IMG_0001
- caplyta June 7 Luis Ortega MD_
- Caplyta Letter to Committee 5.28.2021
- CaplytaMedicaidLetter
- Nurtec email 2021 06
- Nurtec June 17 Katrina Lee
- Nurtec-July 2021 SSSB Meeting Written Correspondence - 986 Spec Pharm.docx
- Perseris Submission for Public Comment
- Sublocade Submission for Public Comment

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

INTRODUCTION

Multiple Sclerosis

- 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 2021)*. Multiple sclerosis is characterized by inflammation, demyelination, and degenerative changes in the CNS. 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])*.
- An estimated 1 million adults in the United States (U.S.) 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 (*Montalban et al 2018, Rae-Grant et al 2018*). These therapies may delay the progression from CIS to clinically definite MS (CDMS) *(Armoiry et al 2018, Miller et al 2012)*. 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 with MS. Its approval was based on the PARADIGMS trial (*Chitnis et al 2018*).
- 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 (*Bafiertam prescribing information 2021*).

Ulcerative Colitis

- Ulcerative colitis is a form of inflammatory bowel disease (IBD) that 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 and Kane 2020, Rubin et al 2019).*
- Precise incidence and prevalence estimates of ulcerative colitis have been limited by a lack of gold standard criteria for diagnosis, inconsistent case ascertainment, and disease misclassification. The existing data suggest that the U.S. incidence rate of ulcerative colitis varies between 2.2 to 19.2 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] 2020).*
- Current pharmacotherapy for ulcerative colitis includes 5-aminosalicylic acid (5-ASA) derivatives, glucocorticoids, immunomodulators (azathioprine, 6-mercaptopurine [6-MP], and methotrexate), and biologic agents (eg, infliximab, Humira [adalimumab]) *(Micromedex 2021, Bernstein et al 2015).* These agents are discussed in separate class reviews.
- Zeposia (ozanimod) is the first sphingosine 1-phosphate (S1P) receptor modulator that is approved for moderate to severe ulcerative colitis in adults in addition to its approval for MS *(Zeposia prescribing information 2021).*
- 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)	-
Kesimpta (ofatumumab)§	-
Lemtrada (alemtuzumab)	-
Mavenclad (cladribine)‖	-
Mayzent (siponimod)	-
mitoxantrone	✔‡
Ocrevus (ocrelizumab)	-
Plegridy (peginterferon β-1a)	-
Ponvory (ponesimod)	-
Rebif (interferon β-1a)	-
Tecfidera (dimethyl fumarate)	✔
Tysabri (natalizumab)	-
Vumerity (diroximel fumarate)	-

Drug	Generic Availability
Zeposia (ozanimod)	-

†Glatopa by Sandoz is an FDA-approved generic for Copaxone (glatiramer acetate).
‡Although brand Novantrone has been discontinued, generic mitoxantrone remains available.
§Ofatumumab was originally approved as an IV formulation for treatment of chronic lymphocytic leukemia as a different product (Arzerra). Only clinical data for ofatumumab use in MS are included in this review.
‖Cladribine injection is indicated for the treatment of active hairy-cell leukemia. This oncology indication is not related to the treatment of MS and will not be discussed in this review.

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

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 in adults	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	Moderately to severely active ulcerative colitis in adults	Moderately to severely active Crohn's disease in adults
Ampyra (dalfampridine)	✔ *	-	-	-	-	-	-
Aubagio (teriflunomide)	-	✔	-	-	-	-	-
Avonex (interferon β-1a)	-	✔	-	-	-	-	-
Bafiertam (monomethyl fumarate)	-	✔	-	-	-	-	-
Betaseron/Extavia (interferon β-1b)	-	✔	-	-	-	-	-
Copaxone (glatiramer acetate)	-	✔	-	-	-	-	-
Gilenya (fingolimod)	-	✔ †	-	-	-	-	-
Kesimpta (ofatumumab)		✔					
Lemtrada (alemtuzumab)	-	-	✔ ‡	-	-	-	-
Mavenclad (cladribine)	-	-	✔ §	-	-	-	-
Mayzent (siponimod)	-	✔	-	-	-	-	-
mitoxantrone	-	-	-	-	✔ ‖	-	-
Ocrevus (ocrelizumab)	-	✔	-	✔	-	-	-

Drug	Improve walking in MS	Relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults	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	Moderately to severely active ulcerative colitis in adults	Moderately to severely active Crohn's disease in adults
Plegridy (peginterferon β-1a)	-	✔	-	-	-	-	-
Ponvory (ponesimod)	-	✔	-	-	-	-	-
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 2021, Aubagio 2021, Avonex 2020, Bafiertam 2021, Betaseron 2021, Copaxone 2020, Extavia 2020, Gilenya 2019, Glatopa 2020, Kesimpta 2020, Lemtrada 2021, Mavenclad 2019, Mayzent 2021, mitoxantrone 2018, Ocrevus 2021, Plegridy 2021, Ponvory 2021, Rebif 2020, Tecfidera 2021, Tysabri 2020, Vumerity 2021, Zeposia 2021)

- 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

Multiple Sclerosis

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

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, 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 controlled trials (RCTs) 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 SC 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 IM + 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 IM, and 0.11 for glatiramer acetate. Glatiramer acetate performed significantly better than IFNβ-1a IM, reducing the risk of exacerbation by 31% (p = 0.027), and IFNβ-1a IM + glatiramer acetate performed significantly better than IFNβ-1a IM, 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, placebo-controlled, RCT. 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 2014[b])*. Neutralizing antibodies to IFN β-1a were identified in < 1% of all groups after 1 year (peginterferon β-1a SC every 2 weeks, 4 patients; peginterferon β-1a SC every 4 weeks, 2 patients; placebo, 2 patients) *(Calabresi et al 2014[b])*. 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 SC 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 SC every 4 week group (ARR 0.291). The peginterferon β-1a SC 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 SC 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 SC every 2 weeks group compared to the placebo-switch group *(Calabresi et al 2014[b], 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 SC. 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 were 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).
- Bioequivalency was demonstrated for Plegridy administered by IM and SC injection in an unpublished, open-label, crossover, single-dose, Phase 1 study of 136 healthy volunteers; this study was the basis for the FDA-approval of the IM route of administration for Plegridy (*Zhao et al 2020*). Injection site reactions were reported less frequently after IM dosing (14.4%) than after SC dosing (32.1%).

ORAL AGENTS

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) at 12 weeks 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, double-blind, RCT. 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 at 12 weeks *(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)*.

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 enrollment 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.
  - ARRs at 96 weeks, the primary outcome, 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 group had a lower risk of 3-month CDP vs placebo (hazard ratio [HR], 0.67; 95% CI, 0.48 to 0.93; p = 0.02). Lesions on MRI were significantly lower in the cladribine 3.5 mg/kg group vs placebo (p < 0.001 for all comparisons).

Oral Sphingosine-1-phosphate (S1P) receptor modulators

Gilenya (fingolimod)
- Gilenya (fingolimod) has been evaluated in 2 large, 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 2014[a])*. 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).

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

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. 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 on MRI 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 IM. Significant reductions in ARR were observed compared to IFNβ-1a IM 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 IM. 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 IM.
  - Clinically significant evidence of bradycardia, second-, or third-degree heart block was not noted after administration of the first dose in either trial.

Ponvory (ponesimod)

- Ponvory (ponesimod) was evaluated in the Phase 3, double-blind, parallel group study (OPTIMUM) in 1133 patients with relapsing forms of MS *(Kappos et al 2021)*. Patients were randomized to receive 20 mg ponesimod (titrated from 2 mg) (n = 567) or 14 mg teriflunomide (n = 566) once daily for 108 weeks. The primary endpoint of ARR was reduced with ponesimod compared to teriflunomide (rate ratio, 0.695; 99% CI, 0.536 to 0.902; p<0.001). In addition, the number of Gd-enhancing T1 lesions and the number of new or enlarging T2 lesions on MRI were also reduced with ponesimod. Confirmed disability progression outcomes at 12 weeks and 24 weeks were not significantly different between ponesimod and teriflunomide.

Oral Fumarates

Tecfidera (dimethyl fumarate)

- Tecfidera (dimethyl fumarate) was evaluated in two Phase 3 studies: DEFINE and CONFIRM *(Fox et al 2012, Gold 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 at 12 weeks *(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 confirmed disability progression at 12 weeks. 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)*.

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 2021*).
- 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%) 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.

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 2021*).

High Efficacy Infusibles and Injectables

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). The most frequently reported adverse effects with alemtuzumab were infusion-associated reactions, infections, and autoimmune events.

Kesimpta (ofatumumab)

- The two Phase 3, double-blind, double-dummy, active-controlled, multicenter, RCTs, the ASCLEPIOS I and II trials, included 1882 patients with relapsing MS who were treated with ofatumumab 20 mg SC every 4 weeks or teriflunomide 14 mg daily for up to 30 months. Approximately 40% of the patients in each group had no prior exposure to DMTs. Ofatumumab significantly reduced the ARR, the primary endpoint, compared with teriflunomide.
  - ASCLEPIOS I: ARR: 0.11 vs 0.22; difference, -0.11; 95% CI, -0.16 to -0.06; $p < 0.001$; RR, 0.49; 95% CI, 0.37 to 0.65; $p < 0.001$.
  - ASCLEPIOS II: ARR: 0.10 vs 0.25; difference, -0.15; 95% CI, -0.20 to -0.09; $p < 0.001$; RR, 0.42; 95% CI, 0.31 to 0.56; $p < 0.001$.
  - Pooled data demonstrated that the percentage of patients with confirmed disability worsening at 3 months was 10.9% vs 15.0% for ofatumumab vs teriflunomide, respectively (HR, 0.66; 95% CI, 0.50 to 0.86; $p = 0.002$). For the confirmed disability worsening at 6 months, the percentage was also lower in the ofatumumab group (8.1% vs 12.0%;

HR, 0.68; 95% CI, 0.50 to 0.92; p = 0.01). There was no significant difference between the groups for disability improvement.
  - For the MRI endpoints, the ofatumumab group had significantly fewer mean number of Gd-enhancing lesions and mean number of new or enlarging lesions per year on T2-weighted MRI (all p < 0.001). Brain volume loss did not differ significantly between groups in either trial *(Hauser et al 2020[a])*.

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%).
    - 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%; 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.
  - 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.
      - As of February 2018, the overall crude incidence rate of malignancies among patients from OPERA I and II who received ocrelizumab in the double-blind period or open-label extension was 0.40 per 100 patient-years of exposure to ocrelizumab. The incidence rate as of the data cutoff of May 2015 after the completion of the DB period was 0.28 for the ocrelizumab group and 0.14 for the IFN β-1a SC group (*Hauser et al 2020[b]*).
      - As of January 2019, the age- and sex-standardized incidence rate of all malignancies in the ocrelizumab all-exposure (all Phase 2 and 3 studies, plus 4 other trials) (0.22 per 100 patient-years; 95% CI, 0.16 to 0.33), remained stable over time, with confidence intervals overlapping and within epidemiological references from the Surveillance, Epidemiology, and End Results [SEER] Program of the National Cancer Institute, which reports

data on cancer incidence in approximately 28% of the general U.S. population (0.31 per 100 patient-years) (*Genentech 2020[a]*)
- Since breast cancer occurred in 6 out of 781 females treated with ocrelizumab (vs in none of 668 females treated with IFN β-1a SC or placebo), the labeling of ocrelizumab recommends that patients follow standard breast cancer screening guidelines (*Genentech 2020[b]*). In an analysis of the all-exposure ocrelizumab population from the trials through January 2019, the incidence rate of female breast cancer using age at event onset methodology was 0.15 (95% CI, 0.08 to 0.27) per 100 patient-years compared to 0.14 per 100 patient-years (95% CI, 0.14 to 0.14) based on SEER (*Genentech 2020[a]*).

- 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; 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; p = 0.04).
  - Additional secondary endpoints included changes in the T25FW, the total volume of hyperintense brain lesions on T2-weighted MRI, and brain volume loss.
    - The proportion of patients with 20% worsening of the T25FW 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.

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 motor 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 double-blind, placebo-controlled, RCTs 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, RCT 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 AAN 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

- The best initial treatment strategy is uncertain, but 2 main concepts include safety focused (IFNs or glatiramer) and efficacy (ie, natalizumab, ocrelizumab, ofatumumab) approaches (*Olek & Mowry 2021*). Retrospective observational studies have supported the earlier initiation of high efficacy DMT to reduce the risk of disability progression; however, evidence from RCTs is needed to determine the appropriate stage of MS in which to use a high efficacy DMT (*He et al 2020*).
- A 2017 systematic review evaluated the effect of high efficacy immunotherapies (ie, fingolimod, natalizumab, alemtuzumab) at different stages of MS (*Merkel et al 2017*). 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 β-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.
- 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 12 mg (RR, 0.40, 95% CI, 0.27 to 0.60; very low quality evidence) was 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 12 mg (mean difference = -0.6; 95% CI, -1.02 to -0.24) was 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).
- A 2020 network meta-analysis of 34 RCTs compared ofatumumab with other DMTs for RRMS *(Samjoo et al 2020)*. For the outcome of ARR, rate ratios were significantly improved with ofatumumab compared with teriflunomide, IFN β-1a SC and IM, IFN β-1b, glatiramer acetate, dimethyl fumarate, and fingolimod; no differences were detected in comparisons with cladribine, ocrelizumab, natalizumab, or alemtuzumab. Values for SUCRA indicated alemtuzumab was most likely to be most effective (96%), followed by ofatumumab (91%), natalizumab (88%), and ocrelizumab (85%).

Ulcerative Colitis

Zeposia (ozanimod)

- The efficacy and safety of ozanimod were evaluated in 2 multicenter, double-blind, placebo controlled RCTs in adult patients with moderately to severely active ulcerative colitis (*Zeposia prescribing information 2021)*. Patients were randomized to oral ozanimod 0.92 mg daily or placebo. All patients received an initial dose escalation of ozanimod or placebo prior to receiving their assigned dose on day 8. Patients with moderately or severely active ulcerative colitis were included if they had an inadequate response or were intolerant to previous therapies, including oral aminosalicylates, corticosteroids, immunomodulators, or biologic agents. In UC Study 1, patients (n = 645) received induction treatment for 10 weeks. In UC Study 2, patients who achieved a clinical response in UC Study 1 or an open-label arm at week 10 (n = 457) were re-randomized to maintenance treatment with ozanimod or placebo for 42 additional weeks (52 weeks total). Use of corticosteroids or aminosalicylates was allowed in UC Study 1, while patients had to be tapered from corticosteroids for entry into UC Study 2. The primary endpoint was clinical remission at week 10 in UC Study 1 and at 52 weeks in UC Study 2. Clinical remission was defined as a 3-component Mayo score (without the physician global assessment) which included the rectal bleeding subscore, stool frequency subscore, and endoscopy subscore.
  - In the UC Study 1, clinical remission was achieved by 18% with ozanimod and 6% of patients with placebo at 10 weeks (treatment difference, 12%; 95% CI, 8 to 17; $p < 0.0001$). In addition, the following secondary endpoints were improved with ozanimod vs placebo, respectively: clinical response (48% vs 26%; $p < 0.0001$), endoscopic improvement (27% vs 12%; $p < 0.0001$), and endoscopic-histologic mucosal improvement (13% vs 4%; $p < 0.001$).
  - In the UC Study 2, clinical remission was achieved by 37% of patients with ozanimod and 19% of patients with placebo at 52 weeks (treatment difference, 19%; 95% CI, 11 to 26). In addition, the following secondary endpoints were improved with ozanimod vs placebo, respectively: clinical response (60% vs 41%; $p < 0.0001$), endoscopic

improvement (46% vs 26%; p < 0.0001), corticosteroid-free clinical remission (32% vs 17%; p < 0.001), and endoscopic-histologic mucosal improvement (30% vs 14%; p < 0.001).

CLINICAL GUIDELINES

Multiple Sclerosis

- 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)*. 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 Gd-enhanced lesion) (Level B). Clinicians may advise discontinuation of DMT in people with SPMS who do not have ongoing relapses (or Gd-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 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)
- 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.

Ulcerative Colitis
- For the treatment of ulcerative colitis, 2019 guidelines from the American College of Gastroenterology (ACG) recommend 5-ASA therapy for induction of remission in mildly active ulcerative colitis, and budesonide, systemic corticosteroids, tumor necrosis factor (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-ASA (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 ulcerative colitis, the AGA strongly recommends using infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or ustekinumab over no treatment (*Feuerstein et al 2020*).

SAFETY SUMMARY

Interferons and glatiramer acetate
- 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 products (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. Cases of hepatic injury have also 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.

Oral agents

- 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. 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.
- Siponimod is contraindicated in patients with a cytochrome P4502C9*3/*3 genotype, presence of Mobitz type II second-degree, third degree AV block or sick 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, cutaneous malignancies, 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 and ponesimod are 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. They are also contraindicated in patients with Mobitz type II second- or third-degree AV block, sick sinus syndrome, or sinoatrial attack unless the patient has a functioning pacemaker. Ozanimod is also contraindicated in patients with severe, untreated sleep apnea and those taking a monoamine oxidase inhibitor. Warnings and precautions for ozanimod and ponesimod include an increased infection risk, macular edema, increased blood pressure, bradyarrhythmia and AV conduction delays, decline in pulmonary function, liver injury and cutaneous malignancies (ponesimod only). Women of childbearing potential should use effective contraception during and for 3 months after stopping ozanimod and 1 week after stopping ponesimod due to fetal risk. The most common adverse events (incidence > 10%) with ozanimod and ponesimod are upper respiratory tract infections, hepatic transaminase elevations, and hypertension (ponesimod only). Zeposia (ozanimod) does not have a recommendation for first-dose cardiac observation like fingolimod, ponesimod, and siponimod.
- 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 the fumarates. 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.

- 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, drug reaction with eosinophilia and systemic symptoms, and elevated blood pressure. Although not approved in pediatric patients, use of teriflunomide was associated with pancreatitis in a pediatric clinical trial. 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).
- 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.

High Efficacy Infusibles and Injectables

- Natalizumab has a boxed warning regarding the risk of PML, which 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), thrombocytopenia, and hepatotoxicity.
- Alemtuzumab is contraindicated in patients with human immunodeficiency virus (HIV) or active infection. 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, decreased immunoglobulin levels, 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.
    - No cases of PML were reported in the controlled Phase 2 or 3 studies or in the OLE of these studies. Outside of clinical trials, as of January 31, 2020, there have been 9 confirmed cases of PML in patients treated with ocrelizumab for MS. Of the 9 cases, 8 patients had been switched from natalizumab (n = 7) or fingolimod (n = 1). In 1 additional case, the patient had no prior exposure to DMTs but had contributing factors for PML including advanced age (78 years) and preexisting grade 1 lymphopenia which progressed to grade 2 during treatment (*Genentech 2020[c], Hauser et al 2020[b], Ng et al 2020*).
  - 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.
- Ofatumumab is contraindicated in patients with active hepatitis B virus infection. The prescribing information contains warnings and precautions regarding the risk of infection, injection-related reactions, reduction in immunoglobulins, and fetal risk. The most common adverse events (incidence > 10%) include upper respiratory tract infection, headache, injection-related reactions, and local injection site reactions.
- 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.

Symptomatic therapy

- 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.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration*

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ampyra (dalfampridine)	Tablet	Oral	Twice daily	• May be taken with or without food. Tablets should only be taken whole; do not divide, crush, chew, or dissolve.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				• 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 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)	Tablet	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 until verification that the plasma teriflunomide concentration is less than 0.02 mg/L. • Transaminase and bilirubin levels should be obtained within 6 months before initiation; transaminase levels should be

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				monitored for at least 6 months after initiation.
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)	Capsule (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, serum aminotransferase, alkaline phosphatase, and total bilirubin levels before initiation of therapy.
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. • 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.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
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)	Capsule	Oral	Once daily Approved for adults and pediatric patients 10 years of age or older. For pediatric patients ≤ 40 kg, a lower dose is recommended. 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. 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 heart rate [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 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 so patients 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

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				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 months before planned conception.
Kesimpta (ofatumumab)	Injection	SC	20 mg at weeks 0, 1, and 2 followed by subsequent dosing of 20 mg once monthly starting at week 4	• Prior to initiation, perform hepatitis B virus screening and tests for quantitative serum immunoglobulins. For patients with low serum immunoglobulins, immunology experts should be consulted.
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.	• Pre-medicate with high-dose corticosteroids prior to Lemtrada infusion for the first 3 days of each treatment course. • 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. • 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 > 200 cells/microliter, whichever occurs later. • Patients should complete any necessary immunizations at least 6 weeks prior to treatment with alemtuzumab. Important monitoring: • Complete blood count with differential, serum creatinine, and urinalysis (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.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
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 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.	• The use of Mavenclad in patients weighing less than 40 kg has not been investigated. • Mavenclad is contraindicated in pregnant women and in 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)	Tablet	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 For MS-related indications: 12 mg/m^2 given as a short IV infusion over 5 to 15 minutes 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	• 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 < 1500 cells/mm^3. • 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.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			develop at any time during treatment with mitoxantrone. .	• Mitoxantrone may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant. • Complete blood counts, including platelets, should be monitored prior to each 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
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	• 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. • 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. • 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. • Hepatitis B virus screening is required before the first dose. • Prior to initiation, quantitative serum immunoglobulin levels should be performed. For patients with low serum immunoglobulins, immunology experts should be consulted.
Plegridy (peginterferon β-1a)	Injection; pen, prefilled syringe for SC use; prefilled syringe for IM use	SC, IM	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 sites for SC administration are the abdomen, back of the upper arm, and thigh; IM injections should be administered in the 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.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ponvory (ponesimod)	Tablet	Oral	Once daily Titration: Initiate 14-day titration, starting with 2 mg once daily and increase to 20 mg by day 15 (refer to prescribing information for titration regimen).	• May be taken with or without food; must be swallowed whole. • Ponvory can cause fetal harm when administered to pregnant women. • Before treatment initiation, obtain complete blood count, ECG, liver function tests, ophthalmic evaluation, and test for varicella zoster virus. • 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.
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)	Capsule (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, serum aminotransferase, alkaline phosphatase, and total bilirubin levels before initiation of therapy.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
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)	Capsule (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, serum aminotransferase, alkaline phosphatase, and total bilirubin levels before initiation of therapy.
Zeposia (ozanimod)	Capsule	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.	• Dosing recommendations for MS and ulcerative colitis are the same. • 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. • 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 disability 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 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.
- 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 2019, Scolding et al 2015, Montalban et al 2018, Rae-Grant 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, Rae-Grant et al 2018)*.
- There are now 9 available oral agents. 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. Cases of PML have been reported in patients taking fingolimod and dimethyl fumarate.
  - Gilenya (fingolimod) is a S1P 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 S1P 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), the third S1P receptor modulator, has to significantly decrease ARR compared to IFNβ-1a; however, unlike other drugs in this class, it does not require first dose cardiac monitoring (*Comi et al 2019, Cohen et al 2019*).
  - Ponvory (ponesimod), a fourth S1P receptor modulator, reduced ARR compared to teriflunomide *(Kappos et al 2021)*.
  - 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 *(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 an oral fumarate that 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 (*Bafiertam prescribing information 2021*).

- 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 liver enzymes, 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, Mavenclad 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 *(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.
- Kesimpta (ofatumumab) is the first self-administered CD20-directed cytolytic antibody indicated for relapsing forms of MS. Ofatumumab has demonstrated superiority to teriflunomide in patients with relapsing forms of MS for the outcome of ARR *(Hauser et al 2020[a])*. Ofatumumab is self-administered monthly by SC injection after an initial loading regimen. Key warnings include the risk for infections, including PML and HBV reactivation. Injection-related reactions, possible reduction in immunoglobulins, and fetal risk (B cell depletion in infants born to mothers treated with ofatumumab during pregnancy) are other warnings. The most common AEs (incidence > 10%) were upper respiratory tract infection, headache, injection-related reactions, and local injection site reactions.
- 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.
- 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*).
- 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 quality of life in MS patients, 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. 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*).

- Zeposia (ozanimod) is the first S1P receptor modulator that is approved for moderate to severe ulcerative colitis in adults, in addition to its approval for MS *(Zeposia prescribing information 2021)*. The role in therapy for S1P receptor modulators in ulcerative colitis is not well-defined.

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Publication Date: June 4, 2021

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/simvastatin, and ezetimibe/rosuvastatin). 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), Ezallor Sprinkle (rosuvastatin capsule), and Roszet (ezetimibe/rosuvastatin) (*Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*).
- 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)	✔
Vytorin (ezetimibe/simvastatin)	✔
Roszet (ezetimibe/rosuvastatin)	-

Abbreviation: ER = extended-release.
*The brands, Lescol and Mevacor, have been discontinued, but the generic formulations are available.

€The brand Nikita was discontinued.
(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 2. FDA-approved indications

Indications	Single-Entity Agents							Combination Products		
	atorvastatin	fluvastatin	lovastatin	pitavastatin	pravastatin	rosuvastatin	simvastatin	amlodipine/ atorvastatin	ezetimibe/ simvastatin	ezetimide/ rosuvastatin
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)		
Adjunct to diet in patients with primary non-familial hyperlipidemia to reduce LDL-C levels										✔
Alone or as adjunct in patients with HoFH to reduce LDL-C										✔
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 CHD			✔ ɣ							
Reduce the risk of non-fatal MI, fatal and non-fatal stroke, revascularization procedures, hospitalization for congestive heart failure, and angina in patients with clinically evident CHD	✔							✔ (atorvastatin)		

Reduce the risk of stroke, MI, and arterial revascularization procedures in patients without clinically evident CHD but with an increased risk of CVD based on age ≥ 50 years old in men and ≥ 60 years old in women, high sensitivity C-reactive protein ≥ 2 mg/L, and the presence of ≥ 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 2020, Caduet 2021, Crestor 2020, Ezallor Sprinkle 2020, Flolipid 2020, Fluvastatin 2020, Lescol XL 2020, Lipitor 2020, Livalo 2020, Lovastatin 2021, Pravachol 2020, Roszet 2021, Vytorin 2020, Zocor 2020, Zypitamag 2020)*

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*).
- The GRAVITY trial compared rosuvastatin (10 or 20 mg) to simvastatin (40 or 80 mg), both in fixed combination with ezetimibe 10 mg in high-risk patients (N = 833). Reductions in LDL-C were greater with rosuvastatin plus ezetimibe compared to simvastatin plus ezetimibe (p < 0.05), with more patients achieving LDL-C goals of < 100 mg/dL and < 70 mg/dL (*Ballantyne et al 2014*).
- 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 [CTTC] 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. Rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, have also occurred with statin use. Treatment with immunosuppressive agents may be required.

- A 2020 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 (A1C) 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	After initiation and/or upon titration, lipid levels should be analyzed within 2 to 4 weeks and dosage	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
		patients with HoFH as an adjunct to other lipid lowering treatments or if such treatments are unavailable, treatment of patients with primary dysbetalipoproteinemia: Tablet: 10 to 80 mg/day HeFH in pediatric patients 10 to 17 years old: Tablet: initial dose 10 mg/day, maximum dose 20 mg/day	adjusted accordingly. Dosage adjustments may be necessary in patients taking cyclosporine, clarithromycin, itraconazole, letermovir, 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	Prior to initiation and periodically during therapy, lipid levels should be analyzed and dosage adjusted accordingly. Dosage adjustments may be necessary in patients taking	ER tablet should be taken at bedtime. ER tablets should be swallowed whole. IR tablet should be taken with an evening meal.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		Tablet: initial 20 mg once daily; maintenance, 10 to 80 mg/day in single or 2 divided doses; maximum, 80 mg/day	danazol, diltiazem, dronedarone, verapamil, or amiodarone.	
Pitavastatin	Tablet: 1 mg 2 mg 4 mg	Hyperlipidemia: Tablet: initial 2 mg once daily; maintenance, 1 to 4 mg/day; maximum, 4 mg/day Reduce TC, LDL-C and apo B in patients with HoFH (ages 8 years and older): Tablet: initial 2 mg once daily; maximum, 4 mg/day	After initiation and/or upon titration, lipid 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.	May be administered with or without food. Tablets may be taken at any time during the day.
Pravastatin	Tablet: 10 mg* 20 mg 40 mg 80 mg	Hyperlipidemia: Tablet: initial 40 mg once daily; maintenance, 40 to 80 mg once daily Prevention of CVD: Tablet: initial 40 mg once daily; maintenance, 40 to 80 mg once daily Pediatric patients: Ages 8 to 13 years old: 20 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	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
		Ages 14 to 18 years old: 40 mg once daily	20 mg/day. Max dose in patients taking clarithromycin is 40 mg/day.	
Rosuvastatin	Tablet: 5 mg 10 mg 20 mg 40 mg Capsule: 5 mg 10 mg 20 mg 40 mg	Tablets: Hyperlipidemia: Initial 10 to 20 mg once daily; maintenance, 5 to 40 mg/day Reduce TC, LDL-C and apo B in patients with HoFH: Initial 20 mg once daily; Ages 7 to 17 years: 20 mg once daily Reduce TC, LDL-C and apo B in pediatric patients with HeFH: Ages 8 to less than 10 years: maintenance, 5 to 10 mg/day Ages 10 to 17 years: maintenance, 5 to 20 mg/day Capsules: Initial 10 to 20 mg once daily; usual starting dose in HoFH is 20 mg once daily Maximum dose: 40 mg once daily	After initiation and/or upon titration, lipid levels should be analyzed within 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 darolutamide and 10 mg once daily when used with gemfibrozil, atazanavir/ ritonavir, lopinavir/ritonavir, or simeprevir. Coadministration with certain antiviral drugs has differing effects on exposure and may increase risk of myopathy.	May be administered with or without food. May be taken at any time during the day.
Simvastatin	Tablet: 5 mg 10 mg 20 mg 40 mg 80 mg Oral suspension: 20 mg/5 mL 40 mg/5 mL	Hyperlipidemia: initial 10 or 20 mg once daily; maintenance, 5 to 40 mg/day Reduce TC and LDL-C in patients with HoFH as an adjunct to other lipid lowering treatments or if such treatments are unavailable: 40 mg once daily Prevention of CVD:	After initiation and/or upon titration, lipid levels should be analyzed after 4 weeks and dosage adjusted accordingly. Dose should be decreased by	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

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		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> Ages 10 to 17 years: initial 10 mg/day; maintenance, 10 to 40 mg/day; maximum dose is 40 mg/day	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) 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	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 evidence of muscle toxicity.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
			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 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.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
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 amiodarone, amlodipine, or ranolazine. Vytorin is contraindicated for use with strong CYP3A4 inhibitors,	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
			gemfibrozil, cyclosporine, or danazol. Use caution in patients receiving ≥ 1 gram daily of niacin-containing products.	
ezetimibe/ rosuvastatin	Tablets: 10/5 mg 10/10 mg 10/20 mg 10/40 mg	Dosage depends on indication for use, LDL-C, and individual risk for cardiovascular disease Recommended dose range is 10 mg/5 mg to 10 mg/40 mg once daily	Starting dose when switching from a statin and ezetimibe is equivalent dose of rosuvastatin and 10 mg of ezetimibe. Initiate dose at 10 mg/5 mg in Asian patients; consider risk: benefit if not adequately controlled on dose of 10 mg/20 mg.	Swallow whole; do not crush, dissolve, or chew tablets

Abbreviations: ApoB = apolipoprotein B, CHD = coronary heart disease, CVD = cardiovascular disease, CYP3A4 = cytochrome 3A4, ER = extended-release, HDL-C = high-density lipoprotein cholesterol, HeFH = heterozygous familial hypercholesterolemia, HoFH = homozygous familial hypercholesterolemia, IR = immediate-release, LDL-C = low-density lipoprotein cholesterol, Max = maximum, TC = total cholesterol, TG = triglycerides.
*Pravachol 10 mg is no longer available; however, generic pravastatin 10 mg remains available.

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	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.

		have not been established.			
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 not been established.	No dosage adjustment required in mild to moderate renal dysfunction. Use with caution in severe renal dysfunction; doses above 40 mg per day have not been studied.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Pregnancy Category X Contraindicated in women who are pregnant or may become pregnant. Potential excretion into breast milk; contraindicated during breastfeeding
Lovastatin	No dosage adjustment required in the elderly. The initial starting dose of lovastatin 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	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Unclassified† Contraindicated in pregnant women Contraindicated during breastfeeding

			dose of 2 mg/day is re-commended.		
Pravastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in children 8 to 18 years of age for the treatment of HeFH. Safety and efficacy in children < 8 years of age have not been established.	Renal dosage adjustment is required in severe renal impairment; an initial dose of 10 mg/day is recommended.	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Unclassified† Contraindicated in pregnant women. Pravastatin is present in breast milk; contraindicated during breastfeeding.
Rosuvastatin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Approved for use in children 8 to 17 years of age for the treatment of HeFH and 7 to 17 years of age for the treatment of HoFH. Safety and efficacy in children < 7 years of age have not been established. Pediatric dosing is approved for Crestor; however, due to marketing exclusivity rights, Ezallor 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	Contraindicated in active liver disease or unexplained persistent elevations in serum transaminases.	Pregnancy Category X Contraindicated in women who are or may become pregnant. Unknown whether excreted in breast milk; contraindicated during breastfeeding.

			monitoring is recommended.		
Combination Products					
amlodipine/ atorvastatin	Safety and efficacy in elderly patients have not been established. Elderly patients have decreased clearance of amlodipine; lower initial doses of amlodipine may be required.	Safety and efficacy in children have not been established. Safety and efficacy of atorvastatin in children < 10 years and amlodipine in children < 6 years of age have not been established	No dosage adjustment required.	Contraindicated in active liver disease.	Unclassified† Contraindicated for use during pregnancy and in women who may become pregnant. Contraindicated for use during breastfeeding.
ezetimibe/ 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.
ezetimibe/ rosuvastatin	Age ≥ 65 years is a risk factor for myopathy and rhabdomyolysis; patients should be monitored for increased risk of myopathy.	Safety and efficacy in children have not been established.	Monitor patients with renal impairment for development of myopathy. Doses should not exceed 10/10 mg daily in patients with severe renal impairment.	Contraindicated in patients with acute liver failure or decompensated cirrhosis.	Unclassified† Contraindicated for use during pregnancy or in women who may become pregnant. Contraindicated during breastfeeding.

Abbreviation: ER=extended-release, HeFH = heterozygous familial hypercholesterolemia, HoFH = homozygous familial hypercholesterolemia.
*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.

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], Vytorin [ezetimibe/simvastatin], and Roszet [ezetimibe/rosuvastatin]) 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), Ezallor Sprinkle (rosuvastatin capsule), and Roszet (ezetimibe/rosuvastatin) (*Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*).
- 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 medication, 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, was 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 2020, 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 (*Handelsman et al* 2020). The recommendations for statin therapy for managing dyslipidemia and prevention of cardiovascular disease are stated as the following:
  - Statin therapy is recommended as the first-line cholesterol-lowering therapy, unless contraindicated; current evidence supports a moderate- to high-intensity statin.
  - For clinical decision making, the risk for new onset diabetes or modest worsening of glycemic control in established diabetes does not justify withholding statins in patients with significant ASCVD risk.
  - Very high-risk individuals such as those with established coronary, carotid, and peripheral vascular disease or those with 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. Rare reports of immune-mediated necrotizing myopathy (IMNM), an autoimmune myopathy, have also occurred with use. 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, 2021

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, salicylic acid, and clascoterone, a topical androgen inhibitor approved by the Food and Drug Administration (FDA) in August 2020. (*Gollnick et al 2016, Zaenglein et al 2016, FDA summary [Winlevi] 2020*).
- 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*). The exact mechanism of clascoterone is unknown; the postulated mechanism is competition against dihydrotestosterone for binding to androgen receptors within the sebaceous gland and hair follicles (*Winlevi prescribing information 2020*, *Cassiopea press release 2019*).
- 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. Clascoterone was primarily studied in patients with moderate to severe acne (*Hebert et al 2020*).
- 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, cholestryramine, 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%, 7.5%	✔
Cleocin-T (clindamycin) lotion 1%	✔
Clindacin-P, Clindacin ETZ (clindamycin) swab 1%	✔
Clindacin Pac, Clindacin ETZ (clindamycin and cleanser kit) swab 1%	✔
Clindagel (clindamycin) gel 1%	✔
clindamycin solution 1%	✔

Drug	Generic Availability
Evoclin (clindamycin) foam 1%	✔
NuCaraClinPAK (clindamycin and moisturizer kit) gel 1%	✔
Ery (erythromycin) pads 2%	-
Erygel (erythromycin) gel 2%	✔
erythromycin solution 2%	✔
Amzeeq (minocycline) topical foam 4%	-
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%, 4%, 5%, 6.5%, 8%, 10%; foaming cloths 6%; lotion 5%, 8%, 10%; wash/lotion kits 2.5/3.7%, 2.5/10%	✔ †
Enzoclear, BenzePrO (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%	-
Vanoxide-HC (benzoyl peroxide/hydrocortisone) lotion 5/0.5%	✔ *
benzoyl peroxide/hydrocortisone lotion 7.5/1%	✔ *
Inova kit (benzoyl peroxide/vitamin E) pad/topical 4/5%, 8/5%	-*
Inova 4/1, 8/2 kit (benzoyl peroxide/salicylic acid/vitamin E) pad/pad/topical 4/1/5%, 8/2/5%	-*
Benzoyl Peroxide – Antibiotic Combinations	
Acanya (benzoyl peroxide/clindamycin) gel 2.5/1.2%	✔
BenzaClin (benzoyl peroxide/clindamycin) gel 5/1%	✔
Neuac (benzoyl peroxide/clindamycin) gel, kit 5/1.2%	✔
NuCaraRxPAK (benzoyl peroxide/clindamycin) 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%, pad 0.1%	✔
Differin (adapalene) cream 0.1%; 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 0.025%	✔
Avita (tretinoin) 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	

Drug	Generic Availability
Epiduo (adapalene/benzoyl peroxide) gel 0.1/2.5%	✔
Epiduo Forte (adapalene/benzoyl peroxide) gel 0.3/2.5%	-
Adainzde (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	
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%, 10/5%; with sulfur suspension 8/4% (SulfaCleanse), 9/4.5% (Clenia Plus), 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%	✔ *
sulfacetamide sodium/salicylic acid external suspension 8/2%, 10/5%	✔ *
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	-
Accutane, Amnesteem, Claravis, Myorisan, Zenatane (isotretinoin) oral capsule 10 mg, 20 mg, 30 mg, 40 mg	✔ §
Androgen Receptor Inhibitor	
Winlevi (clascoterone) cream 1%	-

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;
§Claravis is the reference standard and other products are branded generics considered bioequivalent to Claravis
‖ Avita 0.025% gel is BT rated, considered to be not therapeutically equivalent to other pharmaceutically equivalent products.
(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

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	✔	-	-	-	-

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
Erythromycin	✔	-	-	-	-
Amzeeq (minocycline)	✔	-	-	-	-
Benzoyl Peroxide – Single Entity					
Benzoyl peroxide	✔	-	-	✔	
Benzoyl Peroxide – Antibiotic Combinations					
Benzoyl peroxide/clindamycin	✔ (Acanya, Benzaclin, Onexton)	✔ (Neuac)	-	-	-
Benzoyl peroxide/ erythromycin	✔ (Benzamycin)	-	-	-	-
Benzoyl Peroxide – Other Combinations					
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/Sulfur and Combinations					
Sulfacetamide	✔ (gel, lotion)	-	-	-	-
Sulfacetamide/sulfur	-	-	✔	-	-
Oral Retinoids					
Absorica, Absorica LD, Accutane, Amnesteem, Claravis, Myorisan, Zenatane (isotretinoin)	-	-	-	-	✔
Androgen Receptor Inhibitor					
Winlevi (clascoterone)	✔				

Note: OTC only products are not listed
*Approved ages vary by product.
†Tazorac is also approved for the treatment of psoriasis.

(*Prescribing information: Absorica/Absorica LD 2020, Acanya 2020, Accutane 2010, Aczone 7.5% 2019, Aczone 5% 2018, adapalene topical solution 2020, adapalene/benzoyl peroxide/clindamycin gel 2020, Aklief 2019, Altreno 2020, Amnesteem 2018, Amzeeq 2019, Arazlo 2019, Atralin 2016, Azelex 2019, Benzaclin 2017, Benzamycin 2020, benzoyl peroxide/salicylic acid 2020, BPO 4% gel 2018, Claravis 2018, Cleocin T 2019, Clenia Plus 2021, Clindagel 2017, Differin cream 2011, Differin lotion 2018, Duac 2015, Epiduo 2018, Epiduo Forte 2015, Fabior 2018, Myorisan 2019, Onexton 2020, Retin-A 2019, Retin-A Micro 2017, sodium sulfacetamide monohydrate/salicylic acid 2019, SulfaCleanse 2017, Tazorac gel 2019, Tazorac cream 2019,Vanoxide-HC 2018, Veltin 2019, Winlevi 2020, Zenatane 2019, Ziana 2017, Clinical Pharmacology 2021, Lexi-comp 2021, Micromedex 2021*)

- 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

- 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 one 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 ($p \leq 0.001$) or tretinoin ($p \leq 0.01$).
- 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.

Androgen receptor inhibitor

- In 2 RCTs in patients (n = 1440) aged ≥ 9 years with moderate to severe facial acne, clascoterone cream (n = 709) was associated with significantly higher treatment success compared with vehicle cream (n = 712). Three coprimary endpoints were evaluated: treatment success (a 2-point reduction in IGA compared to baseline and a score of clear or almost clear), absolute change from baseline noninflammatory lesion count, and inflammatory lesion count at week 12. Patients treated with clascoterone cream achieved IGA success vs vehicle cream (Study 1: 18.4 vs 8.7%; difference, 10.1%; 95% CI, 4.1 to 16%; Study 2: 20.9 vs 6.6%; difference, 14.3%; 95% CI, 8.9 to 19.7%) at week 12. There was a significant reduction in absolute noninflammatory lesions from baseline to -20.4 and -19.5 with clascoterone treatment compared with -13 and -10.8 with vehicle in Study 1 and 2, respectively. A significant reduction in inflammatory lesions from baseline to -19.3 and -20.1 vs -15.4 and -12.6 with vehicle in Study 1 and 2, respectively. Adverse event rates were low and mostly mild, mainly trace or mild erythema (*Hebert et al 2020, Winlevi prescribing information 2020*).
  - An open-label, 9-month extension study evaluated the safety of clascoterone (n = 317) vs vehicle (n = 290) in 607 patients. Adverse events occurred in 18.3% of clascoterone patients and 17.9% of vehicle patients. The most frequent treatment-emergent adverse events (TEAEs) with clascoterone were nasopharyngitis, upper respiratory infection, sinusitis and application site acne. A total of 2.8% of clascoterone-treated patients experienced a TEAE that led to discontinuation (swelling, dryness and acne at the application site, mild polycystic ovaries, moderate hair color changes, and severe suicide attempt) vs no patients treated with the vehicle (*Eichenfeld et al 2020*).

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 Acne and Rosacea Society (endorsed by the American Academy of Pediatrics) state that acne management of pediatric patients is similar to acne treatment in older adolescents and adults. For mild acne, benzoyl peroxide, a topical retinoid, or a combination of benzoyl peroxide with an antibiotic or retinoid is recommended. 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*).
- Androgen receptor inhibitors, like clascoterone, have yet to be incorporated into treatment guidelines.

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. Altreno and Atralin product labels recommend caution in patients with a fish allergy due to the potential for allergenicity to fish protein. 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.
- Warnings for topical clascoterone include hypothalamic-pituitary-adrenal (HPA) axis suppression, greater susceptibility to systemic toxicity in pediatric patients, and hyperkalemia.
- 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 2021*, *FDA Drug Safety Communication 2014*, *Micromedex 2021*)

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, Evoclin, NuCaraClinPAK (clindamycin)	Foam, gel, lotion, solution, swab, swab + cleanser kit, gel kit	Topical	Foam and gel (Clindagel): Apply once daily. Gel (Cleocin T), lotion, solution, or swab: Apply twice daily.	If topical antibiotic therapy is longer than a few weeks, the addition of topical benzoyl peroxide is recommended. Indicated in age ≥ 12 years.
Erygel, 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)	Bar, cream, cleanser ER, external liquid, foam, gel, foaming cloths, lotion, wash + lotion kits	Topical	Cream, foam, gel, solution, lotion: Apply once daily.	Improvement is usually noted in 3 to 4 weeks.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Foaming cloths, lotion, cleanser, bar, wash, liquid: Apply 1 to 3 times daily.	
Vanoxide-HC (benzoyl peroxide/ hydrocortisone)	Lotion	Topical	Apply 1 to 3 times daily.	Product expires 3 months after dispensed.
Inova (benzoyl peroxide/ vitamin E)	Pad/topical kit	Topical	As directed.	
Inova 4/1, 8/2 kit (benzoyl peroxide/ salicylic acid/vitamin E)	Pad/pad/topical kit	Topical	As directed.	
Benzoyl Peroxide – Antibiotic Combinations				
Acanya, Benzaclin, Neuac, NuCaraRxPAK, 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)	Cream, gel, lotion, external solution, pad	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.
Altreno, Atralin, Avita, Retin-A, Retin-A Micro (tretinoin)	Lotion, cream, gel, 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.
Adainzde (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				

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Klaron, Ovace, Ovace Plus (sulfacetamide) Avar, Avar LS, Avar-e LS, Avar-e Emollient, Avar-e Green, BP 10-1, Clenia Plus, Plexion, SSS 10-5, SulfaCleanse, Sulfamez, Sumadan, Sumadan XLT, Sumaxin, Sumaxin CP (sulfacetamide/sulfur)	Monotherapy: Cream, foam, wash external 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)	Bar, lotion (sulfur only)	Topical	Apply 1 to 3 times daily.	
sulfacetamide sodium/salicylic acid	External suspension	Topical	Apply as directed by physician	
Oral Retinoids				
Absorica, Absorica LD, Accutane, Amnesteem, Claravis, Myorisan, Zenatane (isotretinoin)	Capsule	Oral	Accutane, 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. 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.
Androgen Receptor Inhibitor				
Winlevi (clascoterone)	Cream	Topical	Twice daily	Indicated in age ≥ 12 years.

Abbreviation: ER = extended release
See the current prescribing information for full details

(*Clinical Pharmacology 2021, Lexi-comp 2021*)

CONCLUSION

- Current treatment of acne vulgaris is primarily topical agents. Guidelines suggest the use of combinations to treat acne (*Eichenfield et al 2013, 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 (minocycline is brand-only). Antibiotics have a slow onset of action and may pose an 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*).
- Topical benzoyl peroxide, available OTC, is often used for initial self-treatment of acne (*Medical Letter 2020*). 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 2021*). 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*). A topical retinoid, alone or in combination with benzoyl peroxide and/or a topic antibiotic, is often used for first-line treatment of inflammatory and noninflammatory acne (*Medical Letter 2020*). Retinoid/antimicrobial combinations are more effective than either component alone, especially in patients with inflammatory acne. All topical retinoids normalize keratinization and appear to have anti-inflammatory effects.
- 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*). Isotretinoin has also been considered the most effective medication for treatment of inflammatory acne (*Medical Letter 2020*). 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. 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*).
- An androgen receptor inhibitor, clascoterone, is a newer treatment for acne with a unique mechanism of action. Phase 3 RCTs have demonstrated its superiority in efficacy over a vehicle cream (*Hebert et al 2020*). Common adverse events

are application site reactions and nasal/respiratory symptoms (*Eichenfeld et al 2020, Hebert et al 2020, Winlevi prescribing information 2020*).

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Publication Date: April 2, 2021

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 (*Centers for Disease Control and Prevention [CDC] 2021*, *Feldman et al 2014*). Epidemiologic studies of adult ADHD have estimated the current prevalence to be 4.4% in the U.S. (*Bukstein 2021*).
  - 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 2021b*).
  - 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 2021*).
- 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 2020*).
  - 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, nonstimulant 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 nonstimulant ADHD medication (*Pharmacist's Letter 2015, Krull 2021a*).
- 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 nonstimulants: 2 selective norepinephrine reuptake inhibitors (SNRIs) atomoxetine and viloxazine extended-release (ER); and 2 alpha$_2$-adrenergic agonists clonidine ER, 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)	-
Azstarys (serdexmethylphenidate/dexmethylphenidate)	-
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)	-
Relexxii (methylphenidate HCl ER)	✔
Ritalin LA (methylphenidate HCl ER)	✔
Daytrana (methylphenidate transdermal system)	-
Nonstimulants	
Strattera (atomoxetine HCl)	✔
Kapvay (clonidine HCl ER)	✔
Intuniv (guanfacine HCl ER)	✔
Qelbree (viloxazine ER)	-

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021, Facts & Comparisons 2021*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	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
Evekeo (amphetamine sulfate)		✓		✓	✓	
Evekeo ODT (amphetamine sulfate)	✓					
Adzenys ER, Adzenys XR-ODT, Dyanavel XR (amphetamine)	✓					
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; methylphenidate ER tablets		✓		✓		
Adhansia XR, Aptensio XR, Concerta, Cotempla XR-ODT, Daytrana, methylphenidate ER (CD), Jornay PM, QuilliChew ER, Quillivant XR, Relexxii, Ritalin LA (methylphenidate ER)	✓					
Azstarys (serdexmethylphenidate/dexmethylphenidate)	✓					
Qelbree (viloxazine ER)	✓					

(*Prescribing Information*: *Adderall 2020*, *Adderall XR 2020*, *Adhansia XR 2021*, *Adzenys ER 2017*, *Adzenys XR-ODT 2018*, *Aptensio XR 2019*, *Azstarys 2021, Concerta 2017*, *Cotempla XR-ODT 2017*, *Daytrana 2019, Desoxyn 2019, Dexedrine Spansule 2019*, *Dyanavel XR 2019*, *Evekeo 2019*, *Evekeo ODT 2021*, *Focalin 2021*, *Focalin XR 2021, Intuniv 2020, Jornay PM 2021, Kapvay 2020, Mydayis 2020, Methylin Oral Solution 2017, methylphenidate chewable tablets 2021, methylphenidate ER 2021, methylphenidate ER (CD) 2021, ProCentra 2017*, *Qelbree 2021, QuilliChew ER 2018*, *Quillivant XR 2018*, *Relexxii 2019, Ritalin 2021*, *Ritalin LA 2021*, *Strattera 2020*, *Vyvanse 2020, Zenzedi 2019*)

* Adderall, Evekeo, ProCentra, and Zenzedi are approved for use in children 3 years of age and older. Evekeo ODT is approved for use in patients 3 to 17 years of age. Daytrana, Desoxyn, Dexedrine Spansule, Intuniv, and Kapvay are approved for use in children 6 years of age and older. Adderall XR, Adhansia XR, Adzenys ER, Adzenys XR-ODT, Aptensio XR, Azstarys, Dyanavel XR, Focalin, Focalin XR, Jornay PM, methylphenidate ER (CD), methylphenidate ER, Methylin Oral Solution, methylphenidate chewable tablets, QuilliChew ER, Quillivant XR, Ritalin, Strattera, and Vyvanse are approved for use in patients 6 years of age and older. Cotempla XR-ODT and Qelbree are approved for use in pediatric patients 6 to 17 years of age. Ritalin LA is approved for use in pediatric patients 6 to 12 years of age. Concerta and Relexxii are 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:
  - Aptensio XR: Pediatric patients younger than 6 years of age experienced higher plasma exposure than patients 6 years and older at the same dose and high rates of AEs, most notably weight loss.
  - 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, SNRIs (atomoxetine, viloxazine ER), and alpha$_2$-adrenergic agonists (clonidine ER, guanfacine ER) 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 (*Adhansia XR FDA Clinical Review 2019, Wigal et al 2020*). 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 (*Adhansia XR FDA Clinical Review 2019)*. 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 (*Childress et al 2020, Jornay PM Prescribing Information 2021*). 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 2020, Weisler et al 2017, Wigal et al 2018a, Wigal et al 2018b, Wigal et al 2019*) (see results below in Table 3 below). An additional 6-week, randomized, placebo-controlled, double-blind, forced dose titration trial in 411 adults with ADHD similarly found that Mydayis significantly improved ADHD-RS-IV scores compared to placebo (LS mean treatment difference for all Mydayis doses combined vs placebo, -10.6; 95% CI, -13.2 to -8.0; p < 0.0001) (*Frick et al 2020*).

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

- Azstarys, a combination of serdexmethylphenidate and dexmethylphenidate, was approved based on results from a randomized, DB, PC analog classroom study *(Azstarys Prescribing Information 2021).* A total of 150 patients aged 6 to 12 years were enrolled. Following an OL, 3-week dose titration phase, patients were randomly assigned during a 1-week parallel treatment period to either the optimized dose Azstarys or placebo. After 1 week, evaluations were done using the SKAMP rating scale over 13 hours in a classroom setting. Mean change in SKAMP from baseline (primary outcome) was significantly greater with Azstarys compared with placebo (placebo-subtracted difference -5.4 [95% CI, -7.1 to -3.7]). The efficacy of Azstarys in adults and pediatric patients 13 to 17 years of age was established by pharmacokinetic bridging between Azstarys and Focalin XR (dexmethylphenidate ER) capsules.
- Qelbree (viloxazine ER), an SNRI, was shown to be superior to placebo in 3 DB, MC, randomized, PC trials in patients with ADHD.
  - Trial 1 enrolled 313 patients aged 6 to 11 years who were randomized to treatment with viloxazine ER 200 or 400 mg or placebo once daily for 8 weeks (*Nasser 2021a*). Improvements in ADHD-RS-5 total scores were reported, with LS mean changes from baseline of -17.6, -17.5 and -11.7 for viloxazine ER 200 mg, 400 mg, and placebo, respectively (p < 0.05 for both comparisons to placebo).

- Trial 2 enrolled 477 patients aged 6 to 11 years who were randomized to either viloxazine ER 100 mg or 200 mg or placebo once daily for 6 weeks (*Nasser 2020*). LS mean changes from baseline in ADHD-RS-5 total scores were -16.6, -17.7, and -10.9 for viloxazine ER 100 mg, 200 mg, and placebo, respectively ($p < 0.05$ and $p < 0.0001$ for viloxazine ER 100 mg and 200 mg vs placebo, respectively).
- A third trial evaluated viloxazine ER in 310 patients aged 12 to 17 years of age who were randomized to viloxazine ER 200 mg, 400 mg, or placebo (*Nasser 2021b*). After 6 weeks of treatment, viloxazine ER 200 mg and 400 mg resulted in LS mean changes from baseline in ADHD-RS-5 total scores of -16.0, -16.5, and -11.4 for viloxazine ER 200 mg, 400 mg, and placebo, respectively ($p < 0.05$ vs placebo for both comparisons).

- 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 nonstimulant 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 nonstimulants (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 2021a*, *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 nonstimulant 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 nonstimulants.
  - In a meta-analysis of 12 clinical trials (*Cunill et al 2013*) (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 nonstimulant 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 2019*) 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.
  - A systematic review and network meta-analysis (*Elliot et al 2020*) of 81 RCTs compared methylphenidate, atomoxetine, dexamfetamine, lisdexamfetamine, guanfacine, mixed amphetamine salts, modafinil, and bupropion for the treatment of ADHD in adults. Treatment with any ADHD pharmacotherapy was associated with statistically significant improvement in patient-reported clinical response vs placebo. When drugs were analyzed individually, only atomoxetine was found to significantly improve patient-reported clinical response compared to placebo (mean difference, -5.9; 95% CI, -12.6 to -0.4). Atomoxetine (mean difference, -3.7; 95% CI, -6.7 to -0.9), sustained-release methylphenidate (mean difference, -5.7; 95% CI, -11.2 to -0.3), and low-dose methylphenidate (mean difference,

-10.4; 95% CI, -19.0 to -2.1) were found to improve clinician-assessed clinical response compared to placebo. No significant differences were observed between individual medications when response was considered as a continuous outcome.
  - 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 cognitive behavioral therapy (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 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; newer agents such as serdexmethylphenidate/dexmethylphenidate [Azstarys] and viloxazine [Qelbree] are not addressed in the current guidelines). 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 recommends that treatment of ADHD in school-age children or adults should begin with a stimulant, either a methylphenidate- or amphetamine-based formulation (*Med Lett Drugs Ther 2020*). 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. Nonstimulants can be used in combination with stimulants or when stimulants are contraindicated, ineffective, or not tolerated.
- 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, guanfacine ER, and viloxazine 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 Concerta and Relexxii tablets are nondeformable and do not appreciably change in shape in the gastrointestinal tract, they 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.
- Viloxazine ER is contraindicated with concurrent use of MAOIs and sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic index. Viloxazine ER carries a boxed warning for suicidal thoughts and behavior in children and adolescents. It also has warnings for effects on heart rate and blood pressure and the potential for somnolence and fatigue. Patients should be screened for bipolar disorder prior to use of viloxazine ER due to the risk of activation of mania or hypomania.
  - Common AEs associated with viloxazine ER include somnolence, nausea, and vomiting.
- The alpha$_2$-adrenergic agonists are contraindicated in patients known to be hypersensitive to any constituent of the product. They carry warnings for increased risk of hypotension, bradycardia, and syncope; sedation and somnolence; rebound hypertension; and cardiac conduction abnormalities.
  - Common AEs associated with clonidine ER include somnolence, fatigue, and irritability while common AEs with guanfacine ER include somnolence, fatigue, and hypotension.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Stimulants					
Evekeo (amphetamine)	4 to 6 h	Tablets	Oral	*ADHD, narcolepsy*: Daily up to divided doses daily *Exogenous obesity*: Divided doses daily	*ADHD and narcolepsy* The first dose should be given upon awakening; additional doses at intervals of 4 to 6 hours.

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Evekeo ODT (amphetamine)	4 to 6 h	Orally disintegrating tablets	Oral	Once or twice daily in the morning	As soon as the blister pack is opened, the tablet should be placed on the patient's tongue and allowed to disintegrate without chewing or crushing. The tablet will disintegrate in saliva so that it can be swallowed.
Adzenys ER (amphetamine ER)	10 to 12 h	Suspension	Oral	Daily in the morning	The bottle should be shaken before administration.
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

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

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
					or orange juice and consumed immediately. A single capsule should not be divided. The chewable tablets must be chewed thoroughly before swallowing. A single dose should not be divided.
Desoxyn (methamphetamine)	4 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	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

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
					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 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

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Methylphenidate ER					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*).
Cotempla XR-ODT (methylphenidate ER)	12 h	Orally disintegrating tablets	Oral	Daily in the morning	As soon as the blister pack is opened, the tablet should be placed on the patient's tongue and allowed to disintegrate without chewing or crushing. The tablet will disintegrate in saliva so that it can be swallowed.
Jornay PM (methylphenidate ER)	7 to 12 h	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.

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Methylphenidate ER (CD)	8 to 12 h	Capsules	Oral	Daily in the morning	The capsule may be swallowed whole or it may be opened and the contents sprinkled onto a small amount (tablespoon) of applesauce and given immediately. The capsule contents must not be crushed or chewed.
QuilliChew ER (methylphenidate ER)	12 h	Chewable tablets	Oral	Daily in the morning	A 10 mg or 15 mg dose can be achieved by breaking in half the functionally scored 20 mg and 30 mg tablets, respectively.
Quillivant XR (methylphenidate ER)	12 h	Suspension	Oral	Daily in the morning	The bottle of Quillivant XR should be shaken vigorously for 10 seconds prior to administration. The suspension is stable for up to 4 months once reconstituted.
Relexxii (methylphenidate ER)	12 h	Tablet	Oral	Daily in the morning	The tablet must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed.
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

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
					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.	
Azstarys (serdexmethylphenidate/ dexmethylphenidate)	10 h	Capsules	Oral	Daily in the morning	The capsule may be swallowed whole or may be administered by sprinkling the capsule contents over 2 tablespoons of applesauce or 50 mL of water. The mixture should be consumed immediately.
Non-stimulants					
Strattera (atomoxetine)	10 to 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.
Qelbree (viloxazine ER)	Throughout the day (specific duration not reported)	Capsule	Oral	Daily	The capsule may be swallowed whole or may be administered by sprinkling the capsule contents over a teaspoon of applesauce. The mixture should be consumed within 2 hours, without chewing.

See the current prescribing information for full details
*References: Prescribing information for individual products, *Azstarys FDA Multi-discipline Review 2021*, *Medical Letter 2020, Pharmacist's Letter 2019, Krull 2020.*

CONCLUSION

- Both CNS stimulants and nonstimulants 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 nonstimulants 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 efficacy of the nonstimulant viloxazine ER in comparison to other nonstimulants is unknown. 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 2021a*).
- 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 2021*).
- 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: July 26, 2021

MEDICATION*	MARKETER	AVAILABILITY
Nuvigil (armodafinil)	Teva Pharmaceuticals	**Brand/Generic:** 50, 150, 200, 250 mg tablets
Provigil (modafinil)	Teva Pharmaceuticals	**Brand/Generic:** 100, 200 mg tablets
Sunosi (solriamfetol)	Jazz Pharmaceuticals	**Brand:** 75, 150 mg tablets
Wakix (pitolisant)	Harmony Biosciences, LLC	**Brand:** 4.45, 17.8 mg tablets
Xyrem (sodium oxybate)	Jazz Pharmaceuticals	**Brand:** 500 mg/mL oral solution
Xywav (calcium, magnesium, potassium, and sodium oxybates)	Jazz Pharmaceuticals	**Brand:** 500 mg/mL oral solution

Therapeutic Classes:
- Central Nervous System (CNS) Stimulants (armodafinil, modafinil)
- Histamine-3 (H_3) Receptor Antagonist/Inverse Agonist (pitolisant)
- CNS Depressants (sodium oxybate/oxybate salts)
- Dopamine and Norepinephrine Reuptake Inhibitor (DNRI) (solriamfetol)

Purpose of Review: To evaluate the safety and efficacy of agents used for narcolepsy, including the new formulation, Xywav (oxybate salts), for formulary consideration.

* Brand names are indicated by bolded text; generic-only products are indicated by non-bolded text

Note: Information on indications, pharmacology, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

SUMMARY

Background

- Narcolepsy is a chronic neurological disorder of hypersomnia and its associated symptoms are potentially debilitating. Narcolepsy is typically classified as type 1 (narcolepsy with cataplexy) or type 2 (narcolepsy without cataplexy) (*Bhattarai & Sumerall 2017, Szabo et al 2019*). Narcolepsy type 1 is estimated to have a prevalence of 25 to 50 per 100,000 people. Narcolepsy typically begins in the teens and early twenties, but occasionally occurs as early as age 5 or after age 40. The prevalence of narcolepsy type 2 is uncertain, as it is less well studied and more difficult to diagnose; however, it has been estimated as 20 to 34 per 100,000 people (*Scammel 2020a*). Excessive daytime sleepiness (EDS) is present in all patients with narcolepsy. Other symptoms include cataplexy, hypnagogic hallucinations, and sleep paralysis; however, only about one-third of patients have all 4 symptoms (*Scammell 2020a*). Patients may also experience fragmented nighttime sleep. Patients with narcolepsy have been shown to be at increased risk for cardiovascular (CV), metabolic, and psychiatric comorbidities compared with individuals without narcolepsy (*Xywav dossier 2020*). Pharmacological interventions are the most common approach for treating narcolepsy. Current medications have been developed to target symptoms; however, most patients do not experience complete resolution despite receiving optimal standard treatment (*Bhattarai & Sumerall 2017, Scammell 2020b).*
- Obstructive sleep apnea (OSA) is a disorder that is characterized by obstructive apneas and hypopneas caused by repetitive collapse of the upper airway during sleep. The diagnosis should be considered whenever a patient presents with symptoms such as EDS, snoring, and choking or gasping during sleep, particularly in the presence of risk factors such as obesity, male gender, and advanced age (*Kline 2019*). Besides EDS, untreated OSA has many potential adverse clinical consequences including impaired daytime function, metabolic dysfunction, and an increased risk of CV disease and mortality. All patients diagnosed with OSA should be offered positive airway pressure (PAP) as initial therapy. Continuous positive airway pressure (CPAP) involves maintenance of a positive pharyngeal transmural pressure so that the intraluminal pressure exceeds the surrounding pressure. CPAP also stabilizes the upper airway through increased end expiratory lung volume. As a result, respiratory events due to upper airway collapse (eg, apneas, hypopneas) are prevented. Other options to PAP include oral appliances or upper airway surgery in severe cases with a surgically correctable upper airway obstruction. Wakefulness-promoting pharmacological agents (eg,

modafinil, armodafinil) may be beneficial as adjunctive therapy for EDS that persists despite adequate and successful conventional OSA therapy (*Kryger 2020*).

- Shift work disorder (SWD) is a circadian rhythm sleep disorder that occurs in individuals who work night shifts. These individuals commonly experience difficulties with both sleep and alertness at desired times, and shift work is increasingly recognized as a risk factor for a variety of adverse health outcomes, including diabetes, cancer, and CV disease. While some shift workers show circadian adjustment to their work schedule, most do not. Up to one-third of shift workers report regular, persistent complaints of insomnia and/or excessive sleepiness that meet formal criteria for SWD (ie, development of sleep disturbances and impairment of waking alertness and performance) (*Cheng & Drake 2019, Morgenthaler et al 2007b*). Minimum measures to improve sleep after a night shift include a regular sleep schedule (ie, "anchor sleep"), light-blocking shades, and ambient noise control. Treatment with modafinil or armodafinil is an option in patients with persistent sleepiness in conjunction with nonpharmacologic measures to improve sleep and alertness. The magnitude of benefit may vary among individuals. The observed benefits in randomized controlled trials (RCTs) have been modest, however, and adverse effects (AEs) may outweigh benefits in some patients (*Cheng & Drake 2019*).

Indications

- Provigil/Nuvigil
  - Provigil (modafinil) received Food and Drug Administration (FDA) approval to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy in December 1998; approval was granted for OSA and SWD in January 2004 (*FDA Web site*).
  - Nuvigil (armodafinil), the R-enantiomer of modafinil, was approved as a new formulation in June 2007 to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, OSA, or SWD (*FDA Web site*).
  - Modafinil and armodafinil are both Schedule IV controlled substances.
- Sunosi (solriamfetol), received FDA approval in March 2019 to improve wakefulness in adult patients with EDS associated with narcolepsy or OSA (*FDA Web site*). Solriamfetol has orphan drug designation in the U.S. for narcolepsy (*Sunosi press release 2019*). Solriamfetol is a Schedule IV controlled substance.
- Wakix (pitolisant), received FDA approval on August 15, 2019 for the treatment of EDS in adults with narcolepsy with orphan and priority review designations. In October 2020, pitolisant gained approval for the additional indication of cataplexy in adults. Pitolisant has shown no abuse potential and is the only unscheduled agent indicated for the treatment of narcolepsy and narcolepsy-cataplexy (*FDA web site*).
- Xyrem/Xywav
  - Xyrem (sodium oxybate) was approved in July 2002 with orphan drug status under priority review for the treatment of cataplexy associated with narcolepsy. Use of Xyrem was expanded to the pediatric population in October 2018 (*FDA Web site*). Xyrem is indicated for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy. A new formulation of oxybate salts, Xywav, received FDA approval in July 2020 for the same indication as Xyrem (*FDA Web site, Xywav dossier 2020*). Xywav contains the same active moiety as Xyrem but is made up of a unique composition of cations (calcium, magnesium, potassium, and sodium oxybates) that contains 92% less sodium than Xyrem at all nightly doses. Xyrem and Xywav are Schedule III controlled substances (*Xywav dossier 2020*).
    - The recommended daily adult dose of Xyrem (6 to 9 g/night) adds 1100 to 1640 mg of sodium to total daily intake, which accounts for 73 to 109% of the total daily sodium intake (no more than 2300 mg and ideally < 1500 mg for most adults) recommended by the American Heart Association (AHA) (*AHA 2017*). The Xyrem product labeling includes a warning regarding the high sodium content and advises monitoring of symptoms and daily sodium intake in patients sensitive to salt intake (eg, those with heart failure [HF], hypertension [HTN], or renal impairment) (*Xyrem prescribing information 2020*).

Pharmacology

- The mechanism(s) through which modafinil/armodafinil promotes wakefulness is unknown, but may involve increased dopaminergic signaling through blocking of dopamine reuptake in a manner distinct from amphetamines (*Scammell 2020a*).
  - PK studies have shown that R-modafinil has a longer half-life than S-modafinil (10 to 14 vs 3 to 4 hours). Additionally, it has been reported that the elimination of S-modafinil is 3 times faster than that of R-modafinil. Because R-modafinil has a longer half-life than modafinil, its administration results in higher plasma concentrations later in the waking day compared with modafinil on a ''mg-to-mg'' basis (*Harsh et al 2006*).
- The mechanism of action of pitolisant in EDS in adult patients with narcolepsy is unclear. However, its efficacy could be mediated through its activity as an antagonist/inverse agonist at histamine-3 (H_3) receptors.
- Sodium oxybate is a central nervous system (CNS) depressant. Its mechanism of action in the treatment of narcolepsy is unknown. Xyrem (sodium oxybate) is the sodium salt of gamma-hydroxybutyrate (GHB), an endogenous compound

and metabolite of the neurotransmitter gamma-aminobutyric acid (GABA). Oxybate salts is a mixture of calcium oxybate, magnesium oxybate, potassium oxybate, and sodium oxybate. It is hypothesized that the therapeutic effects of sodium oxybate and oxybate salts on cataplexy and EDS are mediated through GABA actions at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons (*Xywav prescribing information 2020*).

- Solriamfetol is a selective dopamine and norepinephrine reuptake inhibitor (DNRI) with wake-promoting effects (*Scammell 2020a*).

Clinical Efficacy

- Efficacy measures
  - Objective measures of EDS as assessed by sleep latency (ie, the time interval between attempting to fall asleep and the onset of sleep) measured using polysomnography (PSG):
    - Maintenance of Wakefulness Test (MWT) (*Freedman 2019*)
      - The MWT measures an individual's ability to remain awake during the daytime in a darkened, quiet environment. Patients are instructed to remain awake for as long as possible during serial 40-minute test sessions, and sleep latency is determined as the mean number of minutes patients could remain awake in the first 4 test sessions. Among healthy individuals, the mean sleep latency is approximately 30 minutes, with > 97% of individuals having a mean sleep latency ≥ 8 minutes; thus, a mean sleep latency < 8 minutes is generally considered abnormal. Staying awake for at least 40 minutes during all 4 sessions is strong objective evidence that an individual can stay awake. A mean sleep latency between 8 and 40 minutes has uncertain significance.
    - Multiple Sleep Latency Test (MSLT) (*American Sleep Association Web site, Thorpy 1992*)
      - The MSLT also measures an individual's ability to remain awake during the daytime in ideal quiet conditions. The MSLT consists of 5 nap opportunities to determine both severity of sleepiness and presence of 2 or more sleep onset rapid eye movement (REM) periods. The absence of sleep on any nap opportunity is recorded as a sleep latency of 20 minutes. A mean sleep latency of 0 to 5 minutes indicates severe sleepiness, while 5 to 10 minutes is rated as moderate sleepiness.
  - Subjective measures of EDS:
    - Epworth Sleepiness Scale (ESS) (*Johns 1991*)
      - The ESS is an 8-item questionnaire by which patients rate their perceived likelihood of falling asleep during usual daily life activities.
      - The score ranges from 1 to 24 points; 9 to 24 points indicates abnormal (possibly pathologic) sleepiness.
    - Clinical Global Impression of Change (CGI-C)
      - The CGI-C is a 7-point physician-rated scale that assesses symptom severity and treatment response (range: 1 [very much improved] to 7 [very much worse]).
    - Patient Global Impression of Change (PGI-C)
      - The PGI-C is a 7-point patient-rated scale that assesses their symptom change from baseline (range: 1 [very much improved] to 7 [very much worse]).
  - Sustained Attention to Response Task (SART) (*Fronczek et al 2006*)
    - The SART is an objective laboratory measure of sustained vigilance and attention. Patients are presented with a series of numbers (ranging from 1 to 9) 225 times. Patients must press a button except when the number presented is 3. The SART comprises 3 error scores: the number of times a button was pressed inappropriately ("NO GO"), the number of times key pressing was missed ("GO"), and the sum of these 2 scores.
- Modafinil/armodafinil:
  - A systematic review and meta-analysis (9 RCTs, N = 1054) was conducted to evaluate the efficacy and safety of modafinil (any dose or regimen) vs no active treatment or other drugs in the treatment of narcolepsy (*Golicki et al 2010*). The primary endpoints were elimination of EDS assessed by objective laboratory tests (MSLT, MWT) or validated subjective outcome measures (ESS) and number and duration of severe somnolence, sleep attacks and naps, as reported by patients.
    - Compared with placebo, modafinil significantly increased mean sleep latency assessed by the MSLT (3 studies): weighted mean difference (WMD) 1.11 minutes (95% confidence interval [CI], 0.55 to 1.66); I^2 = 0%; test for overall effect: Z = 3.90 (p < 0.0001). As assessed by the MWT (6 studies), there was a greater increase in mean sleep latency with modafinil vs placebo: WMD 2.82 minutes (95% CI, 2.40 to 3.24); I^2 = 0%; test for overall effect: Z = 13.14 (p < 0.00001). Compared with placebo, modafinil significantly reduced the ESS score (6 studies): WMD -2.73 points (95% CI, -3.39 to -2.08); I^2 = 0%; test for overall effect: Z = 8.17 (p < 0.00001). Modafinil also improved the number (p = 0.006) and duration (p = 0.03) of severe somnolence episodes, sleep attacks, and naps per day as compared with placebo, but did not reduce the number of cataplexy attacks per day (4 studies): WMD 0.02 (95% CI, -0.27 to 0.31); I^2 = 71%; test for overall effect: Z = 0.13 (p = 0.90). Quality of life (QoL) as measured by the Short Form (SF)-36 and validated narcolepsy-specific questionnaire (2 studies) indicated

significant improvement with modafinil vs placebo in 5 out of 7 narcolepsy-specific domains, SF-36 mental health summary scale and 4 (modafinil 200 mg/day) or 5 (modafinil 400 mg/day) SF-36 domains.

- A 12-week, Phase 3, double-blind (DB), placebo-controlled (PC), multicenter (MC) RCT (N = 196) assessed the efficacy and safety of armodafinil for the treatment of EDS in patients with narcolepsy (*Harsh et al 2006*). Patients were randomized to either armodafinil 150 or 250 mg once daily. The co-primary endpoints were change from baseline in mean sleep latency on the MWT 9:00 AM to 3:00 PM and the proportion of patients with at least minimal improvement on the physician-rated CGI-C.
  - At the final visit, mean MWT 9:00 AM to 3:00 PM sleep latency increased 1.3, 2.6, and 1.9 minutes from baseline in the 150 mg, 250 mg, and armodafinil combined groups, respectively, and decreased 1.9 minutes from baseline in the placebo group. Treatment differences from placebo were 3.2, 4.5, and 3.8 minutes in the 150 mg, 250 mg, and armodafinil combined groups, respectively (all $p < 0.01$). The proportion of patients with at least minimal improvement in the CGI-C was significantly higher for the armodafinil 150 mg, 250 mg, and combined groups compared with placebo at all time points during the study ($p < 0.0001$ for both individual doses and the combined group vs placebo at final visit). The proportion of patients rated as minimally, much, and very much improved on the CGI-C from baseline to final visit was 21%, 33% and 16%, respectively, for armodafinil 150 mg; 20%, 35%, and 18%, respectively, for armodafinil 250 mg; 20%, 34%, and 17%, respectively, for the armodafinil combined group; and 17%, 12%, and 3%, respectively, for placebo. Armodafinil 150 and 250 mg/day reduced the mean daily number of unintended sleep episodes by 33% and 44%, respectively, compared with a 10% reduction in the placebo group ($p < 0.0001$ for overall treatment comparison). The mean number of daily naps was reduced by 41%, 44%, and 22%, respectively, for the armodafinil 150 mg, armodafinil 250 mg, and placebo groups ($p = 0.0039$ for overall treatment comparison). The mean number of mistakes/near misses/accidents was reduced by 43% and 30% in the armodafinil 150 mg and 250 mg groups, respectively, compared with a 10% reduction in the placebo group; however, these differences were not statistically significant ($p = 0.1792$ for overall treatment comparison).
- A systematic review and meta-analysis (11 modafinil RCTs [N = 723] and 5 armodafinil RCTs [N = 1009]) evaluated the efficacy of modafinil and armodafinil in treating EDS in patients with OSA (*Kuan et al 2016*). Most trials investigated whether modafinil or armodafinil with concurrent CPAP use improved sleepiness, neurocognitive performance, and functional outcome in patients with sleep apnea. The primary endpoints were sleep latency assessed by the MSLT or MWT, ESS, Karolinska Sleepiness Scale (KSS), and Stanford Sleepiness Scale (SSS).
  - ESS scores in patients receiving CPAP were significantly reduced with modafinil (5 RCTs, WMD, -2.95 [95% CI, -3.73 to -2.17]) and armodafinil (4 RCTs, WMD, -2.78 [95% CI, -3.51 to -2.05]) compared with placebo ($I^2 = 0\%$). Sleep latency assessed by the MWT was significantly increased in the modafinil group (WMD, 2.51 [95% CI, 1.5 to 3.52]) and in the armodafinil group (WMD, 2.71 [95% CI, 0.02 to 5.37]) vs placebo. However, a meta-analysis of data from 3 RCTs that compared the effects of modafinil and placebo on sleep latency, as assessed by the MSLT found no significant differences. Four studies evaluated the effects of modafinil on subjective sleepiness during acute CPAP withdrawal or in CPAP-naïve patients with OSA. There was a significant reduction in daytime sleepiness duration ($p < 0.05$), significant improvements on the ESS ($p = 0.003$), KSS ($p = 0.04$ and $p = 0.01$), SSS ($p = 0.03$), and daytime sleepiness visual analog scale ($p = 0.01$). A non-significant trend of improved self-reported sleepiness on the ESS after armodafinil use among patients with OSA before CPAP treatment was observed in 1 study ($p = 0.066$). The proportion of patients with improvement on the CGI-C was evaluated in 3 RCTs of modafinil and 4 RCTs of armodafinil. There was significant improvement in both the modafinil and armodafinil groups vs the placebo group, with pooled risk ratios (RR) of 1.94 (95% CI, 1.53 to 2.44) and 1.48 (95 % CI, 1.17 to 1.87), respectively. The results on neurocognitive performance were inconsistent.
- A 3-month, Phase 3, DB, PC, MC RCT (N = 209) investigated the efficacy and safety of modafinil for the treatment of sleepiness in patients with SWD (*Czeisler et al 2005*). Patients received modafinil 200 mg 30 to 60 minutes before each night shift. The primary endpoints were the CGI-C rating for sleepiness during the night shift, including the commute to and from work, at the final visit and change between baseline and the final visit in overall mean sleep latency based on nighttime MSLT.
  - Seventy-four percent of patients in the modafinil group were rated as at least minimally improved on the CGI-C at the final visit, as compared with 36% in the placebo group ($p < 0.001$). Overall mean sleep latency, as measured by the MSLT, increased from 2.1 minutes at baseline to 3.8 minutes at the final visit with modafinil (change, 1.7 minutes; $p < 0.001$) but not with placebo (2.04 at baseline vs 2.37 at the final visit; change, 0.3; $p = 0.24$). Sleep latency was significantly greater in the modafinil group than in the placebo group ($p = 0.002$). This improvement in sleep latency with modafinil vs placebo was found at 2:00 AM ($p = 0.02$) and 4:00 AM ($p < 0.001$), but not at 6:00 AM ($p = 0.45$) or 8:00 AM ($p = 0.17$). Patients who were receiving modafinil also had a reduction in the frequency and duration of lapses of attention during nighttime testing of their performance on the Psychomotor Vigilance Test (change from baseline, a reduction in lapse frequency of 2.6 vs an increase of 3.8, respectively; $p < 0.001$), and fewer proportions of patients reported having had accidents or near accidents while commuting home (29%

vs 54%, respectively; < 0.001). Despite these benefits, patients treated with modafinil continued to have excessive sleepiness and impaired performance at night.

- A 12-week, DB, PC, MC RCT (N = 254) assessed the effect of armodafinil on the physiologic propensity for sleep and cognitive performance during usual night shift hours in patients with excessive sleepiness associated with chronic moderate to severe SWD (*Czeisler et al 2009*). The primary endpoints were change from baseline to final visit in overall mean sleep latency as assessed by the MSLT and the proportion of patients with at least minimal improvement in the CGI-C during the night shift and commute to and from work at the final visit.
  - Armodafinil significantly improved mean sleep latency from 2.3 minutes at baseline to 5.3 minutes at final visit, compared with a change from 2.4 minutes to 2.8 minutes in the placebo group (p < 0.001). A total of 89 (79%) armodafinil patients were rated as improved on the CGI-C at the final visit compared with 61 (59%) of the placebo patients (p = 0.001). At the final visit, armodafinil was associated with significant improvement as reported in patient diaries, including maximum level of sleepiness during the night shift (p < 0.001) and commute home (p = 0.003) and the mean number of mistakes, accidents, or near misses during the night shift (p = 0.004), but not during the commute home (p = 0.12) compared with placebo.
- A 40-week, open-label (OL) extension study assessed the long-term efficacy and safety of modafinil in 478 patients with EDS associated with narcolepsy who completed 1 of the 2 pivotal 9-week RCTs of modafinil (*Mitler et al 2000*). A flexible-dose regimen (ie, 200, 300, or 400 mg daily) was followed in 1 study. In the second study, patients received 200 mg/day for 1 week, followed by 400 mg/day for 1 week, then either 200 or 400 mg doses for the duration of the study; the majority (~75%) received 400 mg/day.
  - Disease severity improved in > 80% of patients throughout the 40-week study. At weeks 2, 8, 24, and 40, disease severity was “much improved” or “very much improved” in 49, 58, 59, and 58% of patients, respectively. The mean ESS score improved significantly from 16.5 at OL baseline to 12.4 at week 2 and remained at that level through week 40 (p < 0.001). QoL scores at weeks 4, 8, 24, and 40 were significantly improved vs OL baseline scores for 6 of the 8 SF-36 domains (p < 0.001). The most common treatment-related AEs were headache (13%), nervousness (8%), and nausea (5%). Most AEs were mild to moderate. Forty-three patients (9.0%) discontinued treatment because of AEs.
- The long-term efficacy and safety of armodafinil in patients with EDS associated with treated OSA, SWD, or narcolepsy who completed one of four 12-week pivotal RCTs were assessed in a 12-month, flexible-dose (50 to 250 mg/day), OL extension study. Of 743 enrolled patients (474 with treated OSA, 113 with SWD, and 156 with narcolepsy), 57% of patients completed 12 months or more of treatment (*Black et al 2010*).
  - Compared with baseline, minimal or greater improvement on the CGI-C was reported by most patients in the 3 diagnostic groups (75% to 92%) at final visit; patients in the SWD group reported the greatest improvement. A rating of much or very much improved was reported at the final visit by 65% (295/457) of patients with treated OSA (95% CI, 60.2 to 68.9), 88% (92/105) with SWD (95% CI, 81.3 to 93.9), and 62% (93/150) with narcolepsy (95% CI, 54.2 to 69.8). At baseline, the proportion of patients with a normal ESS score (ie, < 10) was 0.4% (2/454) in the treated OSA group and 3.4% (5/147) in the narcolepsy group. At the final visit, the mean ESS score was reduced by 6.4 (95% CI, -6.90 to -5.94) in the treated OSA group and by 4.3 (95% CI, -5.20 to -3.49) in the narcolepsy group. The proportion of patients with an ESS score < 10 at final visit was 54.8% (249/454) for treated OSA and 31.3% (46/147) for narcolepsy. At final visit, mean global Brief Fatigue Inventory (BFI) scores were reduced by 1.7 (95% CI, -1.88 to -1.43) in the treated OSA group, 2.3 (95% CI, -2.75 to -1.87) in the SWD group, and 1.7 (95% CI, -2.13 to -1.35) in the narcolepsy group; mean worst fatigue scores were reduced by 1.8 (95% CI, -2.13 to -1.57) in the treated OSA group, 2.4 (95% CI, -3.06 to -1.83) in the SWD group, and 1.5 (95% CI, -2.00 to -1.07) in the narcolepsy group. The most commonly reported AEs were headache (25%), nasopharyngitis (17%), insomnia (14%), and upper respiratory tract infection (10%). Most AEs were mild or moderate.

- Pitolisant:
  - The efficacy and safety of pitolisant were evaluated in two Phase 3, active-controlled, DB, PC, MC pivotal RCTs conducted in Europe/South America evaluating the treatment of EDS in adults with narcolepsy with or without cataplexy (HARMONY 1 and HARMONY 1bis) (*Dauvilliers et al 2013*, *Wakix dossier 2019, Wakix FDA clinical review 2019*). Both studies included an 8-week treatment period which consisted of a 3-week dose titration phase followed by a 5-week stable dose phase. During the 3-week flexible dosing period, the dose was determined according to the investigator’s judgement based on individual clinical efficacy and safety. The primary endpoint was the difference in change in ESS scores between the pitolisant and placebo groups at 8 weeks. In both trials, superiority of pitolisant over placebo was tested first, then, if shown to be superior, the non-inferiority of pitolisant vs modafinil was tested based on a non-inferiority margin of 2 ESS points.
    - In HARMONY 1 (*Dauvilliers et al 2013*), 95 patients were randomized to receive pitolisant 10, 20, or 40 mg (expressed as salt form; equivalent to 8.9, 17.8, and 35.6 mg) per day; modafinil 100, 200, or 400 mg per day; or placebo. Of the 94 patients in the intent-to-treat (ITT) analysis, 81% had cataplexy, 45% had received psychostimulants (mostly modafinil or methylphenidate) and 35% were receiving anticataplectic drugs and continued them at stable doses during the trial (sodium oxybate, n = 8; antidepressants, n = 25).

- The primary analysis of between-group differences in mean ESS score at endpoint (adjusted for baseline) showed pitolisant to be superior to placebo (mean difference [MD] -3.0; 95% CI, -5.6 to -0.4; p = 0.024), but not non-inferior to modafinil (MD 0.12; 95% CI, -2.5 to 2.7; p = 0.250).
- A post-hoc analysis of ESS responder rate (final ESS score ≤ 10) showed a significantly greater response with pitolisant vs placebo (13 vs 45%; MD 4.4 [95% CI, 2.1 to 9.2]; p < 0.0006) and a similar response between pitolisant and modafinil (45 vs 46%; MD 1.0 [95% CI, 0.68 to 1.6]; p = 0.908).
- MWT values decreased from baseline in the placebo group but improved in the pitolisant group demonstrating superiority of pitolisant (MD 1.47; 95% CI, 1.01 to 2.14; p = 0.044). MWT also improved from baseline in the modafinil group. There was no statistically significant difference between pitolisant and modafinil (MD 0.77; 95% CI, 0.52 to 1.13; p = 0.173).
- NO GO error scores in the SART were similar between baseline and end of treatment in the placebo group, whereas they decreased in the pitolisant group, with a statistically significant difference between groups (p = 0.038). Changes in the modafinil and pitolisant groups were not statistically different (p = 0.765). There were no differences in changes from baseline between either pitolisant and placebo or pitolisant and modafinil in either the SART GO scores (p = 0.176, p = 0.141) or total SART scores (p = 0.053; p = 0.370).
- The European Quality-of-Life Questionnaire (EQ-5D) values were similar in all 3 groups, whereas patient global impression on treatment (PGO) improved only slightly more for pitolisant or modafinil than for placebo.
- In post-hoc analyses, pitolisant was superior to placebo (MD 0.38; 95% CI, 0.16 to 0.93; p = 0.034) but not non-inferior to modafinil (MD 0.54; 95% CI, 0.24 to 1.23; p = 0.138) for improvement in daily cataplexy rate from baseline.
- AEs occurred in 22 patients receiving pitolisant, 26 receiving modafinil, and 10 receiving placebo. The most frequent AEs were headache for the 3 groups; insomnia, abdominal discomfort, and nausea for pitolisant; and abdominal discomfort, nausea, diarrhea, dizziness, anxiety, and irritability for modafinil.

▪ HARMONY 1bis (unpublished) (*Wakix dossier 2019, Wakix FDA clinical review 2019*) compared pitolisant titrated to a maximum dose of 20 mg per day, modafinil 200 to 400 mg per day, and placebo in 166 patients. Of the 164 patients included in the extended ITT population, a history of cataplexy was present in 50 (75%) patients in the pitolisant group, 50 (77%) in the modafinil group, and 26 (81%) in the placebo group. Patients with severe cataplexy were allowed to remain on their anticataplectic medication at a stable dose except tricyclic antidepressants (TCAs).

- The pitolisant group had a significantly greater ESS score improvement from baseline compared with placebo, demonstrating superiority. The mean change from baseline in ESS score (± standard deviation [SD]) was -4.5 (4.6) for pitolisant and -3.7 (5.6) for placebo (treatment effect: -2.12; 95% CI, -4.10 to -0.14; p = 0.036). The mean change from baseline in ESS score (±SD) was -7.8 (5.8) for modafinil; the non-inferiority of pitolisant compared to modafinil could not be concluded (treatment effect: 2.83; 95% CI, 1.10 to 4.55; p = 0.002), most likely due to an imbalance between dosages of both drugs and the short treatment period.
  - The upper dose of pitolisant was limited to 20 mg daily (one-half the maximum dose allowed in other trials), while modafinil was titrated up to the recommended dosing of 200 mg or 400 mg daily.
- The ESS responder rate (final ESS score ≤ 10 or ESS score reduction ≥ 3) was significantly greater in the pitolisant group (64.2%) compared to the placebo group (34.4%) (RR 2.10; p = 0.002). There was no significant difference between pitolisant and modafinil (64.2% vs 76.9%; RR 0.86; p = 0.052).
- MWT values decreased from baseline in the placebo group but improved in the pitolisant group (p = 0.022). MWT also improved from baseline in the modafinil group; however, no statistically significant difference between pitolisant and modafinil was seen (p = 0.198).
- The NO GO error scores in the SART decreased in the pitolisant group, with a statistically significant treatment difference compared with placebo (p = 0.002); changes in the modafinil and pitolisant groups were not statistically different.
- Differences in weekly cataplexy rate (WCR) between pitolisant and placebo were not significant (MD -1.00; 95% CI, -2.12 to 0.13; p = 0.077), nor were the differences between pitolisant and modafinil (MD 0.05; 95% CI, -0.55 to 0.65; p = 0.865).
- The most frequent AEs were headache in all 3 groups; nausea, nasopharyngitis, and dizziness in the pitolisant group; nasopharyngitis in the modafinil group; and dizziness, diarrhea, insomnia, and fatigue in the placebo group.

○ The efficacy and safety of pitolisant on cataplexy in 106 patients with narcolepsy were evaluated in a DB, PC, MC RCT (HARMONY CTP; *Szakacs et al 2017*). Patients received 3 weeks of flexible dosing (5, 10, or 20 mg as determined by the investigator based on efficacy and tolerance) followed by 4 weeks of stable dosing (5, 10, 20, or 40 mg). The primary endpoint was the change in the average number of cataplexy attacks per week as recorded in patient diaries (ie, the WCR between the 2-week baseline period and the 4-week stable dosing period). The cataplexy reduction was measured by the ratio $WCR_{f/b} = WCR_f/WCR_b$.

- In the stable dosing phase, 64.8% of patients (35/54) in the pitolisant group received the maximum dose of 40 (35.6) mg.
- From a baseline WCR of 9.15 in the pitolisant group and 7.31 in the placebo group, the WCR was significantly reduced by a relative 75% in the pitolisant group (final WCR = 2.27; $WCR_{f/b}$ = 0.25) compared with 38% in the placebo group (final WCR = 4.52; $WCR_{f/b}$ = 0.62; rate ratio [rR] = 0.51; 95% CI, 0.44 to 0.60; p < 0.0001).
  - In post-hoc analyses, this effect remained significant (all p < 0.0001) for each subgroup of patients receiving 10 mg (n = 7), 20 mg (n = 9), or 40 mg (n = 35) as their stable dose.
  - In a pre-specified analysis, the effect of pitolisant was unchanged, irrespective of whether patients used concomitant anticataplectic treatment pre-inclusion. The geometric mean of the ratio $WCR_{f/b}$ for patients who were receiving concomitant anticataplectic treatment (rR 0.49; 95% CI, 0.31 to 0.82; n = 12) or did not receive this medication (rR 0.51; 0.11 to 2.28; n = 93) were not significantly different ($p_{interaction}$ = 0.455).
- For almost all secondary endpoints, a significant superiority of pitolisant was shown (ie, proportion of patients with WCR > 15 at the end of treatment, mean ESS decrease, patient proportion with final ESS ≤ 10, MWT mean change, CGI-C, PGO, and frequency of hallucinations).
- The proportion of patients reporting AEs did not differ significantly between those receiving pitolisant and those receiving placebo (31% for pitolisant vs 35% for placebo); however, double the number of AEs were considered treatment-related with pitolisant compared with placebo (28% for pitolisant vs 12% for placebo; p = 0.048). The most frequent AEs were headache for both treatment groups; irritability, anxiety, and nausea for the pitolisant group; and somnolence for the placebo group.

○ A 12-month, OL, MC, uncontrolled longitudinal study (HARMONY 3) was conducted to evaluate the long-term safety of pitolisant (*Dauvilliers et al 2019*). In addition, a 5-year extension of HARMONY 3 was conducted in the French cohort of patients. A total of 102 patients were treated. Sixteen patients were already treated through the authorization for temporary use (ATU) and 86 patients were naïve to pitolisant.

- In the 12-month analysis (N = 68; 34 prematurely withdrew), the mean change from baseline in ESS score (±SD) was -4.63 (4.91) and about two-thirds (44/68) of patients who completed the study were ESS responders (final ESS score ≤ 10 or ESS score reduction ≥ 3). On the CGI-C scale, investigators rated 94.1% of patients who completed 12 months of treatment as improved. The number of complete (generalized) cataplexy attacks per day decreased by 76% between baseline (0.33) and 12 months (0.08) in the subgroup of 44 patients with completed sleep diaries through the 12-month visit; the number of partial cataplexy attacks per day decreased by 65% between baseline (0.77) and 12 months (0.27). The most frequently reported treatment-emergent AEs (TEAEs) were headache (11.8%), insomnia (8.8%), weight gain (7.8%), anxiety (6.9%), depression (4.9%) and nausea (4.9%).
- In the 5-year extension, the decrease in ESS score (±SD) achieved by the study population at the end of the first 12-month period was maintained and continued during the extended follow-up period, with -4.41 (5.38) after 2 years of treatment (n = 45), -4.45 (6.16) after 3 years of treatment (n = 38), -4.76 (5.73) after 4 years of treatment (n = 34), and -6.07 (7.19) after 5 years of treatment (n = 14). The most commonly reported TEAEs were headache (19.5%), weight gain (18.2%), insomnia (11.7%), anxiety (11.7%), depression (11.7%), and nausea (11.7%) (*Wakix dossier 2019*).
- No new safety signals were identified during long-term exposure to pitolisant for up to 5 years compared with the safety profile identified in previous RCTs.

○ A postmarketing observation study in Europe is ongoing and will follow patients for up to 5 years. The AE profiles in these long-term studies, and in the European postmarketing databases, are similar to the AE profile observed during the short-term clinical trials. Of note, fewer than 100 patients with narcolepsy have received the proposed highest recommended dose of pitolisant (35.6 mg). However, narcolepsy is an orphan indication and no clear association between dose and AEs was evident from the narcolepsy clinical trials (*Wakix FDA summary review 2019*).

- Sodium oxybate/oxybate salts:

○ A systematic review and meta-analysis (N = 6 RCTs and 5 companion reports, N = 741) evaluated the efficacy and safety of sodium oxybate in narcolepsy-cataplexy patients (*Alshaikh et al 2012*). Included trials ranged from 4 to 12 weeks in duration. The dose of sodium oxybate was between 4.5 to 9 g per night in most of the studies. The primary endpoint was elimination of EDS according to subjective or objective indicators.

- Sodium oxybate (usually 9 g/night) was superior to placebo for reducing mean weekly cataplexy attacks (n = 2 RCTs, MD: -8.46, 95% CI, -15.27 to -1.64), heterogeneity: I^2 = 0%, test for overall effect: Z = 2.43 [p = 0.01]); increasing the MWT (n = 2 RCTs, MD: 5.18, 95% CI, 2.59 to 7.78, I^2 = 0%, Z = 3.93 [p < 0.0001]); and reducing sleep attacks (n = 2 RCTs, MD: -9.65, 95% CI, -17.72 to -1.59), I^2 = 13%, Z = 2.35 [p = 0.02]). Data from 3 RCTs indicated an increase in CGI-C scores (RR: 2.42, 95% CI, 1.77 to 3.32, I^2 = 0%, Z = 5.53 [p < 0.00001]). Sodium oxybate did not significantly increase REM sleep vs placebo (n = 2 RCTs, MD: -0.49, 95% CI, -3.90 to 2.92, I^2 = 0%, Z = 0.28 [p = 0.78]). Patients receiving sodium oxybate (9 g per night) experienced more AEs vs placebo,

including nausea (p < 0.00001), vomiting (p = 0.09), dizziness (p = 0.02) and enuresis (p = 0.03); most AEs were mild or moderate.

- A DB, PC, PG, MC RCT (N = 222) assessed the efficacy of sodium oxybate, modafinil, and the combination of the two for EDS in narcolepsy patients previously taking modafinil (*Black & Houghton 2006*). Patients received unchanged doses of modafinil (with sodium oxybate placebo) during a 2-week baseline phase. Following a baseline PSG and MWT, they were randomly assigned to 1 of 4 treatment groups: sodium oxybate placebo plus modafinil placebo, sodium oxybate plus modafinil placebo, modafinil plus sodium oxybate placebo, or sodium oxybate plus modafinil. Sodium oxybate was administered as 6 g nightly for 4 weeks and was then increased to 9 g nightly for 4 additional weeks. The primary endpoint was the MWT; secondary endpoints included ESS score and the CGI-C.
  - Following the switch from modafinil to placebo, the mean average daytime sleep latency on the MWT decreased from 9.74 minutes at baseline to 6.87 minutes after 8 weeks (p < 0.001). In the sodium oxybate group, there was no difference (from 11.29 to 11.97 minutes) suggesting that sodium oxybate was as effective as the previously administered modafinil. In contrast, the sodium oxybate-modafinil group demonstrated an increase in daytime sleep latency from 10.43 minutes to 13.15 minutes (p < 0.001), suggesting an additive effect. The sodium oxybate group also demonstrated a decrease in median average ESS scores, from 15 to 12.0, whereas the sodium oxybate-modafinil group decreased from 15.0 to 11.0 (p < 0.001 for each from baseline). In the sodium oxybate group, sleep attacks decreased from a mean of 10.05 at baseline to 7.10 after 8 weeks (p < 0.001) and the sodium oxybate-modafinil group demonstrated a decrease from 11.82 to 5.55 (p < 0.001). There was no significant difference between the modafinil- and placebo-treated groups. Compared with the placebo group, 48.0% (p = 0.002) of the sodium oxybate group and 46.3% (p = 0.023) of the sodium oxybate-modafinil group were judged to be much improved or very much improved on the GCI-C, compared with 21.8% in the placebo group and 19% in the modafinil group.
- Patients with narcolepsy-cataplexy (N = 55) who had received sodium oxybate for ≥ 6 months (range, 7 to 44 months, mean 21 months) in a long-term, OL sodium oxybate safety trial were enrolled in a DB treatment withdrawal study (*U.S. Xyrem Multicenter Study Group 2004*). Patients were previously stabilized on sodium oxybate using individualized doses providing optimum clinical effect, ranging from 3 to 9 g nightly. A 2-week single-blind (SB) sodium oxybate treatment phase established a baseline for the weekly occurrence of cataplexy. This was followed by a 2-week DB phase in which patients were randomized to receive unchanged drug therapy (n = 26) or placebo (n = 29). The primary endpoint was the change in the number of weekly cataplexy attacks from the baseline to the DB treatment phase.
  - In the sodium oxybate group, there was no median change in the number of cataplexy attacks between the 2-week SB baseline phase and the 2-week DB phase. In contrast, cataplexy attacks increased by a median of 21.0 in the placebo patients during the same 2-week period (p < 0.001); median change from baseline was 39.0 for the placebo group and 16.5 for the sodium oxybate group. The mean frequency of weekly cataplexy attacks over the 2-week baseline period increased from 15.8 to 46.4 at the end of the 2-week DB phase for patients receiving placebo; in patients receiving sodium oxybate, the number of cataplexy episodes was 9.9 and 12.8 at the same time points. There was no evidence of rebound cataplexy in patients who were randomized to placebo following long-term use of sodium oxybate. During the SB phase of the study, AEs were reported in 17 (31%) patients. During the DB phase, AEs were reported by 12 (22%) patients, including 3 patients in the sodium oxybate group, and 9 in the placebo group. No AE led to discontinuation and none were serious.
- The efficacy of sodium oxybate in the treatment of cataplexy and EDS in pediatric patients with narcolepsy was established in a DB, PC, randomized withdrawal (RW) study (*Plazzi et al 2018*). The study enrolled 106 pediatric patients 7 to 17 years of age with a baseline history of ≥ 14 cataplexy attacks in a typical 2-week period prior to any treatment for narcolepsy symptoms. The primary endpoint was change in weekly number of cataplexy attacks from the last 2 weeks of the stable-dose period (baseline) to the 2 weeks of the DB treatment period.
  - Ninety-six (92%) patients completed the stable-dose period, of whom 63 (the efficacy population) were randomly assigned to receive sodium oxybate (n = 31) or placebo (n = 32) for 2 weeks. A preplanned interim analysis of the primary endpoint showed efficacy (p = 0.0002), resulting in discontinuation of the placebo arm following guidance from the data safety monitoring board; 33 patients then received sodium oxybate on an OL basis during the DB period. Patients who were randomly assigned to receive placebo and who were withdrawn from sodium oxybate (32/63 [51%]) had increased weekly cataplexy attacks (median increase of 12.7 attacks per week [first quartile {Q1}, third quartile {Q3} = 3.4, 19.8]) when compared with those randomly assigned to continue treatment with sodium oxybate (median increase of 0.3 attacks per week [-1.0, 2.5]; p < 0.0001).
  - The median change from baseline in ESS-Child and Adolescent (CHAD) scores was greater in the placebo group (3.0 [Q1, Q3 = 1.0, 5.0]), indicating increased sleepiness, compared with the sodium oxybate group (0.0 [-1.0, 2.0]; p = 0.0004).
- The safety and efficacy of oxybate salts were evaluated in an unpublished Phase 3, DB, PC, RW, MC study in 201 adults with narcolepsy with cataplexy currently untreated or treated with or without anticataplectics (*Xywav dossier 2020)*. Enrollment criteria included a history of ≥ 14 cataplexy attacks in a typical 2-week period prior to receiving

any narcolepsy treatment. The study included a 12-week, OL, optimization and titration period to transition patients to oxybate salts; a 2-week stable-dose period; a 2-week DB, RW period; and a 2-week safety follow-up. During the withdrawal period, patients were randomized 1:1 to placebo or to continue oxybate salts. The primary endpoint was the change in the weekly number of cataplexy attacks from the time during the 2 weeks of the stable-dose period to the time during the 2 weeks of the DB, RW period, as determined from patients' daily diaries. The key secondary endpoint was the change in the ESS score from the end of the stable-dose period to the end of the DB, RW period.
    - Prior to randomization, the median (Q1, Q3) number of weekly cataplexy attacks did not differ in patients randomized to placebo (1.1 [0.0, 7.9]) vs those who continued oxybate salts (1.0 [0.0, 4.4]). During the DB, RW period, patients randomized to continue oxybate salts experienced no change (median [interquartile range {IQR}], mean [SD]) in the weekly frequency of cataplexy attacks, while patients randomized to discontinue oxybate salts and take placebo experienced an increase in cataplexy attacks (median [Q1, Q3]: 0.0 [-0.5, 1.7], mean [SD]: 0.12 [5.77] vs 2.4 [0.0,11.6], mean [SD]: 11.46 [24.75] respectively; treatment difference, $p < 0.0001$).
    - Prior to randomization, the median (Q1, Q3) ESS score did not differ in oxybate salts-treated patients who were randomized to placebo vs those who continued oxybate salts treatment (13.0 [9.0, 17.0] vs 14.0 [10.0, 19.0], respectively). At the end of the DB, RW period, the change in median (Q1, Q3) ESS score from baseline for patients randomized to placebo vs oxybate salts was 2.0 (0.0, 5.0) vs 0.0 (-1.0, 1.0), respectively.
  - Oxybate salts have not been specifically studied in a pediatric clinical trial. Use of oxybate salts in pediatric patients ≥ 7 years of age with narcolepsy is supported by evidence from an adequate and well-controlled study of sodium oxybate in pediatric patients 7 to 17 years of age (*Plazzi et al 2018*, see above), a study in adults showing a treatment effect of oxybate salts similar to that observed with sodium oxybate (see above), pharmacokinetic (PK) data of sodium oxybate from adult and pediatric patients, and PK data of oxybate salts from healthy adult volunteers (*Xywav dossier 2020*).
- Solriamfetol:
  - The approval of solriamfetol was based on data from the Treatment of Obstructive sleep apnea and Narcolepsy Excessive Sleepiness (TONES) Phase 3 clinical program, which included 4 PC RCTs.
  - TONES 2 was a12-week, Phase 3, DB, PC, MC RCT (N = 239) that evaluated the safety and efficacy of solriamfetol in the treatment of type 1 or type 2 narcolepsy (*Thorpy et al 2019*). Patients were randomized to solriamfetol 75, 150, or 300 mg once daily. The co-primary endpoints were change from baseline to week 12 in mean sleep latency assessed by the MWT and ESS score. Improvement on the PGI-C was the key secondary endpoint.
    - Statistical significance was met for the co-primary endpoints and the PGI-C for the 150 and 300 mg doses, but not the 75 mg dose. At week 12, the least squares (LS) mean change from baseline on the MWT showed an increase in sleep latency of 12.3 and 9.8 minutes for 150 and 300 mg, respectively vs 2.1 minutes with placebo ($p < 0.0001$) (LS mean differences vs placebo: 10.1 [95% CI, 6.4 to 13.9] and 7.7 [95% CI, 4.0 to 11.3]). For the ESS score, the LS mean change from baseline at week 12 was -6.4, -5.4, and -3.8 for the 300 mg, 150 mg, and 75 mg doses of solriamfetol, respectively, and -1.6 with placebo (LS mean differences vs placebo: -4.7 [95% CI, -6.6 to -2.9]; $p < 0.0001$, -3.8 [95% CI, -5.6 to -2.0]; $p< 0.0001$, and -2.2 [95% CI, -4.0 to -0.3]; $p = 0.0211$). At week 12, higher percentages of patients treated with solriamfetol 150 mg (78.2%) and 300 mg (84.7%) reported PGI-C improvement vs placebo (39.7%; both $p < 0.0001$).
  - TONES 3 was a 12-week, Phase 3, DB, PC, MC RCT (N = 476) that evaluated the safety and efficacy of solriamfetol for the treatment of EDS in patients with OSA with current or prior sleep apnea treatment (*Schweitzer et al 2019*). Patients were randomized to solriamfetol 37.5, 75, 150, or 300 mg once daily. The co-primary endpoints were change from baseline to week 12 in mean sleep latency assessed by the MWT and ESS score. Improvement on the PGI-C was the key secondary endpoint.
    - The co-primary endpoints of change from baseline at week 12 in MWT and ESS were met at all solriamfetol doses, and the key secondary endpoint of PGI-C was met at all doses except the 37.5 mg dose. At week 12, the LS mean differences from placebo for solriamfetol 300, 150, 75, and 37.5 mg were 12.8 [95% CI, 10 to 15.6], 10.7 [95% CI, 8.1 to 13.4], 8.9 [95% CI, 5.6 to 12.1], and 4.5 [95% CI, 1.2 to 7.9] minutes, respectively ($p < 0.0001$ for 300, 150, and 75 mg; $p = 0.085$ for 37.5 mg). For the ESS score, the LS mean differences from placebo were -4.7 [95% CI, -5.9 to -3.4], -4.5 [95% CI,-5.7 to -3.2], -1.7 [95% CI, -3.2 to -0.2], and -1.9 [95% CI, -3.4 to -0.3], respectively ($p < 0.0001$ for 300 and 150 mg; $p = 0.0233$ for 75 mg; $p = 0.061$ for 37.5 mg). At week 12, higher percentages of patients on solriamfetol 75 mg (72.4%; $p < 0.05$), 150 mg (89.7%; $p < 0.0001$), and 300 mg (88.7%; $p < 0.0001$) reported overall improvement on the PGI-C vs placebo (49.1%).
  - TONES 4 was a Phase 3, DB, PC, MC RW study that evaluated the maintenance of efficacy and safety of solriamfetol vs placebo for the treatment of EDS in adults with OSA (*Strollo et al 2019*). After 2 weeks of clinical titration (n = 174, 75 mg once daily starting dose, titrated up or down every 3 days to 75, 150, or 300 mg) and 2 weeks of stable dose administration (n = 148), patients who reported much or very much improvement on the PGI-C and had numerical improvements on the MWT and ESS were randomly assigned to placebo or solriamfetol for 2 additional weeks.

- From baseline to week 4, mean MWT sleep latencies improved from 12.3 to 13.1 minutes to 29.0 to 31.7 minutes, and ESS scores improved from 15.3 to 16.0 to 5.9 to 6.4. Patient-reported EDS decreased from ~15 to 16 to ~6, which is within the normal range. From weeks 4 to 6 (RW phase), solriamfetol-treated patients maintained improvements in MWT and ESS. The LS mean change in MWT mean sleep latency was -12.1 minutes with placebo compared with -1.0 minute with solriamfetol; LS mean difference between solriamfetol and placebo was 11.2 minutes (95% CI, 7.8 to14.6; p < 0.0001). The LS mean changes in ESS scores were 4.5 and -0.1 for placebo and solriamfetol, respectively, resulting in an LS mean difference of -4.6 (95% CI, -6.4 to -2.8; p < 0.0001). During the RW phase, a statistically significant 50.0% of patients who were switched to placebo reported worsening on the PGI-C relative to 20.0% who continued using solriamfetol (-30.0; 95% CI, -46.0 to -14.0; p < 0.001). Similarly, 59.0% of patients switched to placebo worsened, as rated by the physicians on the CGI-C, vs 21.7% who continued using solriamfetol (-37.3; 95% CI, -53.50 to -21.19; p < 0.0001).

- TONES 5 was a Phase 3 OL extension study that evaluated the long-term safety and maintenance of efficacy of solriamfetol for up to 52 weeks in the treatment of patients with narcolepsy or OSA who completed previous trials of solriamfetol (*Malhotra et al 2019*, *Sunosi dossier 2019*). In a 2-week OL titration phase, patients were initiated on solriamfetol 75 mg, titrated to a maximum tolerated dose of 150 or 300 mg, followed by a maintenance phase. During a 2-week PC RW phase ~ 6 months later, patients were randomized either to placebo or to continue solriamfetol at their dose of 75 mg, 150 mg, or 300 mg for 2 weeks. The primary endpoint was change in ESS score during the RW phase.
  - The LS mean change from the beginning to the end of the RW phase for the ESS score was 1.6 with solriamfetol compared with 5.3 with placebo, resulting in an LS mean difference of -3.7 (95% CI, -4.80 to -2.65; p < 0.0001). Similar results were seen in the subgroup analysis of patients with OSA and patients with narcolepsy. The percentage of patients who were reported as worse on the PGI-C at the end of the RW phase was 64.5% for patients randomized to placebo compared to 28.2% for patients on solriamfetol (p < 0.0001). Long-term maintenance of efficacy of solriamfetol was demonstrated by sustained reductions in ESS scores in Group A (12-week narcolepsy or OSA study) for up to 40 weeks and in Group B (Phase 2 studies or 6-week Phase 3 study) for up to 52 weeks. During the RW period, patients did not demonstrate rebound sleepiness or withdrawal after abrupt discontinuation of solriamfetol.

Place in Therapy

- Narcolepsy:
  - The 2007 American Academy of Sleep Medicine (AASM) practice parameters for the treatment of narcolepsy and other hypersomnias of central origin (*Morgenthaler et al 2007a*) recommend pharmacologic therapy based on the diagnosis and targeted symptoms. Most of the agents used to treat EDS have little effect on cataplexy or other REM sleep associated symptoms, while most antidepressants and anticataplectics have little effect on alertness; however, some medications act on both symptoms. Co-administration of 2 or more drug classes may be required in some patients to adequately address their symptoms. Scheduled naps may be beneficial, but seldom suffice as primary therapy for narcolepsy. The guidelines state that modafinil is effective for treatment of EDS due to narcolepsy and sodium oxybate is effective for treatment of cataplexy, EDS, and disrupted sleep due to narcolepsy. Sodium oxybate may be effective for treatment of hypnagogic hallucinations and sleep paralysis. Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for treatment of EDS due to narcolepsy. Antidepressants (TCAs, selective serotonin reuptake inhibitors [SSRIs], venlafaxine) may be effective for treatment of cataplexy. TCAs, SSRIs, and venlafaxine may be effective treatment for sleep paralysis and hypnagogic hallucinations.
  - The European Academy of Neurology (EAN) 2011 guidelines on management of narcolepsy in adults (*Billiard et al 2011*) recommend modafinil as the first-line treatment for EDS associated with narcolepsy when EDS is the most disturbing symptom. Sodium oxybate is recommended when EDS, cataplexy, and poor sleep coexist. The guideline notes that the combination of modafinil and sodium oxybate may be more effective than sodium oxybate alone. Methylphenidate may be an option if the response to modafinil is inadequate; sodium oxybate is not recommended. Naps are best scheduled on a patient-by-patient basis.
  - While armodafinil has been shown in clinical studies to be effective for EDS in narcolepsy, its specific place in therapy is not discussed in the current guidelines.
- OSA:
  - The 2006 AASM practice parameters for the medical therapy of OSA (*Morgenthaler et al 2006*) provide recommendations for patients with OSA who do not adapt well to or respond to initial therapy with CPAP, oral appliances, or surgical modification. Dietary weight loss in obese individuals may be beneficial and should be combined with a primary treatment for OSA. Modafinil is recommended for the treatment of residual EDS in OSA patients who have sleepiness despite effective PAP treatment and who are lacking any other identifiable cause for their sleepiness.
- SWD:

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

Safety

- Modafinil/armodafinil:
  - Warnings and precautions of modafinil/armodafinil include rare serious skin reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN); drug rash with eosinophilia and systemic symptoms (DRESS); multiorgan hypersensitivity; angioedema and anaphylaxis reactions; persistent sleepiness; psychiatric AEs; and CV AEs including chest pain, palpitations, dyspnea, and transient ischemic T-wave changes on electrocardiogram (ECG) in association with mitral valve prolapse or left ventricular hypertrophy. Increased monitoring of heart rate and blood pressure (BP) may be appropriate in patients receiving modafinil/armodafinil. Caution should be exercised when these drugs are prescribed to patients with known CV disease.
  - The most common AEs (≥ 5%) with armodafinil vs placebo were headache (17 vs 9%), nausea (7 vs 3%), dizziness (5 vs 2%), and insomnia (5 vs 1%).
  - The most common AEs (≥ 5%) with modafinil vs placebo were headache (34 vs 23%), nausea (11 vs 3%), nervousness (7 vs 3%), rhinitis (7 vs 6%), diarrhea (6 vs 5%), back pain (6 vs 5%), anxiety (5 vs 1%), insomnia (5 vs 1%), dizziness (5 vs 4%), and dyspepsia (5 vs 4%).
- Pitolisant:
  - Pitolisant is contraindicated in patients with severe hepatic impairment and has not been studied in these patients. Pitolisant is extensively metabolized by the liver and there is a significant increase in pitolisant exposure in patients with moderate hepatic impairment.
  - Pitolisant has a warning for QT prolongation. Use should be avoided with other drugs known to prolong the QT interval. Pitolisant should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes or sudden death, including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval. Patients with hepatic or renal impairment should be monitored for increased QTc.
  - In the PC trials, the most common AEs (occurring in ≥ 5% of patients and at twice the rate of placebo) with the use of pitolisant were insomnia (6%), nausea (6%), and anxiety (5%).
- Solriamfetol:
  - Solriamfetol is contraindicated with concomitant use of monoamine oxidase inhibitors (MAOIs), or within 14 days following discontinuation of an MAOI because of the risk of hypertensive reaction.
  - Warnings and precautions of solriamfetol include BP and heart rate increases and psychiatric symptoms such as anxiety, insomnia, and irritability.
  - The most common AEs (≥ 5% and greater than placebo) in either the narcolepsy or OSA populations vs placebo were headache (16 vs 7%), nausea (7 vs 4%), decreased appetite (9 vs 1%), insomnia (5 vs 4%), and anxiety (6 vs 1%).
- Sodium oxybate/oxybate salts:
  - Sodium oxybate/oxybate salts are contraindicated in combination with sedative hypnotics or alcohol and in patients with succinic semialdehyde dehydrogenase deficiency, a rare inborn error of metabolism.
  - Sodium oxybate/oxybate salts carries a boxed warning concerning CNS depression and the potential for misuse/abuse. Abuse or misuse of illicit GHB is associated with CNS AEs, including seizure, respiratory depression, decreased consciousness, coma, and death.
  - Because of the risks of CNS depression and abuse and misuse, sodium oxybate/oxybate salts are available only through a restricted distribution program under a risk evaluation and mitigation strategies (REMS). Prescribers must be specially certified, and the drug may be dispensed only by a central pharmacy that is specially certified.
  - Other warnings and precautions include respiratory depression and sleep disordered breathing; depression and suicidality; parasomnias; and use in patients sensitive to high sodium intake due to the high salt content (sodium oxybate only).
  - The most common AEs with sodium oxybate in adults (≥ 5% and at least twice the incidence with placebo) were nausea, dizziness, vomiting, somnolence, enuresis, and tremor.
  - The most common AEs with oxybate salts in adults (≥ 5%) were headache, nausea, dizziness, decreased appetite, parasomnia, diarrhea, hyperhidrosis, anxiety, and vomiting.

- The most common AEs in pediatric patients in the oxybate salts RW trial (≥ 5%) were enuresis, nausea, headache, vomiting, weight decreased, decreased appetite, and dizziness.

Dosing

- Armodafinil:
  - Narcolepsy/OSA: 150 mg to 250 mg orally once daily in the morning
    - OSA: up to 250 mg once daily has been well tolerated, but there is no consistent evidence that this dose confers additional benefit beyond the 150 mg dose
  - SWD: 150 mg orally once daily approximately 1 hour prior to the start of the work shift
  - Hepatic impairment: dose should be reduced in patients with severe hepatic impairment
- Modafinil:
  - Narcolepsy/OSA: 200 mg orally once daily in the morning
  - SWD: up to 400 mg once daily has been well tolerated, but there is no consistent evidence that this dose confers additional benefit beyond the 200 mg/day dose
  - Hepatic impairment: dose should be reduced to one-half in patients with severe hepatic impairment
- Pitolisant:
  - Recommended dosage range: 17.8 mg to 35.6 mg per day administered once daily upon awakening.
    - Dose titration as follows:
      - Starting dose: 8.9 mg (two 4.45 mg tablets) once daily
      - Increase dose to 17.8 mg (one 17.8 mg tablet) once daily
      - May increase to a maximum of 35.6 mg (two 17.8 mg tablets) once daily
      - Dose may be adjusted based on tolerability
      - It may take up to 8 weeks for some patients to achieve a clinical response
  - Hepatic and renal impairment: dose adjustments recommended in hepatic and renal impairment; not recommended in patients with end-stage renal disease (ESRD)
    - Moderate hepatic impairment: 8.9 mg once daily, increased after 14 days to a maximum dosage of 17.8 mg once daily.
    - Moderate and severe renal impairment: 8.9 mg once daily, increased after 7 days to a maximum dosage of 17.8 mg once daily.
  - Poor cytochrome P450 (CYP) 2D6 metabolizers: dose should be initiated at 8.9 mg once daily and titrated to a maximum dose of 17.8 mg once daily after 7 days.
  - Co-administration with strong CYP2D6 inhibitors and strong CYP3A4 inducers: dose adjustments recommended (see prescribing information)
- Sodium oxybate/oxybate salts:
  - Adult dosing:
    - Starting dose: 4.5 g per night orally, divided into 2 doses: 2.25 g at bedtime and 2.25 g taken 2.5 to 4 hours later, increased by 1.5 g per night at weekly intervals (additional 0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) to the effective dosage range of 6 to 9 g per night orally
  - Pediatric dosing:
    - Starting dose, titration regimen, and maximum dose: weight-based, administered twice nightly; titrated gradually based on efficacy and tolerability
  - Patients transitioning from sodium oxybate to oxybate salts should initiate therapy at the same dose and regimen as sodium oxybate (g for g).
  - Hepatic impairment: dose should be reduced to one-half of the original dosage per night, divided into 2 doses
  - Co-administration with divalproex sodium: dose of divalproex sodium should be reduced by ≥ 20% in patients already stabilized on sodium oxybate/oxybate salts; a lower starting dose should be used when introducing sodium oxybate/oxybate salts in patients already taking divalproex sodium.
- Solriamfetol:
  - Narcolepsy:
    - Starting dose: 75 mg once daily
    - Recommended dose range: 75 to 150 mg once daily, doubled at intervals ≥ 3 days based on efficacy and tolerability
    - Maximum recommended dose: 150 mg once daily
  - OSA:
    - Starting dose: 37.5 mg once daily
    - Recommended dose range: 37.5 to 150 mg once daily, doubled at intervals of ≥ 3 days based on efficacy and tolerability
    - Maximum recommended dose: 150 mg once daily
  - Renal impairment: dose adjustments required; not recommended in patients with ESRD

Conclusion

- Current treatment options for EDS in narcolepsy include modafinil, armodafinil, pitolisant, solriamfetol, sodium oxybate, oxybate salts, and amphetamine derivatives, thus providing several agents with differing mechanisms of action. Many patients with narcolepsy may require treatment with more than 1 drug class to manage co-existing symptoms. Pitolisant and sodium oxybate/oxybate salts are also FDA-approved for treatment of cataplexy in adults with narcolepsy. Antidepressants such as SSRIs or venlafaxine (used off-label) may be effective for treatment of cataplexy and provide a first- or second-line option. Modafinil, armodafinil, and solriamfetol are also indicated for EDS in patients with OSA, while modafinil and armodafinil are also indicated for SWD.
- Modafinil is generally considered the first-line pharmacologic therapy for narcolepsy. Its efficacy is well established and illicit use is uncommon. There are no apparent clinical advantages of the longer half-life enantiomer, armodafinil, over the racemic mixture, modafinil. These agents have not been compared head-to-head with CNS stimulants, such as dextroamphetamine or methylphenidate. Therapeutic benefits of modafinil and amphetamine derivatives become apparent within days. However, CNS stimulants have limited efficacy data, are associated with high abuse potential, and are associated with more AEs than modafinil/armodafinil. Modafinil/armodafinil may be beneficial for the treatment of OSA patients with residual EDS despite effective conventional treatment. Modafinil/armodafinil have warnings for rare serious skin reactions, angioedema/anaphylaxis, and multiorgan hypersensitivity; caution should be exercised in patients with known CV disease and increased monitoring of BP and heart rate may be appropriate for patients receiving these agents. Modafinil/armodafinil is a substrate, inducer, and inhibitor of CYP450 isoenzymes, resulting in the potential for drug interactions, including reduced efficacy of oral contraceptives. Modafinil/armodafinil have demonstrated variable efficacy for SWD in clinical trials and AEs may outweigh benefits in some patients.
- Pitolisant, a novel H_3 receptor antagonist/inverse agonist, was FDA-approved in August 2019 for the treatment of EDS in adults with narcolepsy and gained the expanded indication for treatment of cataplexy in adults with narcolepsy in October 2020. In two 8-week pivotal RCTs vs placebo and modafinil active control in patients with narcolepsy (a majority of whom had co-existing cataplexy), pitolisant appeared to have similar efficacy to modafinil for improving EDS. In HARMONY 1, a post-hoc analysis indicated that pitolisant reduced daily cataplexy episodes significantly more than placebo but not more than modafinil. In HARMONY 1bis, differences in WCR between pitolisant and placebo were not significant, nor were the differences between pitolisant and modafinil. In the HARMONY CTP trial in narcolepsy patients with severe cataplexy, pitolisant demonstrated a relative reduction in WCR of 75% vs 38% with placebo; improvements were also seen in ESS scores, MWT, and frequency of hallucinations. Differences in dosing titration and dosing ranges may have partially accounted for the lack of effect on cataplexy seen in HARMONY 1 and HARMONY 1bis as compared with HARMONY CTP. A dose-response analysis was not performed in these trials (*Wakix FDA clinical review 2019*).
  - Pitolisant requires a 3-week dose titration and may take up to 8 weeks to achieve a clinical response. Pitolisant does not appear to have significant abuse potential and is the only unscheduled narcolepsy agent. Pitolisant is generally well tolerated and has not been associated with CV AEs or vital sign changes; the most common AEs were headache, insomnia, and nausea. Although some patients in the pitolisant trials were receiving concomitant medication(s) targeting narcolepsy and/or cataplexy, trials specifically evaluating pitolisant in combination with other narcolepsy agents are lacking. Pitolisant is contraindicated in patients with severe hepatic impairment and has a warning for QT prolongation. Pitolisant is metabolized by CYP2D6 and CYP3A4 and has the potential for multiple drug interactions, including some antidepressants. Like modafinil/armodafinil, pitolisant may decrease the efficacy of oral contraceptives. Limited long-term safety and efficacy data are available, particularly at the highest recommended dose. A DB, PC RCT is currently ongoing to assess the safety and efficacy of pitolisant in children 6 to < 18 years of age with narcolepsy with or without cataplexy (*Clinicaltrials.gov Web site*).
- Sodium oxybate/oxybate salts have demonstrated efficacy in reducing EDS and cataplexy in patients with narcolepsy; however, use of these agents presents several challenges. Full therapeutic response may require several weeks to manifest and the dose must be titrated slowly; the split dosing regimen requires patients to wake during the night to administer a second dose. Use of sodium oxybate/oxybate salts is limited by abuse and drug diversion potential, CNS depression, and REMS requirement. Medications that suppress cataplexy often improve sleep paralysis and hypnagogic hallucinations, although these symptoms do not usually require pharmacologic therapy (*Scammell 2020b*). In narcolepsy patients with co-existing EDS, cataplexy, and disrupted nocturnal sleep, sodium oxybate/oxybate salts are the only agents that are effective for all 3 manifestations. They are also the only agents currently indicated for pediatric patients. Data have shown that the combination of modafinil and sodium oxybate may be more effective for the treatment of EDS than sodium oxybate alone. Oxybate salts may be preferred over sodium oxybate to lower daily sodium load in narcolepsy patients with comorbid conditions sensitive to salt intake, such as HTN, HF, or renal impairment.
- Solriamfetol demonstrated efficacy vs placebo for the treatment of EDS in narcolepsy and OSA in 4 RCTs and maintenance of efficacy in an OL extension trial of up to 52 weeks. The placebo subtracted change in sleep latency assessed by the MWT from baseline to end of treatment ranged from 10 to 13 minutes (out of a possible 40 minutes),

a statistically and clinically meaningful treatment effect. However, there are no head-to-head trials with other established narcolepsy agents. The onset of effect of solriamfetol became apparent within 1 week of initiation in clinical trials. Solriamfetol's main safety concern is the potential for BP and heart rate increases, which may be of particular concern in patients with narcolepsy or OSA who already often have CV risk factors such as HTN, diabetes, dyslipidemia, and obesity. In contrast to modafinil/armodafinil and pitolisant, solriamfetol lacks the concern for potential reduced efficacy of concomitant oral contraceptives.

BACKGROUND

Narcolepsy

- Narcolepsy is a rare chronic neurological disorder of hypersomnia that results from dysregulation of the sleep/wake cycle and intrusion of sleep into wakefulness. Its associated symptoms are potentially debilitating to patients.
- Narcolepsy results from the loss of the neuropeptides, orexin-A and orexin-B (also known as hypocretin-1 and hypocretin-2). These neurotransmitters are products of the prepro-orexin gene and are made by neurons in the lateral hypothalamus. Orexin-A and -B have excitatory effects when they bind the ox1 and ox2 receptors on postsynaptic neurons. The orexins are released during wakefulness and increase the activity of many brain regions involved in the promotion of wakefulness, including the locus coeruleus, raphe nuclei, and tuberomammillary nucleus. By increasing the activity of these wake-promoting aminergic neurons, orexins stabilize wakefulness, prevent inappropriate transitions into REM or non-REM sleep, and inhibit REM sleep. Loss of orexins may allow REM sleep-related phenomena (eg, cataplexy, hypnagogic hallucinations, and sleep paralysis) to intrude into wakefulness (*Scammell 2019a*).
- Narcolepsy is typically classified as type 1 (narcolepsy with cataplexy, Na-1) or type 2 (narcolepsy without cataplexy, Na-2). Na-1 results from a loss of cerebrospinal fluid (CSF) orexin-A concentration, whereas Na-2 does not involve low levels of CSF orexin-A (*Bhattarai & Sumerall 2017, Scammell 2020a, Szabo et al 2019*). Na-1 is estimated to have a prevalence of 25 to 50 per 100,000 people. Narcolepsy typically begins in the teens and early twenties, but occasionally occurs as early as age 5 or after age 40. The prevalence of Na-2 is uncertain, as it is less well studied and more difficult to diagnose; however, it has been estimated as 20 to 34 per 100,000 people (*Scammel 2020a*). Males and females are equally affected (*Bhattarai & Sumerall 2017, Sunosi dossier 2019, Szabo et al 2019*).
- EDS is present in all patients with narcolepsy. EDS is characterized by chronic pervasive sleepiness and sleep attacks/inadvertent naps triggered by overwhelming urges to sleep (*Sunosi dossier 2019*). Other symptoms include cataplexy, hypnagogic hallucinations, and sleep paralysis; however, only about one-third of patients have all 4 symptoms (*Scammell 2020a*). A 2013 survey of narcolepsy patients indicated that EDS is the most disabling symptom experienced in their daily lives (*Sunosi FDA summary review*).
- EDS is not specific to narcolepsy and can be due to habitual loss of nighttime sleep, sleep fragmentation, a circadian sleep-wake disorder, a primary neurological disorder, or sedating drugs. In narcolepsy, sleepiness is characterized by a daily underlying irresistible drive for sleep that is associated with impaired cognitive ability, reduced psychosocial functioning and QoL that puts patients at risk of work-related, home, or automobile accidents (*Szabo et al 2019*).
- EDS is typically the first presenting symptom of narcolepsy. All patients with narcolepsy have chronic sleepiness, but they do not sleep more than healthy individuals during a 24-hour period (*Scammell 2020a*). EDS is routinely accompanied by sleep attacks, which are abrupt involuntary sleep episodes lasting from a few seconds to several minutes.
- Sleep paralysis has been described as the disturbing temporary inability to move voluntary muscles at sleep-wake transitions and usually occurs at the point of waking, although it may also occur just before falling asleep. Episodes of sleep paralysis can be frightening because the immobility may be accompanied by hypnopompic hallucinations or a sensation of suffocation (*Bhattarai & Sumerall 2017, Scammell 2020a*).
- Hypnagogic hallucinations are vivid, often frightening visual, tactile, or auditory hallucinations that occur while falling asleep. They probably result from a mixture of wakefulness and the dreaming of REM sleep (*Scammell 2019a*).
- Cataplexy is emotionally-induced transient muscle weakness that manifests as limb, head, or facial weakness. Episodes of cataplexy develop over several seconds and patients remain conscious regardless of the varying duration and severity that may occur. Severe episodes can result in bilateral weakness or paralysis, causing the patient to collapse (*Scammel 2020a, Szabo et al 2019*).
  - Up to 60% of patients with narcolepsy have cataplexy. Cataplexy is usually triggered by positive emotions such as laughing, joking, or excitement and less frequently by negative emotions such as anger or frustration.
- Many patients with narcolepsy fall asleep rapidly but have substantial fragmentation in nocturnal sleep. This sleep maintenance insomnia seems paradoxical in a disorder characterized by EDS, and it may reflect a low threshold to transition from sleep to wakefulness (*Bhattarai & Sumerall 2017, Scammell 2020a).*
- Non-pharmacologic interventions may be of benefit for patients with narcolepsy (*Scammell 2020b*).
  - Regular napping may be sufficient for occasional patients, but most require pharmacologic therapy to reduce sleepiness and cataplexy. One or 2 well-timed, 20-minute naps may improve sleepiness, though some patients may require long naps. Specifically, a short nap around 1:00 or 2:00 PM is often helpful as it can improve alertness for 1

to 3 hours, reducing the need for stimulants in the afternoon. If possible, a brief nap at work or school is often helpful. Medications that may worsen daytime sleepiness (eg, opiates, benzodiazepines, alcohol, antipsychotics) should be avoided. Other medications such as theophylline or excessive caffeine intake may worsen insomnia, contributing to daytime sleepiness. Prazosin and other α-1 antagonists can worsen cataplexy.
  - Patients with narcolepsy are at increased risk for psychiatric co-morbidities, particularly depression and anxiety; have higher than expected rates of hypertension; and increased rates of obesity and diabetes. Thus, psychosocial support and regular screening for depression, hypertension, and obesity are important for patients with narcolepsy.
- Pharmacological interventions are the most common approach for treating narcolepsy. Current medications have been developed to target symptoms; however, most patients do not experience complete resolution despite receiving optimal standard treatment (*Bhattarai & Sumerall 2017, Scammell 2020b).*
- The goal of pharmacologic therapy is to improve alertness and thus performance and safety of important tasks and activities like school or work (*Scammell 2020b*).
  - Many sleep disorders (eg, sleep apnea, periodic leg movements) can coexist with narcolepsy, thereby contributing to symptoms. Such disorders should be addressed before initiating narcolepsy-specific medications.
  - Most of the drugs available to treat narcolepsy target either EDS or cataplexy. Thus, many patients who have both symptoms require more than 1 drug to manage their disease.
  - Since all patients with narcolepsy have some degree of EDS, most require a wakefulness-promoting medication. These agents improve performance (measured by reaction time and simulated driving tasks), but their ability to maintain wakefulness rarely exceeds 70 to 80% of normal. Currently available agents include modafinil/armodafinil and CNS stimulants such as methylphenidate or amphetamines. All are effective; however, modafinil is usually used as first-line therapy since it has been studied in PC RCTs and is associated with fewer AEs than traditional stimulants.
  - About 30% of narcolepsy patients have cataplexy that is substantial enough to warrant treatment. A REM-suppressing medication such as venlafaxine, fluoxetine, atomoxetine (all off-label) may be chosen as first-line agent; sodium oxybate, the sodium salt of GHB, is usually reserved for second-line use in patients who do not respond to these medications. The full therapeutic effect of sodium oxybate may require several weeks of treatment, while the benefit of amphetamines and modafinil become apparent within a few days. AEs of sodium oxybate are more common than with other medications used to treat narcolepsy. Sodium oxybate has the potential for abuse and dependence and is only available through a REMS program.

<u>OSA</u>
- OSA is a chronic disorder that is characterized by obstructive apneas and hypopneas caused by repetitive collapse of the upper airway during sleep. The diagnosis should be considered whenever a patient presents with symptoms such as EDS, snoring, and choking or gasping during sleep, particularly in the presence of risk factors such as obesity, male gender, and advanced age (*Kline 2019*).
  - The most common symptoms of OSA are daytime sleepiness and nocturnal snoring or “choking.” Approximately 20% of patients with OSA have EDS (*Sunosi dossier 2019*).
  - Other symptoms and signs may be suggestive of OSA. For example, sleep maintenance insomnia with repetitive awakenings should prompt consideration of OSA. Some patients with OSA complain of insomnia rather than daytime sleepiness because they are unable to maintain sleep; this phenomenon may be more common in females.
  - Morning headaches are reported by 10 to 30% of patients with untreated OSA. They are usually bifrontal and squeezing in quality, with no associated nausea, photophobia, or phonophobia. They typically occur daily or most days of the week and may last for several hours after awakening in the morning. The cause of the headaches is not well established and may be multifactorial; proposed mechanisms include hypercapnia, vasodilation, increased intracranial pressure, and impaired sleep quality.
  - Other associated symptoms and historical features include the following:
    - Awakening with a sensation of choking, gasping, or smothering
    - Awakening with a dry mouth or sore throat
    - Moodiness or irritability
    - Lack of concentration
    - Memory impairment
    - Decreased libido and impotence
    - Nocturia
    - Awakening with angina pectoris
    - History of hypertension, CV disease, cerebrovascular disease, or renal disease
    - History of type 2 diabetes mellitus
    - Depression
    - Symptoms of fibromyalgia
    - Gastroesophageal reflux disease (GERD)

- History of polycystic ovary syndrome
- OSA is most common among males who are 18 to 60 years old, although it is also common at other ages and in women; the prevalence is similar in postmenopausal women and men.

- Untreated OSA has many potential adverse clinical consequences, including EDS, impaired daytime function, metabolic dysfunction, and an increased risk of CV disease and mortality (*Kryger 2020*).
  - The goals of OSA therapy are to resolve signs and symptoms of OSA, improve sleep quality, and normalize the apnea-hypopnea index (AHI) and oxyhemoglobin saturation level.
  - All patients diagnosed with OSA should be offered PAP as initial therapy.
    - CPAP involves maintenance of a positive pharyngeal transmural pressure so that the intraluminal pressure exceeds the surrounding pressure. CPAP also stabilizes the upper airway through increased end expiratory lung volume. As a result, respiratory events due to upper airway collapse (eg, apneas, hypopneas) are prevented.
  - In patients with mild to moderate OSA who prefer not to use PAP or who fail to respond to it, oral appliances are an alternative therapy that have been shown to improve signs and symptoms of OSA and may be better tolerated in some patients than PAP. Upper airway surgery may supersede oral appliances as alternative therapy in patients with severe, surgically correctable, obstructing lesions of the upper airway.
  - Behavior modification is indicated for all patients who have OSA and a modifiable risk factor. Overweight or obese patients should be encouraged to lose weight. Patients with positional OSA should change their sleep position accordingly. All patients should be advised that alcohol and certain common medications, such as benzodiazepines, may worsen their OSA.
  - A variety of pharmacologic agents have been evaluated in RCTs as potential primary therapy for the management of sleep-disordered breathing in OSA, with the goal of replacing more burdensome therapies such as PAP or oral appliances. However, no pharmacologic agent has proven to be sufficiently effective to warrant replacement of such therapies.
  - Residual sleepiness is reported by approximately 10 to 15% of patients with adequately treated OSA (*Pepin 2020*).
    - Modafinil or armodafinil may be beneficial as adjunctive therapy for EDS that persists despite documentation of adequate and successful conventional therapy. The efficacy of these agents, particularly modafinil, for treatment of residual sleepiness in patients with OSA has been demonstrated in multiple RCTs and meta-analyses (*Kryger 2020, Pepin 2020*).

SWD

- Individuals who work night shifts commonly experience difficulties with both sleep and alertness at desired times, and shift work is increasingly recognized as a risk factor for a variety of adverse health outcomes including diabetes, cancer, and CV disease. While some shift workers show circadian adjustment to their work schedule, many others do not (*Cheng & Drake 2019*).
  - Those who do not adjust commonly experience excessive sleepiness during work and significant sleep disturbance. It is estimated that one-third or more of shift workers experience impairments of sufficient severity to meet formal criteria for SWD (ie, development of sleep disturbances and impairment of waking alertness and performance) (*Morgenthaler et al 2007b*).
  - Both sleep duration and sleep quality are commonly affected in shift workers. Shift workers generally report 30 to 60 minutes less sleep compared with day workers, and individuals with SWD report even greater reductions in sleep, with an average decrease of approximately 90 minutes.
  - Shift workers commonly report difficulty with sleep initiation and maintenance. Disturbances during wakefulness include excessive sleepiness, impaired cognitive function, decreased psychomotor functioning, and altered social and emotional functioning.
- Minimum measures to improve sleep after a night shift include a regular sleep schedule (ie, “anchor sleep”), light-blocking shades, and ambient noise control. If family or social responsibilities prohibit one 7- to 9-hour sleep period, a regularized 3- to 4-hour morning "anchor" sleep with a second variably timed sleep period is recommended (*Cheng & Drake 2019*).
- For patients with persistent difficulties obtaining adequate sleep despite sleep hygiene measures, options include use of a short-acting hypnotic agent, exogenous melatonin, and behavioral treatment of insomnia (sleep scheduling and cognitive-behavioral therapy). The choice among these depends on availability and cost, presence of contraindications, and patient preference (*Cheng & Drake 2019*).
  - Modafinil and armodafinil are options in patients with persistent sleepiness in conjunction with nonpharmacologic measures to improve sleep and alertness. The magnitude of benefit may vary among individuals. The observed benefits in RCTs have been modest, however, and AEs may outweigh benefits in some patients.

INDICATIONS

Table 1. FDA-approved indications for narcolepsy agents

Indication	armodafinil	modafinil	pitolisant	sodium oxybate/oxybate salts	solriamfetol
Narcolepsy	√	√	√	√	√
Narcolepsy-cataplexy			√	√	
OSA	√	√			√
SWD	√	√			

- Armodafinil is indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, OSA, or SWD.
  - Limitations of Use
    - In OSA, armodafinil is indicated to treat excessive sleepiness and not as treatment for the underlying obstruction. If CPAP is the treatment of choice for a patient, a maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating and during treatment with armodafinil for excessive sleepiness.
- Modafinil is indicated to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy, OSA, or SWD.
  - Limitations of Use
    - In OSA, modafinil is indicated to treat excessive sleepiness and not as treatment for the underlying obstruction. If CPAP is the treatment of choice for a patient, a maximal effort to treat with CPAP for an adequate period of time should be made prior to initiating and during treatment with modafinil for excessive sleepiness.
- Pitolisant is indicated for the treatment of EDS or cataplexy in adult patients with narcolepsy.
- Sodium oxybate/oxybate salts are indicated for the treatment of cataplexy or EDS in patients ≥ 7 years of age with narcolepsy.
- Solriamfetol is indicated to improve wakefulness in adult patients with EDS associated with narcolepsy or OSA.
  - Limitations of Use
    - Solriamfetol is not indicated to treat the underlying airway obstruction in OSA. Ensure that the underlying airway obstruction is treated (eg, with CPAP) for at least 1 month prior to initiating solriamfetol for EDS. Modalities to treat the underlying airway obstruction should be continued during treatment with solriamfetol. Solriamfetol is not a substitute for these modalities.
- Off-label Uses (*Micromedex 2020; Class IIb or higher recommendation; evidence favors efficacy*) (see Appendix J for description of recommendation, efficacy, and evidence ratings)
  - Armodafinil
    - Bipolar disorder, depressed phase, in combination with conventional medications (Class IIb; Category B)
  - Modafinil
    - Attention deficit hyperactivity disorder (adult and pediatric) (Class IIb, Category B [adult]; Category A [pediatric]
    - Depression, unipolar or bipolar (Class IIb; Category B)
    - Depression; adjunct – fatigue (Class IIb; Category B)
    - Sleep deprivation (Class IIa; Category A)
    - Steinert myotonic dystrophy syndrome (Class IIb; Category B)
  - Sodium oxybate
    - Fibromyalgia (Class IIb; Category B)

PHARMACOLOGY

- Modafinil/armodafinil
  - The mechanism(s) through which armodafinil/modafinil promotes wakefulness is unknown. Armodafinil (R-modafinil) has pharmacological properties similar to those of modafinil (a mixture of R- and S-modafinil), to the extent tested in animal and *in vitro* studies. The R- and S-enantiomers have similar pharmacological actions in animals.
  - Armodafinil and modafinil have wake-promoting actions similar to sympathomimetic agents including amphetamine and methylphenidate, although their pharmacologic profile is not identical to that of the sympathomimetic amines.
  - Modafinil-induced wakefulness can be attenuated by the α1-adrenergic receptor antagonist, prazosin; however, modafinil is inactive in other *in vitro* assay systems known to be responsive to α-adrenergic agonists such as the rat vas deferens preparation.
  - Armodafinil is an indirect dopamine receptor agonist. Modafinil is not a direct- or indirect-acting dopamine receptor agonist. Both armodafinil and modafinil bind *in vitro* to the dopamine transporter and inhibit dopamine reuptake. For modafinil, this activity has been associated *in vivo* with increased extracellular dopamine levels in some brain regions of animals. In genetically engineered mice lacking the dopamine transporter (DAT), modafinil lacked wake-promoting activity, suggesting that this activity was DAT-dependent. However, the wake-promoting effects of modafinil, unlike those of amphetamine, were not antagonized by the dopamine receptor antagonist haloperidol in

rats. In addition, α-methyl-p-tyrosine, a dopamine synthesis inhibitor, blocks the action of amphetamine, but does not block locomotor activity induced by modafinil.
  - In the cat, equal wakefulness-promoting doses of methylphenidate and amphetamine increased neuronal activation throughout the brain. Modafinil at an equivalent wakefulness-promoting dose selectively and prominently increased neuronal activation in more discrete regions of the brain. The relationship of this finding in cats to the effects of modafinil in humans is unknown.
  - In addition to its wake-promoting effects and ability to increase locomotor activity in animals, modafinil produces psychoactive and euphoric effects, alterations in mood, perception, thinking, and feelings typical of other CNS stimulants in humans. Modafinil has reinforcing properties, as evidenced by its self-administration in monkeys previously trained to self-administer cocaine; modafinil was also partially discriminated as stimulant-like.
  - Based on nonclinical studies, 2 major metabolites, acid and sulfone, of modafinil or armodafinil, do not appear to contribute to the CNS-activating properties of the parent compounds.
- Pitolisant:
  - The mechanism of action of pitolisant in EDS in adult patients with narcolepsy is unclear. However, its efficacy could be mediated through its activity as an antagonist/inverse agonist at H_3 receptors.
- Sodium oxybate/oxybate salts
  - Sodium oxybate is a CNS depressant. The mechanism of action of sodium oxybate in the treatment of narcolepsy is unknown. Sodium oxybate is the sodium salt of GHB, an endogenous compound and metabolite of the neurotransmitter GABA. Oxybate salts is a mixture of calcium oxybate, magnesium oxybate, potassium oxybate, and sodium oxybate. It is hypothesized that the therapeutic effects of sodium oxybate and oxybate salts on cataplexy and EDS are mediated through GABA actions at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons.
- Solriamfetol
  - The mechanism of action of solriamfetol to improve wakefulness in patients with EDS associated with narcolepsy or OSA is unclear. However, its efficacy could be mediated through its activity as a DNRI (*Sunosi prescribing information 2019*). Solriamfetol does not release norepinephrine, differentiating it from the noradrenergic-releasing effects of amphetamines (*Sunosi dossier 2019*).

CLINICAL EFFICACY

STUDY DESIGN ABBREVIATIONS: AC = active control; CI = confidence interval, DB = double-blind; HR = hazard ratio; MC = multi-center; OL = open-label; OR = odds ratio; PC = placebo-controlled; PG = parallel-group; RCT = randomized controlled trial; RR = relative risk; SB = single-blind; SC = single-center; XO = crossover

***Search Strategy**: Studies supporting the FDA-approved indications were identified using search terms "solriamfetol," "armodafinil," "modafinil," "sodium oxybate," "oxybate salts," "pitolisant," "obstructive sleep apnea," "cataplexy," "narcolepsy," and "shift work sleep disorder" through October 14, 2020. Manufacturer submitted data were also reviewed when available. A comprehensive PubMed literature search was performed for human studies published in English. Assessment of each study's design (eg, randomization, blinding methodology, appropriateness of treatment outcomes, etc.), validity and importance was completed. Review of patient data in groups to which they were randomized (intention to treat analysis), accounting for patient withdrawals, and baseline characteristics was completed.*

Modafinil/armodafinil

Narcolepsy

Study 1. Harsh et al, *Curr Med Res Opin.* 2006;22(4):761-774

Study Objective: Evaluate the efficacy and safety of armodafinil for the treatment of EDS in patients with narcolepsy	
Study Design, Follow-up	**Treatment Groups** (N = 196)
• 12-week, Phase 3, DB, PC, PG, MC, RCT	• Armodafinil 150 mg once daily (n = 64) • Armodafinil 250 mg once daily (n = 67) • Placebo (n = 63) • Study medication was administered before 8:00 AM (~30 min before breakfast) throughout the study. • Armodafinil was initiated at a dose of 50 mg/day in all patients; doses were increased to 100 mg/day on day 2 and titrated upward in 50 mg increments every 2 days until the final dose was achieved.
Inclusion Criteria	**Exclusion Criteria**

• Age 18 to 65 years • Diagnosis of narcolepsy according to the International Classification of Sleep Disorders (ICSD) criteria • No medical or psychiatric disorders other than narcolepsy that could have caused EDS • Mean sleep latency ≤ 6 min on the MSLT (Appendix B) and a Clinical Global Impression of Severity (CGI-S) rating ≥ 4 (moderately ill)	• Clinically significant uncontrolled medical or psychiatric illnesses (treated or untreated) • Probable diagnosis of a current sleep disorder other than narcolepsy in the opinion of the investigator • Consumption of > 600 mg/day of caffeine • History of alcohol, narcotic, or other drug abuse • Any disorder that might interfere with drug absorption, distribution, metabolism, or excretion • Use of disallowed drugs (modafinil, melatonin, sodium oxybate, lithium, St. John's Wort, methylphenidate, amphetamines, pemoline, antipsychotic agents, benzodiazepines, zolpidem, MAOIs, anticoagulants, anticonvulsants, barbiturates) • Use of clinically significant amounts of nonprescription drugs within 7 days of the screening visit • Use of anticataplectic drugs (ie, clomipramine, SSRIs, venlafaxine), other than sodium oxybate, were permitted if they did not contribute to patients' sleepiness and if doses were stable for at least 1 month prior to baseline
Co-primary Endpoints	**Secondary Endpoints**
• Change from baseline in mean sleep latency on the MWT 9:00 AM to 3:00 PM (Appendix C) • Proportion of patients with at least minimal improvement on the CGI-C	• Mean changes from baseline in the MWT 3:00 PM to 7:00 PM mean sleep latency • Attention and memory as assessed by the Cognitive Drug Research (CDR) battery (average of first 4 test sessions at 9:30 AM, 11:30 AM, 1:30 PM, and 3:30 PM) • ESS scores (Appendix D) • CGI-C ratings • BFI (score for global fatigue and score for worst fatigue over the previous 24 hours; range 1 to 10; a score ≥ 7 indicates severe fatigue [*Mendoza et al 1999*]) • Data from diaries (sleepiness, mistakes/near misses/accidents, and caffeine use)

- **Results:**
  - At baseline, the placebo and armodafinil 150 mg and 250 mg groups were generally well matched, although patients in the armodafinil 250 mg group were significantly younger than patients in the other groups ($p < 0.05$).
  - At screening, CGI-S ratings were similar across groups, with the majority of patients having marked or severe illness (mean sleep latency < 3 min on the MSLT), and no differences were found between groups in MSLT. In the placebo group, 65% of patients had cataplexy vs 69% and 66% in the armodafinil 150 mg and 250 mg groups, respectively.
  - Study discontinuation rates were 25% (n = 16) in the armodafinil 150 mg group; 16% (n = 11) in the armodafinil 250 mg group; and 14% (n = 9) in the placebo group (18.4% total discontinuation rate).
  - At the final visit, mean MWT 9:00 AM to 3:00 PM sleep latency increased 1.3, 2.6, and 1.9 min from baseline in the 150 mg, 250 mg, and armodafinil combined groups, respectively, and decreased 1.9 min from baseline in the placebo group. Treatment differences from placebo were 3.2, 4.5, and 3.8 min in the 150 mg, 250 mg, and armodafinil combined groups, respectively (all $p < 0.01$).
  - Mean MWT 3:00 PM to 7:00 PM sleep latency at the final visit increased 1.5, 1.6, and 1.6 min in the 150 mg, 250 mg, and armodafinil combined groups, respectively, and decreased 1.2 min from baseline in the placebo group. Treatment differences relative to placebo were 2.7, 2.8, and 2.8 min, for the 150 mg, 250 mg, and armodafinil combined groups, respectively. The differences for the armodafinil combined group vs placebo and the 150 mg group vs placebo were significant ($p < 0.05$ for both comparisons). The armodafinil groups, individually and collectively, also had numerically longer mean MWT 3:00 PM to 7:00 PM sleep latencies when compared with placebo at weeks 4, 8, and 12. These differences did not achieve statistical significance.
  - The proportion of patients with at least minimal improvement in the CGI-C was significantly higher for the armodafinil 150 mg, 250 mg, and combined groups compared with placebo at all time points during the study ($p < 0.0001$ for both individual doses and the combined group vs placebo at final visit). The proportion of patients rated as minimally, much, and very much improved on the CGI-C from baseline to final visit was 21%, 33% and 16%, respectively, for armodafinil 150 mg; 20%, 35%, and 18%, respectively, for armodafinil 250 mg; 20%, 34%, and 17%, respectively, for the armodafinil combined group; and 17%, 12%, and 3%, respectively, for placebo.

- At final visit, power of attention was significantly improved in the armodafinil 150 mg/day and armodafinil combined groups compared with placebo ($p < 0.05$). Although there were numerical differences in favor of both armodafinil dose groups and the combined group compared with placebo at each visit, statistical significance was not observed until the final visit. Effects on mean continuity of attention were numerically improved for the armodafinil groups compared with placebo, but the difference did not achieve statistical significance. At final visit, armodafinil (both doses and the combined group) demonstrated significantly greater improvements in quality of episodic secondary memory relative to placebo ($p < 0.05$). Improvement was observed at the week 4 visit and was maintained throughout the study. Armodafinil 250 mg and the combined group demonstrated significantly greater improvement in speed of memory relative to placebo ($p < 0.05$) at final visit.
- Differences in the change from baseline on the ESS were statistically significant in favor of each armodafinil group compared with placebo at weeks 8 ($p < 0.01$ for all comparisons) and 12 ($p < 0.01$) and at final visit (mean ± SD change from baseline: 150 mg/day, -4.1 ± 5.13, $p = 0.0044$; 250 mg/day, -3.8 ± 4.73, $p = 0.0015$; combined group, -3.9 ± 4.91, $p = 0.0006$). At week 4, there was a statistically significant difference in favor of armodafinil 150 mg/day ($p = 0.0402$). In patients receiving armodafinil 250 mg/day, the difference was not statistically significant ($p = 0.0760$). At the final visit, 21% of patients in the armodafinil 150 mg/day group ($p = 0.0312$) and 28% of patients in the armodafinil 250 mg/day group ($p = 0.0023$) had an ESS score < 10, compared with only 7% of patients in the placebo group.
- Improvements on the BFI in the armodafinil 150 mg/day, 250 mg/day, and combined armodafinil group at final visit were statistically greater than placebo (mean change from baseline: 150 mg/day, -1.5 ± 2.14, $p = 0.0007$; 250 mg/day, -1.3 ± 2.09, $p = 0.0018$; combined group, -1.4 ± 2.11, $p = 0.0002$; placebo, -0.3 ± 1.89). There was a trend toward improvement from baseline in mean worst fatigue scores over the previous 24 hours at final visit, but the differences with armodafinil (all groups) vs placebo were not statistically significant ($p > 0.05$).
- Treatment with armodafinil 150 and 250 mg/day reduced the mean daily number of unintended sleep episodes by 33% and 44%, respectively, compared with a 10% reduction seen in the placebo group ($p < 0.0001$ for overall treatment comparison). The mean number of daily naps was reduced by 41%, 44%, and 22%, respectively, for the armodafinil 150 mg, armodafinil 250 mg, and placebo groups ($p = 0.0039$ for overall treatment comparison). The mean number of mistakes/near misses/accidents was reduced by 43% and 30% in the armodafinil 150 mg/day and 250 mg/day groups, respectively, compared with a 10% reduction in the placebo group. These differences, however, did not achieve statistical significance ($p = 0.1792$ for overall treatment comparison). Caffeine use, which was measured by the number of caffeinated drinks consumed each day, remained similar in the armodafinil and placebo groups (mean change from baseline, -0.7, -1.6, and 0.6 for armodafinil 150 mg, armodafinil 250 mg, and placebo, respectively).
- Headache, nausea, dizziness, and decreased appetite were the most commonly reported AEs. Most were considered mild to moderate, occurred with the greatest frequency during the first 2 weeks of therapy, and were self-limiting.
- There were no significant effects of armodafinil on nighttime sleep, including sleep initiation, continuity, or sleep stage variable as assessed by PSG. There was no change in the incidence of self-reported cataplexy.

- **Authors' conclusion:**
  - In patients with EDS associated with narcolepsy, armodafinil, at doses of 150 or 250 mg/day, significantly improved wakefulness throughout the day, clinician ratings of overall clinical condition, and some measures of memory and attention compared with placebo.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Cephalon
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - Both objective and subjective measures were used to assess efficacy.
  - **Study limitations:**
    - The study was of short duration and did not provide information on the long-term efficacy and safety of armodafinil.
    - The study was not powered to detect differences between the 150 mg and 250 mg armodafinil doses. In addition, there was a significant difference in baseline MWT sleep latency between the 150 mg and 250 mg dose groups. Thus, additional research is needed to clarify the dose proportionality of armodafinil in the narcolepsy population.
    - The effect of armodafinil on memory processes requires further study.

Study 2. Golicki et al, *Med Sci Monit.* 2010;16(8):177-186

Study Objective: Evaluate the efficacy and safety of modafinil vs no active treatment or other drugs in the treatment of narcolepsy

Study Design, Follow-up	Treatment Groups
• Systematic review and meta-analysis (9 RCTs, N = 1054) • Three studies were SC; 4 were MC in 1 country and 2 were MC in more than 1 country. • Sample size varied between 10 and 283; however, only 3 studies included > 100 patients. • All studies were DB and 5 were XO.	• Modafinil any dose or regimen (n = 629) • Placebo or other active treatment (n = 425) • All studies compared modafinil with placebo and 1 also with sodium oxybate in patients with narcolepsy previously treated with modafinil in fixed doses for 4 weeks.
Inclusion Criteria	**Exclusion Criteria**
• Prospective, PG, or XO RCTs, SB or DB published as full text in peer reviewed journals • Study participants with adult (> 17 years old) narcolepsy with or without cataplexy	• Retrospective studies • Studies comparing different doses of modafinil • Secondary publication of an already included study
Primary Endpoints	**Secondary Endpoints**
• Elimination of EDS assessed by objective laboratory tests (MSLT, MWT) or validated subjective outcome measures (ESS) • Number and duration of severe somnolence, sleep attacks and naps, as reported by patients	• QoL assessed by validated generic questionnaires (SF-36) or validated sleep specific questionnaires • Disease severity assessed by the CGI-S • Performance assessed with the 4-choice reaction time test (FCRTT) • Steer Clear Performance Test (SCPT) • Physician evaluation of alerting effect on visual analog scale (VAS) • AEs • Withdrawals due to AEs

- **Results:**
  - Most of the included studies were of good quality and 1 was of poor quality. Five studies did not provide information on allocation concealment, and 4 had adequate allocation concealment. None of the studies reported proper intent-to treat (ITT) analysis; in 2 studies it was unclear and in 3 studies the authors provided analysis for all randomized patients who received study medication and had at least 1 post-baseline measure for efficacy (modified ITT [mITT]). Follow-up ranged from 2 to 9 weeks.
  - A fixed effect model was used by default, but if heterogeneity was detected, a random effects model was used.
  - Modafinil vs placebo:
    - The MSLT was used in 3 studies. In 2 PG studies, there was a greater increase in mean sleep latency with modafinil as compared with placebo: WMD 1.11 min (95% CI, 0.55 to 1.66); I^2 = 0%; test for overall effect: Z = 3.90 (p < 0.0001). The XO study presented median values, which were higher in the modafinil treatment phase compared with the placebo treatment phase (6.6 min vs 3.2 min; p < 0.05).
    - The MWT was used in 6 studies. In 4 PG studies and 2 XO studies, there was a greater increase in mean sleep latency with modafinil as compared with placebo: WMD 2.82 min (95% CI, 2.40 to 3.24); I^2 = 0%; test for overall effect: Z = 13.14 (p < 0.00001). There were similar increases in mean sleep latency in both the PG and XO studies.
    - The ESS scale was used in 6 studies. In 3 PG studies and 1 XO study, there was a greater reduction in the mean ESS score: WMD -2.73 points (95% CI, -3.39 to -2.08); I^2 = 0%; test for overall effect: Z = 8.17 (p < 0.00001). The ESS score was lower with modafinil vs placebo in both the XO and PG studies. In 1 XO study, the median ESS score decreased from 14.5 points during placebo treatment to 12.5 points after 3 weeks of modafinil treatment (p < 0.05). In another PG study which reported median values, no significant change in median average ESS score in the modafinil group was seen as compared with the placebo group (from 14 points to 15 points vs from 16 points to 16 points; p = 0.77).
    - Modafinil also improved the number (p = 0.006) and duration (p = 0.03) of severe somnolence episodes, sleep attacks, and naps per day as compared with placebo.
    - Elimination of cataplexy was assessed in 4 studies. There was no significant effect of modafinil as compared with placebo in 3 XO studies, as well as in 1 PG study: WMD 0.02 (95% CI, -0.27 to 0.31); I^2 = 71%; test for overall effect: Z = 0.13 (p = 0.90).
    - QoL was measured in 2 PG studies using the SF-36 and validated narcolepsy-specific questionnaire. At the end of a 9-week treatment period, patients receiving modafinil compared with those receiving placebo had significantly higher scores in 5 out of 7 narcolepsy-specific domains, SF-36 mental health summary scale and 4 (modafinil 200 mg/day) or 5 (modafinil 400 mg/day) SF-36 domains.

- CGI-S was assessed in 4 studies. In 1 XO study, CGI-S was non-significantly higher during the 4-week modafinil treatment period compared with the placebo phase (2.29 vs 2.0; p = 0.19). Two out of 3 PG studies showed significantly larger numbers of patients who improved according to physician assessment as compared with placebo groups. One study did not show a significant effect. The pooled effect estimate was significant (RR 1.6, 95% CI, 1.32 to 1.95); however, there was moderate heterogeneity (I^2 = 46%), introduced by Black and Houghton 2006 (see study 9 below), which enrolled patients already treated with modafinil and used different doses of the drug. Pooled CGI data from 2 studies showed significant improvement with no corresponding heterogeneity (RR 2.83, 95% CI, 1.90 to 4.20; I^2 = 0%).
- FCRTT was assessed in 3 studies. In 1 XO study, the modafinil treatment phase compared with the placebo treatment phase was associated with significant reductions in the number of gaps and the percentage of errors, and non-significant reduction in the mean reaction time. In another XO study and PG study, no significant difference between the modafinil and placebo groups were observed.
- SPCT was assessed in 2 studies. Significant improvement in driving ability was observed in the modafinil group as compared with the placebo group (WMD -2.54, 95% CI, -4.24 to -0.85).
- Physician evaluation of alerting effect on VAS scale was used in 1 XO study. No significant difference between the modafinil and placebo treatment phase was seen for alerting effect.

○ Modafinil vs sodium oxybate:
- No significant difference was observed between modafinil and sodium oxybate groups in the change of the mean sleep latency as measured by the MWT (MD -1.11 (95% CI, -3.02 to 0.8). The ESS score decreased in sodium oxybate group from 15 to 12 points and increased in modafinil group from 14 to 15 points (see study 9 below).

○ Safety:
- Modafinil was associated with more patient withdrawals from treatment due to AEs (4% vs 1.6% in placebo group); however, pooled RR was not significant: 2.06 (95% CI, 0.83 to 5.09); I^2 = 14%; test for overall effect: Z = 1.57 (p = 0.12).
- Significantly more patients reported nausea in the modafinil group as compared with placebo group. Other reported AE rates were similar between the groups.
- In the study comparing modafinil with sodium oxybate, non-significantly fewer patients in modafinil group compared to sodium oxybate group discontinued treatment due to AEs (3.2% vs 7.3%). Any AE rate was also similar in the modafinil and sodium oxybate groups (54% vs 60%). The most commonly reported AE was nausea, which was rare in the modafinil compared to the sodium oxybate group (3.2% vs 22%; RR 0.15, 95% CI, 0.03 to 0.62). Other AE rates were similar in modafinil and sodium oxybate groups.

• **Authors' conclusion:**
○ On the basis of 9 included studies, it can be concluded that in patients with narcolepsy modafinil in comparison with placebo was associated with significant benefit in terms of elimination of EDS assessed by objective laboratory tests or validated subjective outcome measures, but was not different from placebo in elimination of cataplexy as measured by the number of attacks per day. In addition, modafinil improved QoL of narcolepsy patients measured both by generic and a narcolepsy-specific questionnaire, and was associated with greater likelihood of improvement according to physician assessment.
○ On the basis of 1 study, it can be concluded that modafinil had a similar effect on EDS as sodium oxybate.
○ Modafinil has not been compared directly to methylphenidate, a common treatment of EDS, in any RCTs.

• **Study Appraisal:**
○ **Study sponsorship:**
- The review was partially based on Health Technology Assessment (HTA) report prepared by 2 of the authors to support Polish reimbursement application of modafinil manufactured by Torrex Chiesi. Both authors received grants from Torrex Chiesi Poland Sp.zo.o.

○ **Study rating:**
- N/A

○ **Study strengths:**
- The MA included a large number of RCTs, structured assessment of study quality, and pooled assessment of the modafinil treatment effect.

○ **Study limitations:**
- The length of follow-up of the included studies was short (2 to 9 weeks).
- Due to the small number of trials it was not possible to formally assess the presence of publication bias.
- More than half of the included studies were of XO design. Pooling of XO and PG group studies is considered controversial by some researchers. In this analysis, results of XO and PG studies were pooled separately in subgroups, and then all together.

Study 3. Mitler et al. *Sleep Med.* 2000;1(3):231-243

- A 40-week, OL extension study assessed the long-term efficacy and safety of modafinil in 478 patients with EDS associated with narcolepsy who completed 1 of the 2 pivotal 9-week RCTs of modafinil. A flexible-dose regimen (ie, 200, 300, or 400 mg daily) was followed in 1 study. In the second study, patients received 200 mg/day for 1 week, followed by 400 mg/day for 1 week. Investigators then prescribed either 200 or 400 mg doses for the duration of the study; the majority of patients (~75%) received 400 mg/day. The study was completed by 341 patients (71%).
  - At week 2, CGI-C scores indicated improvement in disease severity in 394/477 (83%) patients from OL baseline which was sustained through week 40. CGI-C scores indicated no change in disease severity in 7 ± 10% of patients and a worsening of symptoms in 9 ± 10% of patients. A total of 236 of 477 patients (49%) were considered much improved or very much improved at week 2. The percentage of patients considered to be much improved or very much improved increased significantly to 58, 59, and 58%, respectively, at weeks 8, 24, and 40 ($p < 0.001$ vs week 2 at all time points). The mean ESS score improved significantly from 16.5 at OL baseline to 12.4 at week 2 and remained at that level through week 40 ($p < 0.001$). QoL scores at weeks 4, 8, 24, and 40 were significantly improved vs OL baseline scores for 6 of the 8 SF-36 domains ($p < 0.001$).
  - The most common treatment-related AEs were headache (13%), nervousness (8%), and nausea (5%). Most AEs were mild to moderate in severity. Forty-three patients (9.0%) discontinued treatment because of AEs.
  - The authors concluded that modafinil was effective for the long-term treatment of EDS associated with narcolepsy and significantly improved perceptions of general health. Modafinil was well tolerated, with no evidence of tolerance developing during 40 weeks of treatment.

Study 4. Black et al. *J Clin Sleep Med.* 2010;6(5):458-66

- The long-term efficacy and safety of armodafinil in patients with EDS associated with treated OSA, SWD, or narcolepsy who completed one of four 12-week pivotal RCTs was assessed in a 12-month, flexible-dose (50 to 250 mg/day), OL extension study. Of 743 enrolled patients (474 with treated OSA, 113 with SWD, and 156 with narcolepsy), 57% of patients (420/743) completed 12 months or more of treatment.
  - Compared with baseline, minimal or greater improvement on the CGI-C was reported by most patients in the 3 diagnostic groups (75 to 92%) at final visit; patients in the SWD group reported the greatest improvement. A rating of much or very much improved was reported at the final visit by 65% (295/457) of patients with treated OSA (95% CI, 60.2 to 68.9), 88% (92/105) with SWD (95% CI, 81.3 to 93.9), and 62% (93/150) with narcolepsy (95% CI, 54.2 to 69.8). At baseline, the proportion of patients with a normal ESS score (ie, < 10) was 0.4% (2/454) in the treated OSA group and 3.4% (5/147) in the narcolepsy group. At the final visit, mean ESS score was reduced by 6.4 (95% CI,
    -6.90 to -5.94) in the treated OSA group and by 4.3 (95% CI, -5.20 to -3.49) in the narcolepsy group. The proportion of patients with an ESS score < 10 at final visit was 54.8% (249/454) for treated OSA and 31.3% (46/147) for narcolepsy. At final visit, mean global BFI scores were reduced by 1.7 (95% CI, -1.88 to -1.43) in the treated OSA group, 2.3 (95% CI, -2.75 to -1.87) in the SWD group, and 1.7 (95% CI, -2.13 to -1.35) in the narcolepsy group; mean worst fatigue scores were reduced by 1.8 (95% CI, -2.13 to -1.57) in the treated OSA group, 2.4 (95% CI, -3.06 to -1.83) in the SWD group, and 1.5 (95% CI, -2.00 to -1.07) in the narcolepsy group.
  - The most commonly reported AEs were headache (25% [180/731]), nasopharyngitis (17% [123/731]), insomnia (14% [99/731]), and upper respiratory tract infection (10% [76/731]). Most AEs were mild or moderate in intensity. Modest increases were observed in vital sign measurements (BP [3.6/2.3 mm Hg], heart rate [6.7 beats per min (bpm)]) across all patient groups; most of the changes occurred by month 3. Discontinuations due to AEs occurred in 13% of patients (95/743) during the 12-month period.
  - The authors concluded that armodafinil remained effective and was generally well tolerated. Increased monitoring of BP may be appropriate in patients on armodafinil. Armodafinil represents an option for long-term treatment of patients with EDS associated with treated OSA, SWD, or narcolepsy.

<u>OSA</u>

Study 5. Kuan et al, *Clin Ther.* 2016;38(4):874-888

Study Objective: Evaluate the efficacy of modafinil and armodafinil in treating EDS in patients with OSA	
Study Design, Follow-up	**Treatment Groups**
• Systematic review and meta-analysis (N = 11 modafinil RCTs and 5 armodafinil RCTs)	• Modafinil 200 to 400 mg daily x 1 to 12 weeks (N = 723) • Armodafinil 150 to 250 mg daily x 2 to 12 weeks (N = 1009) • Placebo • Sample sizes of the 16 RCTs ranged from 20 to 392.
Inclusion Criteria	**Exclusion Criteria**

• RCTs that: ○ Compared the outcomes of the use of placebo and either modafinil or armodafinil in patients with OSA ○ Described all inclusion and exclusion criteria used for patient selection ○ Reported doses and durations of study drugs	• Trials that included patients < 18 years of age or duplicate reports of patient cohorts
Primary Endpoints	**Secondary Endpoints**
• Sleep latency assessed by the MSLT or MWT • ESS • Karolinska Sleepiness Scale (KSS) (Appendix E) • Stanford Sleepiness Scale (SSS) (Appendix F)	• CGI-C • Patient-reported daily function assessed using the 10-item Functional Outcomes of Sleep Questionnaire (FOSQ-10), which measures functional status for disorders of EDS • Psychomotor Vigilance Tests

- **Results:**
  - Most trials investigated whether modafinil or armodafinil with concurrent CPAP use improved sleepiness, neurocognitive performance, and functional outcome in patients with sleep apnea. In 2 studies, CPAP was stopped during modafinil treatment. One study of modafinil and 1 study of armodafinil included untreated patients with OSA. Two studies of modafinil did not specify whether patients received CPAP.
  - Six studies reported acceptable methods of randomization and 6 studies described methods of allocation concealment. All studies reported patient blinding and the outcomes assessors used, and 1 trial reported the blinding of clinicians. Two studies used an ITT analysis without loss to follow-up. For all studies, the acceptable percentage of patients lost to follow-up was < 20%, except in 2 studies in which the levels were 20% and 21%.
  - A pooled estimate of the MDs in sleepiness parameters vs placebo were calculated using a random effects model.
  - Subjective sleepiness:
    - Subjective sleepiness in patients with OSA receiving CPAP was assessed using ESS in 5 RCTs of modafinil and 4 RCTs of armodafinil. Modafinil (WMD -2.95 [95%CI, -3.73 to -2.17]) and armodafinil (WMD -2.78 [95%CI, -3.51 to -2.05]) significantly improved subjective sleepiness compared with placebo ($I^2 = 0\%$).
    - Four studies evaluated the effects of modafinil on subjective sleepiness during acute CPAP withdrawal or in CPAP-naïve patients with OSA. There was a significant reduction in daytime sleepiness duration ($p < 0.05$) and significant improvements on the ESS ($p = 0.003$ [1 study]), KSS ($p = 0.04$ and $p = 0.01$ [2 studies]), SSS ($p = 0.03$ [1 study]), and daytime sleepiness VAS ($p = 0.01$ [1 study]). A non-significant trend of improved self-reported sleepiness on the ESS after armodafinil use among patients with OSA before CPAP treatment was observed in 1 study ($p = 0.066$).
  - Objective sleepiness:
    - Sleep latency with CPAP use was assessed using the MWT after modafinil treatment in 4 studies and after armodafinil treatment in 3 studies. Sleep latency was significantly prolonged in the modafinil group vs the placebo group (WMD 2.51 [95% CI, 1.5 to 3.52]) and armodafinil was associated with significant improvement vs placebo (WMD 2.71 [95% CI, 0.02 to 5.37]). However, a meta-analysis of data from 3 RCTs that compared the effects of modafinil and placebo on sleep latency, as assessed by the MSLT found no significant differences.
  - Overall clinical impression and daily functioning:
    - The proportion of patients with improvement on the CGI-C was evaluated in 3 RCTs of modafinil and 4 RCTs of armodafinil. There was significant improvement in both the modafinil and armodafinil groups vs the placebo group, with pooled RR of 1.94 (95% CI, 1.53 to 2.44) and 1.48 (95 % CI, 1.17 to 1.87), respectively.
    - The FOSQ was used in 4 RCTs that evaluated modafinil. Data were pooled on changes from baseline in total scores from 3 RCTs. In 1 study, the modafinil group showed significant improvement compared with placebo with an MD of 1.28 (95% CI, 0.64 to 1.91). The other 2 trials were not included because of incomplete data. One study found a non-significant trend toward improvement with modafinil in total FOSQ score ($p = 0.093$) and another study reported a non-significant trend in the vigilance subdomain of the FOSQ in the modafinil group ($p = 0.06$). One study reported that armodafinil treatment resulted in significant improvement in the subdomains of general productivity ($p = 0.01$) and social outcome ($p = 0.005$) compared with placebo. However, 2 RCTs conducted in an earlier period yielded divergent results regarding the effects of the medications.
  - Neurocognitive and driving performance:
    - Psychomotor vigilance tests indicated significant reductions in mean reaction time in 3 RCTs. Simulated driving performance was significantly improved in patients with OSA and acute CPAP withdrawal ($p = 0.018$) and in those awaiting CPAP initiation ($p < 0.0001$). One study reported a significant improvement in the composite Driving Safety Score ($p = 0.03$), assessed using the Cognitive Research Corporation Driving Simulator, in CPAP-naïve patients with OSA who received armodafinil compared with placebo.
  - AEs:

- Headache was the most commonly reported AE with both medications with RR of 1.78 (95% CI, 1.20 to 2.65) in the modafinil group and 2.04 (95% CI, 1.36 to 3.05) in the armodafinil group. Most AEs were generally of mild to moderate severity. Other AEs included nausea, anxiety or nervousness, insomnia, and dizziness.

- **Authors' conclusion:**
  - Modafinil or armodafinil treatment significantly improved sleepiness, clinical global impression, and total FOSQ scores in patients with OSA and excessive sleepiness with or without concurrent CPAP use. The results on neurocognitive performance were inconsistent. Most AEs were well tolerated.
- **Study Appraisal:**
  - **Study sponsorship:**
    - No funding was received from any industry or organization.
  - **Study rating:**
    - N/A
  - **Study strengths:**
    - Eligibility criteria were applied systematically and explicitly.
  - **Study limitations:**
    - The sample size of some of the included RCTs was small.
    - Most of the trials were short-term, with a maximum duration of 12 weeks.
    - Some numeric data analyzed statistically were estimated using graphics in the original publications because complete data were unavailable.
    - Concurrent use of CPAP was not consistent across all trials.
    - Patients were normotensive at baseline; thus, the study findings cannot be extrapolated to hypertensive patients.

SWD

Study 6. Czeisler et al. *Mayo Clin Proc*. 2009;84:958-972.

Study Objective: Evaluate the effect of armodafinil on the physiologic propensity for sleep and cognitive performance during usual night shift hours in patients with excessive sleepiness associated with chronic moderate to severe SWD	
Study Design, Follow-up	**Treatment Groups** (N = 254)
• 12-week, Phase 3, DB, PC, PG, MC, RCT • Patients were evaluated at weeks 4, 8, and 12 during an overnight laboratory night shift scheduled immediately after a sequence of ≥ 3 consecutive work night shifts.	• Armodafinil 150 mg 30 to 60 minutes before each night shift and no later than 11:00 PM (n = 127) • Placebo (n = 127) • Patients received a dose of 50 mg on the first night, 100 mg on the second and third nights, and 150 mg on all subsequent nights. Patients took study medication only on nights when they worked the night shift or attended the sleep laboratory.
Inclusion Criteria	**Exclusion Criteria**
• Age 18 to 65 years • Worked 5 or more night shifts per month (each shift ≤ 12 hours, with ≥ 6 hours worked between 10:00 PM and 8:00 AM and with ≥ 3 shifts occurring on consecutive nights) and planned to maintain this schedule for the duration of the treatment • Diagnosis of SWD according to the ICSD • SWD of moderate or greater severity, as documented by a CGI-S rating ≥ 4 for sleepiness on work nights, including the commute to and from work • Chronic (≥ 3 months) excessive sleepiness during night shifts, which was corroborated by a mean sleep latency of 6 minutes or less on a nighttime MSLT • Insomnia, as indicated by daytime sleep efficiency of 87.5% or less (determined by 8-hour PSG)	• History of substance abuse or medical or psychiatric disorders that could account for excessive sleepiness during the night shift • Any disorder that might interfere with drug PK • Known sensitivity to stimulants or modafinil • Consumption of an average of > 600 mg/day of caffeine during the 7 days preceding the baseline visit • Use of prescription drugs disallowed by the protocol or clinically important amounts of nonprescription drugs within 7 days of the screening visit
Primary Endpoints	**Secondary Endpoint**
• Change from baseline to final visit (12-week or last post-baseline measurement) in overall mean sleep	• Patient sleepiness assessed using the KSS

latency (averaged across the last 4 nighttime sessions at 2:00, 4:00, 6:00, and 8:00 AM) as assessed by the MSLT • Proportion of patients with at least minimal improvement in the CGI-C during the night shift and commute to and from work at the final visit (12-week or last post-baseline measurement)	• The CDR was administered at 12:30, 2:30, 4:30, 6:30, and 8:30 AM of each laboratory night shift. ○ The CDR battery included tests of memory (eg, numeric working memory test, word recognition test, immediate word recall test, delayed word recall test, and picture recognition test) and attention ○ Composite factors derived from the CDR included quality of episodic secondary memory (ability to encode, store, and retrieve verbal and pictorial information of an episodic nature), speed of memory (time required to retrieve information from episodic and working memory), power of attention (ability to focus attention), and continuity of attention (ability to sustain attention).

- **Results:**
  - Of the 254 patients randomized, 245 (96%) received at least 1 dose of study drug and 172 patients completed the study (84 placebo, 93 armodafinil).
  - The armodafinil and placebo groups were similar in baseline demographic variables and illness severity ratings. Overall, 138 (56%) of 245 patients were rated by the investigator as moderately ill, and 107 (44%) of 245 patients were rated as markedly, severely, or extremely ill. Most patients (212/245; 87%) were permanent night shift workers.
  - Sixty-eight (28%) of 245 patients withdrew from the study (30 in the armodafinil group and 38 in the placebo group). Reasons for discontinuing were AEs (7 in the armodafinil group and 4 in the placebo group), consent withdrawn (3 in the armodafinil group and 16 in the placebo group), loss to follow-up (3 in the armodafinil group and 5 in the placebo group), nonadherence with study procedures (6 in the armodafinil group and 2 in the placebo group), and other (11 in the armodafinil group and 11 in the placebo group). No patients discontinued participation because of lack of efficacy.
  - Patients were severely sleepy at baseline, with mean (SD) sleep latencies on the MSLT of 2.3 (1.6) min for the armodafinil group and 2.4 (1.6) min for the placebo group. The mean KSS score was 7.4 (1.4) in the armodafinil group and 7.3 (1.3) in the placebo group and 97 (87%) of 112 patients in the armodafinil group and 87 (84%) of 104 in the placebo group had a KSS score ≥ 6.
  - Armodafinil significantly improved mean (SD) sleep latency from 2.3 (1.6) min at baseline to 5.3 (5.0) min at final visit, compared with a change from 2.4 (1.6) min to 2.8 (2.9) min in the placebo group ($p < 0.001$).
  - Of 112 armodafinil patients, 89 (79%) were rated as improved on the CGI-C at the final visit compared with 61 (59%) of the 104 placebo patients ($p = 0.001$).
  - The sleep latency for individual MSLT sessions at all 5 time points (midnight to 8:00 AM) at the final visit was greater for patients who received armodafinil than for patients who received placebo ($p < 0.001$ at midnight, 2:00 AM, 4:00 AM; $p = 0.007$ at 6:00 AM; $p = 0.02$ at 8:00 AM).
  - For the armodafinil group, 64 (57%) of 112 patients were very much improved or much improved at the final visit compared with 37 (36%) of 104 patients in the placebo group ($p = 0.002$). The proportion of patients with at least minimal improvement on the CGI-C of sleepiness was significantly greater for armodafinil than for placebo at the 4-week (armodafinil, 89/110 patients [81%]; placebo, 59/100 [59%]; $p < 0.001$), 8-week (armodafinil, 77/99 [78%]; placebo, 45/93 [48%]; $p < 0.001$), and 12-week (armodafinil, 75/96 [78%]; placebo, 50/89 [56%]; $p = 0.001$) assessments.
  - Patient-reported levels of sleepiness during the night shift on the KSS were significantly reduced for the armodafinil group compared with the placebo group at all visits ($p \leq 0.001$ at week 4 and 8; $p \leq 0.01$ at week 12, results shown in graphical form).
  - At the final visit, armodafinil was associated with significant improvement in most items assessed in the electronic diaries, including maximum level of sleepiness during the night shift and commute home and the mean number of mistakes, accidents, or near misses compared with placebo (Table 2).

Table 2. Changes in ratings of sleepiness on the electronic diaries

Characteristic	Placebo (n = 104)			Armodafinil (n = 112)			p-value[c]
	No. of pts[a]	Baseline[b]	Δ from baseline[b]	No. of pts[a]	Baseline[b]	Δ from baseline[b]	
During night shift							

Unintended sleep episodes	88	1.1 (1.0)	-42%	92	1.2 (2.6)	-72%	< 0.001
Intended sleep episodes	79	0.6 (0.6)	-13%	85	0.7 (1.6)	-36%	0.01
Maximum level of sleepiness	99	7.5 (1.0)	-1.1 (1.0)	109	7.5 (1.1)	-2.0 (1.1)	< 0.001
Level of sleepiness during commute home	99	5.9 (1.4)	-0.6 (1.0)	109	5.9 (1.7)	-1.2 (1.2)	0.003
No. of mistakes, near misses, or accidents							
During night shift	66	0.8 (1.0)	-46%	84	1.2 (3.4)	-64%	0.04
During commute home	50	0.3 (0.6)	-47%	60	0.3 (0.4)	-66%	0.12
No. of caffeinated drinks/day	99	1.8 (3.9)	0.0 (1.4)	109	1.3 (1.2)	-0.4 (0.7)	

a Patient numbers represent data from those for whom baseline and post-baseline data were available to calculate change from baseline.
b Values are mean (SD) or percentage.
c Values are based on change from baseline compared with placebo.

- Armodafinil significantly improved standardized memory assessments ($p < 0.001$), mean power of attention ($p = 0.001$), and continuity of attention ($p < 0.001$).
- AEs reported by ≥ 5% of armodafinil patients and more frequently than placebo were headache (15/123 [12%] in the armodafinil group and 12/122 [10%] in the placebo group), nausea (9/123 [7%] in the armodafinil group and 4/122 [3%] in the placebo group), nasopharyngitis (7/123 [6%] in the armodafinil group and 4/122 [3%] in the placebo group), and anxiety (6/123 [5%] in the armodafinil group and 2/122 [2%] in the placebo group). Most AEs were considered mild or moderate.
- Armodafinil did not adversely affect daytime sleep variables (eg, sleep latency, sleep duration, and sleep-stage distribution) compared with placebo.

- **Authors' conclusion:**
  - In patients with excessive sleepiness associated with chronic SWD of moderate or greater severity, armodafinil significantly improved wakefulness during scheduled night work, raising mean nighttime sleep latency above the level considered to indicate severe sleepiness during the daytime. Armodafinil also significantly improved measures of overall clinical condition, long-term memory, and attention.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Cephalon
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - Both objective and subjective measures were used to assess efficacy.
  - **Study limitations:**
    - The study was of short duration and did not provide information on long-term efficacy and safety.
    - There is no validated measure for assessing excessive sleepiness in SWD. Although the MSLT is sensitive to changes in sleepiness during nighttime hours and is recommended for assessing sleepiness at night in this population, it has not been specifically validated as a clinical instrument for measuring nighttime sleepiness.
    - The study did not provide assessments of actual work performance or safety.
    - Most patients enrolled were permanent night shift workers. This may limit the generalizability of these results to individuals working alternative shift schedules.
    - This study was performed in SWD patients with both excessive sleepiness and insomnia, who may represent a more severely affected group; therefore, additional studies may be necessary to quantify the effects in a patient population with less severe SWD.
    - The study did not include patients with SWD associated with starting work in the early morning.

Study 7. Czeisler et al. *N Engl J Med*. 2005;353:476-486.

Study Objective: Evaluate the efficacy and safety of modafinil for the treatment of sleepiness in patients with SWD	
Study Design, Follow-up	**Treatment Groups** (N = 209)
• 3-mo, Phase 3, DB, PC, PG, MC, RCT • Patients were evaluated monthly during an overnight laboratory shift after having worked for 3 or more consecutive nights.	• Modafinil 200 mg 30 to 60 minutes before each night shift (n = 99) • Placebo (n = 110)
Inclusion Criteria	**Exclusion Criteria**

• Age 18 to 60 years • Worked each month ≥ 5 night shifts for ≤ 12 hours, with ≥ 6 hours worked between 10:00 PM. and 8:00 AM and ≥ 3 shifts occurring consecutively. • Diagnosis of SWD according to the ICSD • Chronic excessive sleepiness (≥ 3 months) during night shifts • CGI-S rating of moderately ill or worse for sleepiness on work nights, including the commute home from work; an average latency to sleep onset of ≤ 6 during 20-minute nap opportunities at 2-hour intervals during the night, as measured by the MSLT; and a sleep efficiency of ≤ 87.5% as determined by daytime PSG	• Diagnosis by history and/or diagnostic PSG of a concurrent sleep disorder other than chronic SWD • Presence of clinically significant, uncontrolled psychiatric or medical conditions • Abuse of alcohol, narcotics, or other drugs • Caffeine consumption averaging > 600 mg per day within 1 week of baseline • Use of protocol-prohibited prescription medications (eg, any medication that could make a patient feel sleepy, or clinically significant use of over-the-counter [OTC] drugs within 2 weeks of baseline)
Primary Endpoints	**Secondary Endpoints**
• Rating on the CGI-C test for sleepiness during the night shift, including the commute to and from work, at the final visit • Change between baseline and the final visit (ie, at the third month or at withdrawal from the study) in overall mean sleep latency on the basis of results of the nighttime MSLT	• Patient sleepiness assessed using the KSS • Frequency and duration of lapses of attention during performance on the Psychomotor Vigilance Test ○ This endpoint served as a validated and objective measure of alertness at night

- **Results:**
  - Of 209 patients randomized, 204 patients received the drug and153 patients completed the study (placebo, 81; modafinil 72).
  - At baseline, there were no significant differences in demographic variables, shift-work type, sleepiness, performance, and results on PSG between the group that received modafinil and the one that received placebo.
  - Patients were severely sleepy at baseline, with overall mean (±SD) sleep latencies of 2.0 ± 1.8 minutes and 2.1 ± 1.5 minutes for the placebo and modafinil groups, respectively.
  - Seventy-four percent of patients in the modafinil group were rated as at least minimally improved on the CGI-C test at the final visit, as compared with 36% in the placebo group ($p < 0.001$) (Table 3).
  - Overall mean (± standard error of the mean [SEM]) sleep latency, as measured by the MSLT, increased from 2.1 min at baseline to 3.8 min at the final visit with modafinil (change, 1.7 ± 0.4 min; $p < 0.001$) but not with placebo (2.04 at baseline vs 2.37 at the final visit; change, 0.3 ± 0.3; $p = 0.24$). Sleep latency was significantly greater in the modafinil group than in the placebo group ($p = 0.002$). This improvement in sleep latency with modafinil vs placebo was found at 2:00 AM ($p = 0.02$) and 4:00 AM ($p < 0.001$), but not at 6:00 AM ($p = 0.45$) or 8:00 AM ($p = 0.17$).

Table 3. CGI-C at final visit

CGI-C rating	Number (%) of patients	
	Placebo (n = 104)	Modafinil (n = 89)
Very much improved	8 (8)	21 (24)
Much improved	13 (13)	28 (31)
Minimally improved	16 (15)	17 (19)
No change	61 (59)	20 (22)
Minimally worse	4 (4)	2 (2)
Much worse	2 (2)	1 (1)
Very much worse	0 (0)	0 (0)
p-value		< 0.001

  - Differences between modafinil and placebo in the Psychomotor Vigilance Test were statistically significant.
    - The median number of lapses of attention in 20-minute tests during the night was 12.50 at baseline and 10.25 at the final visit for the modafinil group (median change from baseline, -2.6; $p = 0.012$). In the placebo group, the median number of lapses per test bout was 16.13 at baseline and 23.75 at the final visit (median change from baseline, 3.8; $p = 0.008$). The groups did not differ significantly at baseline ($p = 0.797$), but they did differ significantly at the final visit ($p = 0.005$), and the change in lapses of attention during performance of the Psychomotor Vigilance Test from baseline to the final visit was significant for modafinil vs placebo ($p < 0.001$).

- The duration of lapses showed a similar result, decreasing from baseline (780 msec) to the final visit (669 msec) for patients receiving modafinil and increasing from baseline (852 msec) to the final visit (1235 msec) for those receiving placebo; This resulted in a significant difference at the final visit (p = 0.004) and in the change from baseline to the final visit in favor of modafinil vs placebo (p = 0.019).
- Sleepiness levels on the KSS were also significantly reduced for patients receiving modafinil (baseline mean, 7.3; final visit mean, 5.8; change, -1.5 ± 0.2), as compared with placebo (baseline, 7.1; final visit, 6.7; change, -0.4 ± 0.2) (p < 0.001).

○ As compared with placebo, modafinil reduced the maximum level of sleepiness during the night-shift (p < 0.001 for the change from baseline vs placebo) and the level of sleepiness during the commute home (p = 0.01), and 25% fewer patients receiving modafinil reported having had accidents or near accidents during the commute home (p < 0.001). Modafinil treatment during night shifts had no statistically significant effects on unintentional or intentional sleep episodes, mistakes, accidents or near accidents, or caffeine consumption (Table 4).

Table 4. Variables derived from patient diaries

Variable	Placebo (n = 108)			Modafinil (n = 96)			p-value
	Baseline	After baseline	Change	Baseline	After baseline	Change	
During night shift							
Maximum level of sleepiness — score†	7.4±1.0	6.6±1.3	-0.9±1.0	7.3±0.9	5.4±1.5	-1.9±1.4	< 0.001
No. of unintentional sleep episodes†	1.2±1.3	0.6±0.7	-0.6±1.0	1.0±1.1	0.2±0.4	-0.8±0.9	0.20
No. of intentional sleep episodes†	0.5±0.8	0.4±0.5	-0.1±0.5	0.4±0.5	0.2±0.4	-0.2±0.4	0.13
No. of caffeinated drinks consumed†	1.3±1.1	1.1±0.9		1.3±1.2	1.0±1.0		0.10
Patients reporting mistakes, accidents, or near accidents — no. (%)§		59 (55)			46 (48)		0.34
During commute home							
Level of sleepiness — score†	5.9±1.8	5.4±1.7	-0.6±1.2	5.5±1.8	4.4±1.6	-1.1±1.5	0.012
Patients reporting unintentional sleep episodes — no. (%)§		47 (44)			34 (35)		0.24
Patients reporting accidents or near accidents — no. (%)§		58 (54)			28 (29)		< 0.001¶
During days after night shift							
No, of caffeinated drinks consumed‡**	1.0±1.3	0.6±0.7	-0.4±1.0	0.9±1.1	0.7±0.8	-0.2±1.0	0.61
Sleep efficiency — %**††	78.0±20.7	87.5±14.1	9.5±18.3	80.3±19.9	87.5 ±14.4	7.3±18.5	0.55

* Plus–minus values are means ±SD. Patients recorded responses in electronic diaries on actual work nights. Sleepiness scores were obtained with the use of the KSS. Analysis includes patients with baseline values and values after baseline. For each patient, baseline values and values after baseline are average values calculated before and after the start of DB treatment.
† Data were available for 84 patients receiving placebo and for 79 patients receiving modafinil.
‡ p-value is for the change from baseline for modafinil vs placebo.
§ Values are for the number of patients with a value after baseline. Patients were counted once.
¶ p-value is for modafinil vs placebo.
‡ Data were available for 85 patients receiving placebo and for 78 patients receiving modafinil.
** The time interval was from the end of the night shift until 60 minutes after waking up from the last sleep episode.
†† Data were available for 84 patients receiving placebo and for 78 patients receiving modafinil. Sleep efficiency was calculated as the sleep duration divided by the time spent in bed multiplied by 100 so that scores could range from 0 to 100%.

○ During days following night off, there were no significant differences in caffeine use and sleep efficiency between the modafinil and placebo group.
○ There were no significant differences between modafinil and placebo with respect to any measurement of daytime sleep, including sleep duration, latency, and efficiency, and the proportion and distribution of sleep stages.
○ The use of prescription or nonprescription sleeping pills was not specifically monitored, although concomitant use of medications was queried. Of the 96 patients in the modafinil group, 1 reported use of a prescription hypnotic vs none of the 108 placebo patients. Five of the 96 modafinil patients reported use of OTC sleep aids vs 1 of the 108 placebo patients (p = 0.102).
○ Headache was the most common AE reported in both treatment groups.
○ More patients in the modafinil group than in the placebo group had insomnia (6 vs 0%, respectively; p = 0.01).

- **Authors' conclusion:**
  ○ Treatment with 200 mg of modafinil reduced the extreme sleepiness in patients with SWD and resulted in a small but significant improvement in performance as compared with placebo. However, the residual sleepiness that was observed in the treated patients underscores the need for the development of interventions that are even more effective.

- **Study Appraisal:**
  - **Study sponsorship:**
    - Cephalon
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - Both objective and subjective measures were used to assess efficacy.
  - **Study limitations:**
    - The study was of short duration and did not provide information on long-term efficacy and safety.
    - There is no validated measure for assessing excessive sleepiness in SWD. Although the MSLT is sensitive to changes in sleepiness during nighttime hours and is recommended for assessing sleepiness at night in this population, it has not been specifically validated as a clinical instrument for measuring nighttime sleepiness.
    - The study did not provide assessments of actual work performance.
    - The vast majority of participants were permanent night shift workers; thus, the study findings are not generalizable to other types of shifts that include nighttime hours.

Pitolisant

Study 8. Dauvilliers et al, *Lancet Neurol.* 2013;12:1068-1075 (HARMONY 1)

Study Objective: Evaluate the safety and efficacy of pitolisant in patients with EDS in narcolepsy	
Study Design, Follow-up	**Treatment Groups** (N = 95)
• Phase 3, AC, DB, double-dummy, PC, PG, MC, RCT • The study was conducted in 32 sleep disorder centers in 5 European countries	• Pitolisant (n = 32) • Modafinil (n = 33) • Placebo (n = 30) • Treatment duration was 8 weeks: 3 weeks of flexible dosing followed by 5 weeks of stable dosing ○ Patients took a low dose of study drug (pitolisant 10 mg or modafinil 100 mg or placebo) during the first 7 days, then a medium dose (pitolisant 20 mg or modafinil 200 mg or placebo) for the next 7 days. ○ On day 14, doses were adjusted on the basis of individual clinical efficacy and safety; no specific recommendations were provided to investigators for dose adjustment. ○ Patients could then receive 10, 20, or 40 mg of pitolisant or 100, 200, or 400 mg of modafinil or placebo. ○ On day 21, investigators could decrease the dose in the case of insufficient tolerance only. ○ Patients continued at their assigned stable dose for an additional 5 weeks. ○ On day 49, patients made a control visit, and treatment was stopped at day 56. Patients then received 1 week of placebo in a withdrawal phase. • Within the pitolisant group, the maximum dose of 40 mg was reached by 61% of patients. • Note: Doses are expressed in terms of the salt form: 5, 10, 20, and 40 mg are equivalent to 4.45, 8.9, 17.8, and 35.6 mg (*Wakix FDA clinical review 2019*).
Inclusion Criteria	**Exclusion Criteria**
• Age ≥ 18 years • Diagnosis of narcolepsy with or without cataplexy and self-reported daily EDS for ≥ 3 months Diagnosis was confirmed by PSG, an MSLT performed within the previous 5 years showing a	• Patients could not have psychostimulants for 14 or more days before baseline but could remain on their anticataplectic drugs (sodium oxybate or antidepressants) at stable doses 1 month before and throughout the trial. • Use of TCAs

mean sleep latency ≤ 8 min with ≥ 2 REM periods, and an ESS score ≥ 14	• Another disorder that could be the main cause of EDS in patients without cataplexy (eg, sleep-related breathing disorder with sleep apnea index ≥ 10 per hr or apnea or hypopnea index of ≥ 15 per hr, or a periodic limb movement (PLM) disorder with arousal index of ≥ 10) • History of substance abuse • Serious CV disorder • Hepatic or renal abnormalities • Psychiatric disorder
Primary Endpoint	**Secondary Endpoints**
• The difference in change in ESS scores between the pitolisant and placebo groups after the 8-week treatment period	• MWT • SART (Appendix G) • CGI-C targeting EDS and cataplexy • EQ-5D (defines health using 5 dimensions: Mobility, Self-Care, Usual Activities, Pain/Discomfort, and Anxiety/Depression; overall health is rated on 100-point visual analogue scale [VAS]) (*Herdman et al 2011*) • Patient's global opinion (PGO) of their treatment • Symptoms of cataplexy assessed by patients' sleep diaries（symptoms recorded were sleep attacks, episodes of severe sleepiness, cataplexy attacks, hypnagogic or hypnopompic hallucinations, sleep paralysis, nocturnal awakening, and nocturnal sleep time) • Post-hoc analyses included: ○ Daily cataplexy rate defined as ≥ 1 cataplexy episode during baseline or study treatment period. ○ ESS responder rates defined as patients with a final ESS of ≤ 10

- **Results:**
  - ○ Patients who had at least 1 dose of study drug and provided at least 1 post-baseline value were included in the ITT population.
  - ○ Most of the baseline characteristics were similar among groups. Of the 94 patients included in the ITT analysis, 76 (81%) had a history of cataplexy, 42 (45%) had taken psychostimulants (mostly modafinil or methylphenidate; 13 of 30 patients in the placebo group, 13 of 31 in the pitolisant group, and 11 of 33 in the modafinil group), and 33 (35%) were using anticataplectic drugs and continued them at stable dosage during the trial; of those using anticataplectic drugs, 8 (4 in the placebo group, 2 in the pitolisant group, and 2 in the modafinil group) were on sodium oxybate and 25 used antidepressants. At baseline, the mean daily cataplexy rate was 0.92 in the placebo group, 1.2 in the pitolisant group, and 1.1 in the modafinil group. Fifty-seven (61%) patients were considered still cataplectic during the trial and reported ≥ 1 cataplexy episodes during the trial. The duration of narcolepsy ranged from 10.6 to 14.9 years. The per-protocol (PP) population comprised 79 patients who completed the study: 25 in the placebo group, 26 in the pitolisant group, and 28 in modafinil group.
  - ○ A step-down approach was used for multiple treatment comparisons: superiority of pitolisant over placebo was tested first, then, if shown to be superior, the non-inferiority of pitolisant vs modafinil was tested based on a non-inferiority margin of 2 ESS points.
  - ○ In the ITT analysis, patients in the pitolisant group had a significantly greater improvement from baseline in ESS scores compared with the placebo group (Table 5).
    - ▪ Because the superiority criterion of pitolisant over placebo was met, the non-inferiority of pitolisant to modafinil was tested; the results showed that pitolisant was not non-inferior to modafinil (Table 5).
  - ○ During the trial, ESS decreased at a similar rate in the pitolisant and modafinil groups (data shown graphically). There were no statistically significant between-group differences in analysis of all randomly allocated patients and the PP population (data not shown).
  - ○ MWT values decreased from baseline in the placebo group but improved in the pitolisant group, demonstrating superiority of pitolisant. MWT also improved from baseline in the modafinil group. There was no statistically significant difference between pitolisant and modafinil (Table 5).
  - ○ NO GO error scores in the SART were similar between baseline and end of treatment in the placebo group, whereas they decreased in the pitolisant group, with a statistically significant difference between groups (Table 5).

Changes in the modafinil and pitolisant groups, however, were not statistically different. There were no differences in changes from baseline between either pitolisant and placebo or pitolisant and modafinil in either the SART GO scores or total SART scores (Table 5).

- The proportion of patients who had improvements in EDS assessed by the CGI-C by the end of treatment was largest in the modafinil group and smallest in the placebo group (Table 5). There were little between-group differences in change in severity of cataplexy assessed by the CGI-C.
- EQ-5D values were similar in all 3 groups, whereas PGO on treatment improved only slightly more for pitolisant or modafinil than for placebo (Table 5). The differences were not statistically significant (*Wakix FDA clinical review 2019*).
- The small number of occurrences of other parameters collected in the sleep diaries (hallucinations, sleep attacks, and severe sleepiness) precluded any formal comparison between groups.
- In post-hoc analyses, pitolisant was superior to placebo but not non-inferior to modafinil in terms of improvement in daily cataplexy rate from baseline (Table 5). The percentage reduction in cataplexy rate from baseline to Week 8 was -65% in the pitolisant group, -35% in the modafinil group, and -9% in the placebo group. In other post-hoc analyses, the percentage of responders (with final ESS scores ≤ 10) also differed between the pitolisant and placebo groups and were similar between pitolisant and modafinil (Table 5).

Table 5. Primary and secondary endpoint efficacy results (ITT population)

Endpoint	Placebo		Pitolisant		Modafinil		Treatment difference (MD [95% CI]; p-value)	
	Baseline/final	Δ over trial*	Baseline/final	Δ over trial*	Baseline/final	Δ over trial*	Pitolisant vs placebo (superiority test)	Pitolisant vs modafinil (NI test)
ESS (Δ = final – baseline)	18.9 (2.5)/ 15.6 (4.3)	-3.4 (4.2)	17.8 (2.5/ 12.0 (6.2)	-5.8 (6.2)	18.5 (2.7)/ 11.6 (6.0)	-6.9 (6.2)	-3.0 (-5.6 to -0.4) p = 0.024	0.12 (-2.5 to 2.7); p = 0.250
MWT	8.4 (1.8)/ 7.6 (3.0)	0.88	7.4 (2.3)/ 9.7 (2.8)	1.32	8.8 (2.5)/ 15.1 (2.7)	1.72	1.47 (1.01 to 2.14); p = 0.044	0.77 (0.52 to 1.13); p = 0.173
SART NO GO	8.0 (1.8)/ 8.1 (1.8)	1.0	9.2 (2.0)/ 7.5 (1.9)	0.82	8.5 (2.0)/ 7.1 (1.9)	0.84	0.81 (0.67 to 0.99); p = 0.038	0.97 (0.81 to 1.17); p = 0.765
SART GO	3.5 (0.7)/ 2.7 (0.7)	0.76	3.5 (1.1)/ 2.1 (0.6)	0.6	3.2 (0.7)/ 2.5 (0.6)	0.79	0.79 (0.56 to 1.12); p = 0.176	0.77 (0.54 to 1.20); p = 0.141
SART total	11.5 (2.1)/ 11.4 (2.1)	1.0	12.5 (2.1)/ 10.0 (2.2)	0.8	11.6 (2.1)/ 10.4 (2.2)	0.89	0.80 (0.64 to 1.00); p = 0.053	0.90 (0.71 to 1.14); p = 0.370
CGI-C EDS improved (n/N[%])	--	14/25 (56%)	--	19/26 (73%)	--	24/28 (86%)	--	--
CGI-C cataplexy improved (n/N[%])	--	6/25 (24%)	--	9/26 (35%)	--	8/28 (29%)	--	--
EQ-5D	64 (19.2)/ 70.2 (17.7)	--	65.3 (21.3)/ 73.8 (17.8)	--	58.7 (19.4)/ 72.6 (16.5)	--	--	--
PGO improved (n/N[%])	--	14/25 (56%)	--	24/28 (81%)	--	24/28 (86%)	--	--
ESS responder (post-hoc analysis) (n/N[%])	--	4/30 (13%)	--	14/31 (45%)	--	15/33 (46%)	4.4 (2.1 to 9.2); p < 0.0006	1.0 (0.68 to 1.6); p = 0.908
Cataplexy rate (post-hoc analysis)	0.43 (0.7)/ 0.39 (0.6)	0.92	0.52 (0.6)/ 0.18 (0.4)	0.38	0.4 (0.6)/ 0.26 (0.5)	0.64	0.38 (0.16 to 0.93); p = 0.034	0.54 (0.24 to 1.23); p = 0.138

Abbreviation: NI = non-inferiority
Data are mean (geometric mean) unless otherwise stated
*= change calculated as final-baseline, unless otherwise stated

- The most frequent AEs were headache for the 3 groups, insomnia, abdominal discomfort, and nausea for pitolisant, and abdominal discomfort, nausea, diarrhea, dizziness, anxiety, and irritability for modafinil. There were no clinically relevant between group differences in terms of intensity or resolution of AEs across the 3 groups. Nine AEs reported as severe occurred during the treatment period, of which 6 were deemed treatment-related: 1 with pitolisant (abdominal discomfort) and 5 with modafinil (abdominal pain, abnormal behavior, amphetamine-like withdrawal symptoms, lymphadenopathy, and inner ear disorders).
- No patient receiving placebo or pitolisant experienced a Diagnostic and Statistical Manual of Mental Disorders (DSM)-5-defined withdrawal syndrome during the withdrawal phase compared with 3 patients in the modafinil group.

- **Authors' conclusion:**

- EDS can be improved by pitolisant for at least 2 months, as judged by 2 objective tests in addition to the ESS; pitolisant might also have some anticataplectic activity. Whereas the wake-promoting activity of pitolisant does not differ from that of modafinil, it seems to be better tolerated.

- **Study Appraisal:**
  - **Study sponsorship:**
    - Bioprojet, France (Bioprojet Pharma was acquired by Harmony Biosciences in 2017)
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - Pitolisant was tested for superiority to placebo first; if shown to be superior, the non-inferiority of pitolisant vs modafinil was tested. However, the study did not attempt to directly compare the efficacy of pitolisant with modafinil.
    - A treatment difference of -3.0 points on the ESS corresponds to a decrease from severe to moderate EDS and is clinically meaningful (*Wakix FDA summary review 2019*).
    - The secondary endpoint of MWT, although not pre-specified in the statistical analysis plan, provided evidence suggesting that pitolisant had a meaningful effect on an objective measure of sleepiness (*Wakix FDA clinical review 2019*).
  - **Study limitations:**
    - The sample size was small.
    - The study took place only in Europe.
    - The study duration was short and did not provide an assessment of whether tolerance to pitolisant could develop.
    - The flexible dosing scheme and multiple patient visits may have affected the efficacy outcomes with less responsive patients being more likely to be titrated to the highest dose. Parameters for dose titration were not pre-specified, but were left to the investigator's discretion.
    - The data from this single trial did not provide definitive data about dose/dose response. No direct comparisons between the pitolisant 20 and 40 mg doses were conducted (*Wakix FDA clinical review 2019*).
    - Severely ill patients and those with unstable co-morbidities were excluded from the trial; thus, efficacy cannot be extrapolated in these populations.
    - The primary endpoint only included a subjective measure (ESS) of wakefulness.
      - Currently, the ESS scale has fallen out of favor with the FDA because it requires patients to assess a hypothetical situation with which they may or may not have had experience and is subject to recall bias. However, the FDA accepted the ESS for this application based on precedents from other narcolepsy development programs (*Wakix FDA summary review 2019*).
    - Non-inferiority of pitolisant to modafinil was not demonstrated.
    - Cataplexy rate was not assessed as a primary endpoint nor was it a pre-specified secondary endpoint.
    - Patients who were previously receiving modafinil (33% of the trial population) may have been unblinded to treatment assignment due to its effects.
    - Continuation of anticataplectic medications in a subpopulation of patients precludes extrapolation of the study findings to drug-free patients.
    - The study did not detect a difference in QoL scores or overall patient opinion on treatment in pitolisant-treated patients (*Wakix FDA clinical review 2019*).

Study 9. Wakix dossier 2019; Wakix FDA clinical review 2019. NCT 01638403 (HARMONY 1bis) (unpublished)

Study Objective: Evaluate the safety and efficacy of pitolisant in patients with EDS in narcolepsy	
Study Design, Follow-up	**Treatment Groups** (N = 166)
• 8-week, Phase 3, AC, DB, PC, PG, MC, RCT • The study was conducted in 32 sleep disorder centers in 5 European countries (Argentina, Austria, Finland, France, Germany, Hungary, Italy, Spain).	• Pitolisant (n = 67) • Modafinil (n = 66) • Placebo (n = 33) • Doses were flexibly titrated over 3 weeks to a maximum of 20 mg/day pitolisant or 400 mg/day modafinil; at the end of week 3, doses were locked and patients entered a 5-week stable-dose period. ○ For the first 7 days, all patients took a low dose (pitolisant 5 mg, modafinil 100 mg, or placebo), then a medium dose (pitolisant 10 mg, modafinil 200 mg, or placebo) for the next 7 days. On day 14, doses were adjusted based on clinical efficacy and safety.

	• A total of 76% of patients in the pitolisant group reached a dose of 20 mg. • Following the 8-week treatment period, all patients received placebo during the 1-week withdrawal phase.
Inclusion Criteria	**Exclusion Criteria**
• Age ≥ 18 years • Diagnosis of narcolepsy with or without cataplexy according to ICSD-2 (self-reported EDS occurring almost daily) with an ESS score ≥ 14 • Patients had to be free of drugs or discontinue any psychostimulant medications for ≥ 14 days at the start of the baseline period. Patients with severe cataplexy were allowed to remain on their anticataplectic medication at stable dose except TCAs; the authorized anticataplectic treatment had to be administered for ≥ 1 month prior to the trial and doses had to be stable throughout the trial.	• Any disorder that could be the main cause of EDS in patients without cataplexy (eg, sleep-related breathing disorder with apnea index ≥ 10 events/hour, apnea-hypopnea index ≥ 15 events/hour of sleep, PLM arousal index ≥ 10 events/hour, shift work, chronic sleep deprivation, or circadian sleep wake rhythm disorder) • Current or recent (within 1 year) history of a substance abuse or dependence disorder including alcohol abuse • Serious CV disorders • Severe renal or hepatic abnormalities • Psychiatric or neurological disorders • Prior severe AEs to CNS stimulants
Primary Endpoint	**Secondary Endpoints**
• Difference in mean final ESS score between the pitolisant and placebo groups after 8 weeks of treatment	• ESS responder rate (defined as final ESS score ≤ 10 or ESS score reduction ≥ 3) • MWT • SART • CGI-C • EQ-5D • PGO of treatment and symptoms of cataplexy assessed by patients' sleep diaries

- **Results:**
  - Baseline demographics (age [median 40 years], gender [50% male], ethnicity [90% Caucasian]) were similar in the 3 groups, as were symptoms of narcolepsy and baseline severity assessments (mean ESS score ~18). History of cataplexy was present in 50 (75%) patients in the pitolisant group, 50 (77%) in the modafinil group, and 26 (81%) in the placebo group. The duration of narcolepsy ranged from 10 to 15 years. The proportion of patients receiving concomitant medications was similar in the treatment groups (30.8 to 33.3%). No patients were receiving antidepressants. No patients in the pitolisant or modafinil groups were receiving sodium oxybate vs 6% in the placebo group.
  - Twelve patients prematurely withdrew from the study (pitolisant, n = 7; modafinil, n = 3; placebo, n = 2), primarily due to an AE (pitolisant, n = 4; modafinil, n = 1), patient decision (pitolisant, n = 2, modafinil, n = 1, placebo, n = 1), or lack of efficacy (pitolisant, n = 1; placebo, n = 1). There were 163 patients included in the ITT population (pitolisant, n = 66; modafinil, n = 65; placebo, n = 32). One patient in the modafinil group was withdrawn due to not fulfilling the inclusion criteria.
  - For the primary analysis, superiority of pitolisant to placebo was tested first. If pitolisant was superior to placebo (MD of ESS score statistically significant [$p < 0.05$]), then non-inferiority of pitolisant and modafinil was assessed. Non-inferiority was based on lower bound of the 95% CI of the difference (pre-defined non-inferiority value: -2).
  - The pitolisant group had a significantly greater ESS score improvement from baseline compared with placebo, demonstrating superiority. The mean change from baseline in ESS score (±SD) was -4.5 (4.6) for pitolisant and -3.7 (5.6) for placebo (treatment effect: -2.12; 95% CI, -4.10 to -0.14; $p = 0.036$).
  - The mean change from baseline in ESS score (±SD) was -7.8 (5.8) for modafinil.
    - The non-inferiority of pitolisant compared to modafinil could not be concluded (treatment effect: 2.83; 95% CI, 1.10 to 4.55; $p = 0.002$), most likely due to an imbalance between dosages of both drugs and the short treatment period; the upper dose of pitolisant was limited to 17.8 mg daily (one-half the maximum dose allowed in other trials), while modafinil was titrated up to the recommended dosing of 200 mg or 400 mg daily. Between 66% and 79% of patients were taking modafinil 400 mg daily.
  - The ESS responder rate (final ESS score ≤ 10 or ESS score reduction ≥ 3) was significantly greater in the pitolisant group (64.2%) compared to the placebo group (34.4%) (RR 2.10; $p = 0.002$). Pitolisant treatment resulted in fewer ESS responders compared to modafinil (43 [64.2%] vs 50 [76.9%], respectively), but this difference was not statistically significant (RR: 0.86; $p = 0.052$). Superiority of pitolisant was seen over placebo in MWT values. The values decreased from baseline in the placebo group but improved in the pitolisant group ($p = 0.022$). MWT also improved from baseline in the modafinil group; however, no statistically significant difference between pitolisant and

modafinil was seen (p = 0.198). The NO GO error scores in the SART decreased in the pitolisant group, with a statistically significant treatment difference compared with placebo (p = 0.002); changes in the modafinil and pitolisant groups were not statistically different. No significant difference on the EQ-5D scores or PGO was found between pitolisant and the placebo group. Results of the secondary endpoints are shown in Table 6.

Table 6. Secondary endpoint results (ITT population)

Endpoint	Pitolisant (n = 67)	Modafinil (n = 65)	Placebo (n = 32)
ESS responder (final ESS score ≤ 10 or ESS score reduction ≥ 3), n (%)			
Change	43 (64.2%)	50 (76.9%)	11 (34.4%)
Relative risk	Pitolisant vs placebo: 2.10; p = 0.002 Pitolisant vs modafinil: 0.86; p = 0.052		
MWT			
Baseline	6.65	5.84	7.90
Final	7.79	7.45	6.51
Change (ratio of final/baseline)	1.17	1.28	0.82
Treatment effect, ratio of mean change (95% CI)	Pitolisant vs placebo: 1.57 (1.12 to 2.20); p = 0.022 Pitolisant vs modafinil: 1.05 (0.80 to 1.38); p = 0.198		
SART-NO GO			
Baseline	8.21	8.88	7.53
Final	6.73	6.50	7.76
Change (ratio of final/baseline)	0.82	0.73	1.03
Treatment effect, ratio of mean change (95% CI)	Pitolisant vs placebo: 0.77 (0.65 to 0.91); p = 0.002 Pitolisant vs modafinil: 0.92 (0.79 to 1.07); p = 0.259		
SART-GO			
Baseline	3.23	2.94	3.05
Final	2.71	2.33	2.60
Change (ratio of final/baseline)	0.84	0.79	0.85
Treatment effect, ratio of mean change (95% CI)	Pitolisant vs placebo: 0.99 (0.77 to 1.27); p = 0.910 Pitolisant vs modafinil: 0.94 (0.73 to 1.21); p = 0.641		
SART-total			
Baseline	11.08	11.71	10.54
Final	8.90	8.44	9.94
Change (ratio of final/baseline)	0.82	0.74	0.94
Treatment effect, ratio of mean change (95% CI)	Pitolisant vs placebo: 0.83 (0.6 to 0.99); p = 0.043 Pitolisant vs modafinil: 0.93 (0.77 to 1.11); p = 0.407		
Cataplexy rate (arithmetic mean)			
Baseline	0.84	0.87	1.25
Final	1.69	0.79	1.85
Change, MD (± SD)	0.85 (3.75)	−0.33 (1.02)	0.59 (1.16)
Treatment effect, MD (95% CI)	Pitolisant vs placebo: −1.00 (−2.12 to 0.13); p = 0.077 Pitolisant vs modafinil: 0.05 (−0.55 to 0.65); p = 0.865		
CGI-C EDS improved, n (%)	44 (65.7%)	49 (75.4%)	11 (34.4%)
CGI-C cataplexy improved, n (%)	31 (46.3%)	32 (49.2%)	10 (31.3%)
PGO improved, n (%)	14 (20.9%)	28 (43.1%)	9 (28.1%)

- TEAEs were reported in 34 (50.7%) patients in the pitolisant group, 31 (47.7%) patients in the modafinil group, and 13 (39.4%) patients in the placebo group. The most frequent AEs were headache in all 3 groups; nausea, nasopharyngitis, and dizziness in the pitolisant group; nasopharyngitis in the modafinil group; and dizziness, diarrhea, insomnia, and fatigue in the placebo group. There were no serious AEs reported during the study. There were 19 severe AEs, 8 of which were regarded as treatment-related: 5 with pitolisant (cataplexy, n = 2; somnolence, n = 2; abdominal pain, n = 1) and 3 with modafinil (somnolence, migraine, abdominal pain, each n = 1).
- Patients in the placebo group experienced significant decreases from baseline in systolic and diastolic BP compared to those in the pitolisant or modafinil groups. No patients in the pitolisant group were reported to have withdrawal syndrome, whereas 1 patient in the modafinil group and 1 in the placebo group met the criteria for withdrawal syndrome.
- The mean change from baseline in Beck Depression Inventory (BDI) was similar between groups: pitolisant, -1.7; modafinil, -1.3 and placebo, -1.1 (p = 0.547).
  - The BDI Short Form scores indicated presence of depression (≥ 6) or indicated suicide risk (score of > 0 on BDI item G). The BDI-SF is a 13-question self-report measure of depression severity. Scores on each question can

range from 0 to 3 on a Likert scale; the maximum total score on the questionnaire is 39. Scores of 0 to 4 indicate minimal depression, 5 to 7 indicate mild depression, 8 to 15 indicate moderate depression, and 16 to 39 indicate severe depression. The BDI-SF asks about sadness, guilt, energy level, appetite, and depressive cognitions, and Item G asks specifically about suicidal ideation (*Wakix FDA clinical review 2019*).

- **Conclusion:**
  - Pitolisant, dosed up to 20 mg once daily, was efficacious on EDS compared with placebo. The effects of pitolisant (up to a submaximal dose of 20 mg/day) and modafinil (up to 400 mg/day) on all EDS measures did not differ substantially. In addition, all 3 treatments were considered to be well tolerated. Withdrawal syndrome was seen with modafinil but not with pitolisant.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Bioprojet, France
  - **Study rating:**
    - N/A
  - **Study strengths:**
    - Although not as impressive as the results of the HARMONY I study, a decrease of 2 points on the ESS is still considered clinically meaningful based on published literature. The maximum dose of pitolisant in this study was 20 mg (whereas it was 40 mg in HARMONY I) (*Wakix FDA summary review 2019*).
    - The lack of effect on cataplexy could have been related to the lower maximum dose (20 mg) as compared with the dose in HARMONY 1 and HARMONY CTP (40 mg) (*Wakix FDA clinical review 2019*).
    - The secondary endpoint of MWT, although not pre-specified in the statistical analysis plan, provided evidence suggesting that pitolisant had a meaningful effect on an objective measure of sleepiness (*Wakix FDA clinical review 2019*).
  - **Study limitations:**
    - The sample size was relatively small.
    - The study took place only in Europe.
    - The study duration was short.
    - The trial did not assess persistence of effect after treatment was discontinued (*Wakix FDA clinical review 2019*).
    - The primary endpoint only included a subjective measure (ESS) of wakefulness.
    - Non-inferiority of pitolisant to modafinil was not demonstrated, likely due to the imbalance in pitolisant and modafinil dosing selection.
    - The data from this single trial did not provide definitive data about dose/dose response. No direct comparisons between the pitolisant 20 and 40 mg doses were conducted (*Wakix FDA clinical review 2019*).
    - Cataplexy was not assessed as a primary or a pre-specified secondary endpoint.
    - The study did not detect a difference in QoL scores or overall patient opinion on treatment in pitolisant-treated patients (*Wakix FDA clinical review 2019*).
    - Severely ill patients and those with unstable co-morbidities were excluded from the trial; thus, efficacy cannot be extrapolated in these populations.

Study 10. Dauvilliers et al, *Sleep*. 2019;21;42(11):1-11 (HARMONY 3)

Study Objective: Evaluate the safety and maintenance of efficacy of pitolisant in the long-term in the treatment of EDS in patients with narcolepsy with or without cataplexy	
Study Design, Follow-up	**Treatment Group** (N = 102, 75 with cataplexy)
• 12-month, Phase 3, OL, single-arm, MC, longitudinal, uncontrolled trial • Patients were recruited from 7 centers in France and 1 in Hungary	• Pitolisant • Eligible patients went through a 1-month individual titration period at the initiation of treatment, except for patients coming from the French Compassionate Use Program (CUP) who were already treated by pitolisant and could continue at their established dose at inclusion. • Patients received pitolisant 5 mg once daily for the first 7 days, and 10 mg for the next 7 days. Then, during the third week, the dose could be increased up to 20 mg once daily if safety and tolerability were good and, during the fourth week, doses could be adjusted according to individual benefit/tolerance ratio between 5 to 20 mg once daily. After 1 month, the dose could be increased

	• to 40 mg once daily if the investigator judged that the efficacy of 20 mg was not sufficient. Thereafter, the dose remained stable for a 2-month period. During the follow-up visits scheduled in all patients at 3, 6, 9, and 12 months, an individual dose adjustment could be performed again (5, 10, 20, or 40 mg once daily). • Six patients dropped out before being titrated to 40 mg (4 at 1 month and 2 at 3 months).
Inclusion Criteria	**Exclusion Criteria**
• Age ≥ 18 years • Diagnosis of narcolepsy with or without cataplexy and ESS score ≥ 12 ○ When typical cataplexy was not present, an overnight PSG followed by a positive MSLT within the past 5 years had to show a mean sleep latency ≤ 8 minutes with ≥ 2 sleep-onset rapid eye movement periods. • Patients could be naive to pitolisant ("*de novo*" subgroup) or formerly treated with pitolisant ("exposed" subgroup) during previous single-blind or DB studies or have been switched from the CUP to this study.	• Any other cause of daytime sleepiness, including an untreated sleep apnea syndrome sleepiness • History of substance abuse, severe psychiatric, or neurological disorder • Serious CV disorder • Severe hepatic or renal impairment • Use of TCAs or H_1-receptor antagonists
Primary Endpoint	**Secondary Endpoints**
• Incidence of TEAEs at 12 months	• BDI • ESS score and responder rate • CGI-C • EQ-5D • Symptoms in patient sleep diaries (partial and generalized cataplexy attacks, hypnagogic hallucinations, sleep paralysis, and sleep attacks)

• **Results:**

○ The study group included 73 *de novo* patients (52 with cataplexy) and 13 exposed patients (11 with cataplexy) with a period of at least 3 months without pitolisant between a previous participation in a pitolisant trial (except 1 with only a 1-week washout); all 86 patients had an up-titration at the start of the study. The other 16 exposed patients (12 with cataplexy) were directly switched from the French CUP and were included at their previous established dose without titration. Hence the length of exposure to pitolisant was longer for the subgroup of previously exposed patients (mean 548 days ± 308 days) as some of them were treated since more than 1 year in the CUP before being enrolled in this study, whereas "*de novo*" patients were exposed for a maximum of 1 year (mean 260 ± 143 days). Two thirds (N = 68) of treated patients completed the 12-month treatment period: 60.3% of the *de novo* patients (N = 44, 31 with cataplexy) and 82.8% of the previously exposed patients (N = 24, 20 with cataplexy).

○ At inclusion, the subgroup of exposed patients (N = 29), including those already treated in the CUP, had a lower mean ESS score than *de novo* patients. They also had a better health status evaluated with EQ-5D and less depressive symptoms as assessed by a lower BDI score. Eighteen patients of the whole population (17.6%) had history of depression or depressive syndrome, with 9 (8.8%) suffering from an ongoing depression at baseline.

○ During the 12 months of treatment, 52.9% of patients were receiving co-medications, the most frequent being methylphenidate (22.5%) and modafinil (17.6%). The co-medications taken at inclusion remained unchanged during the study in 37% of patients, increased (or new treatment added) in 50%, decreased in 7.4% or were discontinued in 5.5%.

○ At 3 months of treatment, 67.5% (56/83) of patients were taking 40 mg pitolisant QD. At the end of the 12 months, 76.5% (52/68) of the completers were treated with the 40 mg daily dose and among them, 65.4% were on monotherapy.

○ Overall, 34 (33.3%) patients prematurely discontinued the trial, mainly during the first 3 months (31/34), including 29 *de novo* patients (39.7% of this subgroup) and 5 (17.2%) exposed patients.

Safety

○ During the first 12-month treatment period, a total of 58 patients (56.9%) reported 168 TEAEs. The TEAE frequency tended to decrease with time: 54.8% (92/168) were observed during the first 3 months and 12.5% (21/168) during the last 3 months. Overall, 43.5% of TEAEs were considered related to the study drug: migraine (n = 2), insomnia (1), irregular sleep (1), nausea (1), depression (1), rash (1), vertigo (1), libido decrease (1), premature ejaculation

(1), spontaneous abortion (1). The most common TEAEs were headache (11.8%), insomnia (8.8%), weight gain (7.8%), anxiety (6.9%), depression (4.9%), and nausea (4.9%). Most TEAEs were mild to moderate; only 22 (13.1%) were severe, of which only half were considered related to the study drug. Seven patients (6.9%) experienced a serious (all non-life-threatening) TEAE. All serious TEAEs were unrelated to pitolisant, except 1 miscarriage that was possibly related. The proportion of treatment-related TEAEs was twice as great in the subgroup who took additional anti-narcoleptic agents in comparison to patients treated with pitolisant alone (53.7 vs 29.2%; p = 0.012).

- TEAE frequency was not substantially increased or different in subpopulations including the elderly (≥ 65 years of age), patients with depressive symptoms at inclusion, patients with CV or gastrointestinal disorders, renal impairment, hepatic impairment, patients with allergies, patients receiving a concomitant treatment with a possible CYP450 interaction (eg, paroxetine), or patients treated with SSRIs only.
- Five cases of depression were reported during the 12-month treatment period. Two of them were considered related to the study drug. The proportion of patients with moderate or severe depressive symptoms (BDI score ≥ 8) was relatively stable during the trial (16.6% at baseline vs 19.1% at 12 months).

Efficacy

- Sleepiness
  - Compared to baseline, the mean ESS score (± standard error [SE]) decreased from the first month of treatment (-3.37 ± 0.42; n = 93) and continued to decline after 3 (-4.39 ± 0.51) and 6 months (-4.90 ± 0.54). This change occurred at a similar rate in the *de novo* or previously exposed patients. In the whole patient population who completed the 12-month treatment (n = 68), the mean decrease from baseline in ESS score was -4.6 ± 0.59 at the end of the period. With last observation carried forward (LOCF) method applied to the missing data of the whole population (N = 102; ie, taking into account the patients who left the trial before 12 months), the reduction was -4.0 ± 0.49. The decrease was significant whether patients had previously been exposed to pitolisant or not (p < 0.001 for both) and of similar magnitude in both subgroups (-4.2 and -4.9, respectively).
  - At the end of the 12-month treatment period, two-thirds of patients were ESS responders with minimum decrease of 3 units; the highest responder rate was observed in the *de novo* subgroup (70.5%). More than one-third of patients (25/68) had normalized sleepiness (ESS < 11) at 12 months (27.3% for *de novo* patients and 54.2% for exposed patients); their mean ESS score decreased from 15.3 ± 0.6 at baseline to 6.6 ± 0.6 at 12 months. In the 44 patients (among 68) who completed a diary at 12 months, the mean daily number of sleep attacks decreased by 27% (from 1.36 ± 0.21 to 0.99 ± 0.14; change -0.37; 95% CI, -0.80 to 0.06).
- Cataplexy
  - In the subgroup of patients with completed sleep diaries (n = 44), the number of complete (generalized) cataplexy attacks per day decreased by 76% between baseline (0.33 ± 0.25) and 12 months (0.08 ± 0.05): change -0.25; 95% CI, -0.67; 0.17]), and by 65% (from 0.77 ± 0.37 to 0.27 ± 0.08 per day; change -0.49; 95% CI, -1.09 to 0.10) for partial cataplexy. The mean daily number of all (generalized and partial) cataplexy episodes decreased by 68% between baseline and 12 months (1.09 ± 0.53 to 0.35 ± 0.10 per day; p = 0.055). Considering the subgroup of *de novo* patients on pitolisant monotherapy (N = 15), generalized and partial cataplexy attacks were reduced by 80% (0.71 to 0.14 per day) and 82% (0.93 to 0.17 per day), respectively.
- Other symptoms
  - The mean frequency of hallucinations decreased by 54% between baseline and 12 months (from 0.13 ± 0.06 to 0.06 ± 0.03 per day; change -0.06 [95% CI, -0.14 to 0.01]). The mean frequency of sleep paralysis was reduced by 63% (from 0.16 ± 0.06 to 0.06 ± 0.04, change -0.10 [95% CI, -0.21 to 0.00]; p = 0.023). The EQ-5D score improved in *de novo* (from 62.1 ± 2.4 at baseline to 71.2 ± 2.6 at 12 months; p < 0.001) patients and, to a lesser extent, in previously exposed patients (from 71.8 ± 3.0 at baseline to 74.5 ± 2.9 at 12 months). The CGI-C improved for almost all patients who completed the 12-month treatment period (93.2% and 95.6% of *de novo* and exposed patients, respectively). The total duration of nocturnal sleep remained unchanged.

Five-year extension phase (*Wakix dossier 2019*)

- The 5-year extension phase included a total of 77 French patients who received pitolisant; 16 ATU patients had already been treated through the CUP before entering the 5-year extension phase of the study and 61 patients were considered naïve to treatment. The baseline demographics and characteristics were similar between groups.
- The mean length of pitolisant exposure for naïve patients (n = 31) and ATU patients (n = 16) was 799 days and 1859 days, respectively.
- The most commonly reported TEAEs were headache (19.5%), weight gain (18.2%), insomnia (11.7%), anxiety (11.7%), depression (11.7%), and nausea (11.7%).The incidence of TEAEs decreased over time, with the highest incidence during Month 1 (16.6%) and < 10% after Month 6.
- Throughout the entire study extension treatment period, 26 (33.8%) patients reported TEAEs leading to temporary or permanent discontinuation of study treatment. The number of patients with TEAEs was higher in subgroups with pitolisant prescribed as add-on therapy to pre-existing narcolepsy treatments, particularly when added to psychostimulants, and the number of patients with TEAEs was lowest in the pitolisant monotherapy subgroup.

- At enrollment, 15 (19.5%) patients had a history of depression or depressive syndrome. Six new cases of depression occurred during the study, but only 3 were considered to be treatment-related. The overall BDI evaluation did not show any increase in depressive symptom severity.
- EDS, measured by ESS score, decreased during the first 12 months of the study, and the reduction was maintained throughout the 5-year extension. The mean ESS score (±SD) of the overall 5-year extension study population decreased from baseline by -3.47 (4.20) at month 1 and continued to decrease at months 3 and 6, with a mean score reduction (±SD) from baseline of -4.03 (4.70) and -4.22 (4.54), respectively. The reduction in ESS score (±SD) was maintained up to the end of the 12-month period and continued during the extended follow-up period, with −4.41 (5.38) after 2 years of treatment (n = 45), -4.45 (6.16) after 3 years of treatment (n = 38), -4.76 (5.73) after 4 years of treatment (n = 34), and -6.07 (7.19) after 5 years of treatment (n = 14).
- Sleep diaries were collected from all compliant patients who had completed their diaries as requested; this included 34 patients at baseline; 32 patients at month 3; 25 patients at months 12 and 18; 17 patients at year 2; 14 patients at year 3; and 2 patients at year 5. The mean daily number of total and partial cataplexy episodes, as well as hallucinations, improved during the 5-year extension phase; at the end of the first 12-month treatment period, total cataplexy episodes, partial cataplexy episodes, and hallucinations decreased by 87.2%, 60%, and 50%, respectively, and this reduction was maintained throughout the extended follow-up period for patients who continued. Other sleep parameters remained relatively stable or improved slightly.

- **Authors' Conclusion:**
  - Pitolisant was well tolerated and improved most major narcolepsy symptoms when given alone or in combination with other anti-narcoleptic agents for a long period. It remains to be definitively determined whether it constitutes a useful first-line therapy for patients with narcolepsy.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Bioprojet, France
  - **Study limitations:**
    - There was potential for selection bias, both in the patients who entered the study from the CUP who had been on pitolisant previously, as well as from those who dropped out (nearly one-third), during the 1-year treatment period. Patients already exposed to pitolisant were more likely to be compliant, being *a priori* good responders with good tolerance.
    - Since the study did not include a placebo or a control group, it did not provide conclusive data about the duration of pitolisant's treatment effect (*Wakix FDA clinical review 2019*).

Study 11. Szakacs et al, *Lancet Neurol.* 2017;16:200-207 (HARMONY CTP)

Study Objective: Evaluate the safety and efficacy of pitolisant in patients with narcolepsy with cataplexy	
Study Design, Follow-up	**Treatment Groups** (N = 105)
• 7-week, Phase 3, DB, MC, PC, RCT • The study was conducted in 16 sleep disorder centers in 9 countries (Bulgaria, Czech Republic, Hungary, Macedonia, Poland, Russia, Serbia, Turkey, and Ukraine)	• Pitolisant (n = 54) • Placebo (n = 51) • Treatment included 3 weeks of flexible dosing (5 mg, 10 mg, or 20 mg once daily) followed by 4 weeks of stable dosing (5, 10, 20, or 40 mg once daily). ○ During the flexible dosing period, patients took 5 mg of pitolisant or placebo once a day for the first 7 days, then 10 mg of pitolisant or placebo once a day for the next 7 days. ○ During the week 2 visit, the dose was assessed and could remain at 10 mg, be increased to 20 mg, or decreased to 5 mg by the investigators on the basis of individual clinical efficacy and safety; no specific recommendations were provided to investigators for dose adjustment. ○ At visit 3, investigators adjusted doses again to establish the final dose (5, 10, 20, or 40 mg) for the 4-week stable dosing period. ○ At the end of the stable dosing period, all patients entered a 1-week withdrawal period during which time they received placebo.

	• In the stable dosing phase, 64.8% of patients (35/54) in the pitolisant group received the maximum dose of 40 mg.
Inclusion Criteria	**Exclusion Criteria**
• Age ≥ 18 years • Diagnosis of narcolepsy with cataplexy according to the ICSD-2 criteria • Three or more cataplexies per week and an ESS score ≥ 12 • Ongoing anticataplectic treatment with sodium oxybate or antidepressants was allowed if doses were stable for ≥ 1 month before randomization and throughout the trial.	• Any other disorder with EDS (eg, sleep-related breathing disorder with sleep apnea index ≥ 10 per hr or apnea or hypopnea index of ≥ 15 per hr, or a PLM disorder with arousal index of ≥ 10) • History of substance abuse • Serious CV disorder • History of substance abuse • Serious CV disorder • Severe hepatic or renal abnormalities • Psychiatric disorder • Concomitant use of psychostimulants or sedative medications
Primary Endpoint	**Secondary Endpoints**
• Change in the average number of cataplexy attacks per week between the 2 weeks of baseline and the 4 weeks of stable dosing (WCR).	• WCR changes in patients maintained or not in their anticataplectic treatment • Mean change in ESS score • Proportion of patients with final ESS score ≤ 10 (a validated cutoff) • Proportion of patients with abnormally high cataplexy rate (WCR > 15, a non-validated cutoff corresponding to the median of the sample) • MWT • CGI-C • PGO on efficacy • EQ-5D • Number of days with hallucinations

- **Results:**
  - Baseline demographics and narcolepsy characteristics of the 2 groups were similar. The number of cataplexy episodes per week was 11 in the pitolisant group and 9.2 in the placebo group at pre-screening. The mean ESS score was 17.3 in the pitolisant group and 17.1 in the placebo group. In the previous 3 months, 41% of patients in the pitolisant group had received ≥ 1 anticataplectic medication vs 80% in the placebo group. The percentages of patients continuing anticataplectic medications during the trial were 7% in the pitolisant group and 16% in the placebo group.
  - Five patients from the pitolisant group and 9 patients from the placebo group (13.3%) withdrew from the study; 8 patients did not comply (7 in the placebo group and 1 in the pitolisant group), 4 showed lack of efficacy (2 in each group) and 2 patients from the pitolisant group were unable to continue study visits.
  - The reduction of cataplexy by 75% in the pitolisant group ($WCR_{f/b}$ = 0.25) was significantly higher than in the placebo group (38%; $WCR_{f/b}$ = 0.62; rR = 0.51, 95% CI, 0.44 to 0.60, p < 0.0001, Table 7).
    - In post-hoc analyses, this effect remained significant (all p < 0.0001) for each subgroup of patients receiving 10 mg (n = 7), 20 mg (n = 9), or 40 mg (n = 35) as their stable dose.
    - By comparing WCR in both groups at each week, a significant benefit of pitolisant was observed from week 5, improving until the last week (rR = 0.37, 95% CI, 0.07 to 0.69). In a pre-specified analysis, the effect of pitolisant was unchanged, irrespective of whether patients used concomitant anticataplectic treatment pre-inclusion. The geometric mean of the ratio $WCR_{f/b}$ for patients who were receiving concomitant anticataplectic treatment (rR 0.49, 95% CI, 0.31 to 0.82, n = 12) or did not receive this medication (rR 0.51, 0.11 to 2.28, n = 93) were not significantly different ($p_{interaction}$ = 0.455).
  - Superiority of pitolisant was observed for most of the secondary endpoints (Table 7).

Table 7. Primary and secondary endpoint efficacy results (ITT population)

Endpoint	Pitolisant (n = 54)			Placebo (n = 51)			Treatment effect	
	Baseline	Final	Change	Baseline	Final	Change	Effect (95% CI)	p-value
WCR*	9.15	2.27	0.25	7.31	4.52	0.62	0.51 (0.43 to 0.60)	< 0.0001
WCR > 15 (n/N[%])	15/54 (28%)	4/54 (7%)	--	9/51 (18%)	12/51 (24%)	--	0.05 (0.01 to 0.40)	0.005

ESS score	17.4	12.0	-5.4	17.3	15.4	-1.9	-3.48 (-5.03 to -1.92)	0.0001
ESS responders	--	20/51 (39%)	--	--	9/50 (18%)	--	3.28 (1.08 to 9.92)	0.035
MWT (min)‡	3.54	6.91	1.95	4.08	4.32	1.06	1.85 (1.24 to 2.74)	0.003
Improvement in GCI cataplexy (n/N[%])	--	36/54 (67%)	--	--	17/51 (33%)	--	4.00 (1.54 to 10.38)	0.004
Improvement in CGI EDS	--	37/54 (69%)	--	--	12/51 (24%)	--	7.07 (2.55 to 19.59)	0.0002
Improvement in PGO (score < 3, n/N[%])	--	43/54 (79%)	--	--	22/51 (43%)	--	--	--
EQ-5D sum score†	6.4	6.0	-0.4	6.5	6.4	-0.1	-0.33 (-0.70 to 0.03)	0.075
No. of hallucinations per week*	0.41	0.16	0.39	0.57	0.32	0.57	0.50 (0.31 to 0.83)	0.007

*WRC was the primary outcome; the geometric mean was calculated and 0 values replaced with 0.1; change calculated as the final value/baseline measurement; treatment effect analyzed as a ratio rate derived from Poisson regression after adjusting to baseline.
†Arithmetic mean; change calculated as final measurement-baseline measurement; treatment effect derived from a linear model adjusting for baseline.
‡Geometric means; change calculated as the final value/baseline measurement; treatment effect derived from linear model of log-transformed values and adjusted for baseline. Other statistical analyses used logistical regression to identify odds ratio.

- In the pitolisant group, 19 (35%) patients reported AEs vs 16 (31%) in the placebo group (p = 0.528).
- The most frequent AEs were headache for both treatment groups; irritability, anxiety, and nausea for the pitolisant group; and somnolence for the placebo group.
- Double the number of AEs were considered treatment-related with pitolisant compared with placebo (28% [15 of 54 in the pitolisant group vs 12% [6 of 51] in the placebo group; p = 0.048), but all were of mild-to-moderate intensity, except for 1 case of severe nausea that resolved without sequelae after pitolisant discontinuation.
- BDI score decreased significantly between baseline and end of treatment in the pitolisant group compared with placebo (-1.8 vs -0.8; p = 0.02). Duration of nocturnal awakenings also did not differ significantly between groups. No withdrawal syndrome was reported with pitolisant, although 1 was observed with placebo.

- **Authors' conclusion:**
  - Pitolisant was well tolerated and could be useful to improve not only cataplexy but also EDS and hallucinations in patients with narcolepsy. If confirmed in long-term studies, pitolisant might constitute a useful first-line therapy for cataplexy in patients with narcolepsy, for whom there are currently few therapeutic options.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Bioprojet, France
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - The study enrolled patients with severe cataplexy.
    - A pre-specified analysis examined the effect of concomitant anticataplectic medication in reducing the WCR.
  - **Study limitations:**
    - The sample size was small.
    - The study duration was short and did not provide an assessment of whether tolerance to pitolisant could develop.
    - The flexible dosing scheme and multiple patient visits may have affected the efficacy outcomes with less responsive patients being more likely to be titrated to the highest dose.
      - A pooled analysis of dose-response conducted by the applicant in the ITT populations in HARMONY 1, HARMONY 1bis, and HARMONY CTP found that pitolisant appeared to have a linear dose-response effect (*Wakix FDA clinical review 2019*).

Study 12. Lehert & Falissard, *Sleep.* 2018;41(12):1-13

Study Objective: Evaluate the safety and efficacy of medical treatments for narcolepsy using a network meta-analysis	
Study Design, Follow-up	**Treatment Groups**
• Network meta-analysis (N = 14 RCTs) • All of the studies were of short duration, from 2 to 12 weeks	• Modafinil (n = 10 RCTs) • Pitolisant (n = 3 RCTs) • Sodium oxybate (n = 4 RCTs) • Ten, 4, and 3 studies compared modafinil, sodium oxybate, and pitolisant with placebo, respectively. Eight

	studies compared only 1 treatment with placebo, whereas the 6 other studies compared multiple treatments, respectively (3 or 4 treatments). For the 4 studies of sodium oxybate, the 2 studied dosages 6 and 9 g/d were compared in 3 studies, whereas the low dose (6 g/d) was only compared with placebo in 1 study. Three studies assessed pitolisant: 2 for the 40 mg and 1 study for the 20 mg dose (unpublished, results available).
Inclusion Criteria	**Exclusion Criteria**
• RCTs enrolling adults with narcolepsy with or without cataplexy • RCTs comparing the identified treatment with placebo, as well as comparisons with other treatments • RCTs that provided data on at least 1 of the following selected outcomes for both efficacy and safety: the ESS, the MWT, number of cataplexy attacks during the treatment exposure, and safety reporting of AEs during the treatment exposure	• Non-randomized trials • Retrospective studies • Trials not assessing ≥ 1 efficacy or safety endpoint
Primary Endpoints	**Secondary Endpoints**
• EDS measured by ESS and MWT • WCR ○ To provide a unique primary endpoint and to reduce type 1 multiplicity in the analysis, the ESS and MWT were combined into the EDS mean Z score, to define the narcolepsy score (NS) as the mean of EDS and WCR Z scores (ESS and WCR used minus their values such that larger values indicated patient improvement).	• Overall safety score (OSS), defined as the TEAE incidence rate during the exposure period • Benefit/risk (B/R) ratio ○ The unitless BR ratio was defined as the residual value of the linear fit between NS and OSS, or the simple ratio NS/OSS.

- **Results:**
  - Network meta-analysis compared the efficacy and safety of multiple treatments, multi-arm studies, and multi-criteria treatment decisions, based on a random-effects model that assumed heterogeneity between studies, with corrections for multi-arm studies.
  - Armodafinil studies were pooled with modafinil studies; however, a comparison between the 2 groups was conducted to confirm the relevance of this method.
  - Treatment ranking by P scores measured the extent of certainty that any one treatment was better than another treatment, averaged over all competing treatments, equivalently with the surface under the cumulative ranking curve (SUCRA) defined as the rank of treatment within the range of treatments.
  - Most of the included trials were acceptable for internal validity, external validity, and statistical methodology.
    - In 1 study, the 2 study arms were selected after 16 weeks of OL modafinil, potentially favoring the modafinil group over the placebo group.
    - In *Black & Houghton 2006* (see study 14), all patients were treated with modafinil at the established dose until randomization, and the abrupt withdrawal from modafinil potentially created an artificially worsened placebo group when treatment arms were changed. In this study, the highest doses of sodium oxybate were given without previous titration, unlike as in other trials, and this may have penalized the drug safety profile.
  - For ESS (12 studies), only 3 interventions reached a significant MD when compared with placebo: pitolisant 40 mg (-3.05; 95% CI, -5.24% to -0.85%; p < 0.001), sodium oxybate 9 g (-2.94; 95% CI, -5.04% to -0.85%; p < 0.001), and modafinil (-2.37; 95% CI, -3.41% to -1.32%; p < 0.001), without statistical differences between them. Homogeneity across studies (p = 0.16), and slight between-design inconsistency (p = 0.02) were found.
  - The MWT (12 studies) measured the mean changes in time (minutes) from baseline. There was significant heterogeneity across studies (p < 0.001), and no between-day design inconsistency (p = 0.601) was found. Significant relative benefits when compared with placebo were found for pitolisant 40 mg (4.88 min; 95% CI, 0.57% to 9.20%; p = 0.009) and modafinil (1.85 min; 95% CI, 0.16% to 3.55%; p < 0.001).
  - Cataplexy was reported in 8 studies, and the difference between treatments was calculated by standardized mean difference (SMD) converted by linear calibration into decrease of weekly rate of cataplexies (DWCR). Significant reductions were observed for pitolisant 40 mg (SMD = -0.52; 95% CI, -0.90% to -0.13%; p < 0.001) (DWCR = -5.9) and sodium oxybate 9 g (SMD = -0.41; 95% CI, -0.79% to 0.032%; p = 0.023) (DWCR = -5.2). No marked or significant heterogeneity across studies (p = 0.51) or between-design inconsistency (p = 0.09) were found.

- **Authors' conclusion:**
  - Modafinil (200 to 400 mg/d), sodium oxybate 9 g/d, and pitolisant up to 40 mg/d had similar efficacy in reducing EDS. Only sodium oxybate 9 g/d and pitolisant up to 40 mg/d demonstrated a comparable beneficial effect on cataplexy. Overall, pitolisant at a maximal dose of 40 mg/d was shown to have a slightly better safety profile and the highest BR ratio.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Bioprojet Pharma
    - The authors are consultants for Bioprojet Pharma.
  - **Study rating:**
    - N/A
  - **Study strengths:**
    - The network meta-analysis compared 6 different interventions involving placebo, modafinil, pitolisant, and sodium oxybate.
  - **Study limitations:**
    - Sodium oxybate and pitolisant were both compared with placebo and modafinil, but not between each other. Methodological issues exist for comparing sodium oxybate in the context of RCTs; unlike the other drug treatments, sodium oxybate induces deep sleep and has multiple contraindications, which would make blinding difficult or impossible.

Sodium oxybate/oxybate salts

Narcolepsy with cataplexy

Study 13. Alshaikh et al, *J Clin Sleep Med.* 2012;8(4):451-458

Study Objective: Evaluate the efficacy and safety of sodium oxybate in narcolepsy-cataplexy patients	
Study Design, Follow-up	**Treatment Groups** (N = 741)
• Systematic review and meta-analysis (N = 6 RCTs and 5 companion reports) • The duration of the RCTs ranged from 4 to 8 weeks, except for 1 study that lasted for 12 weeks. Sodium oxybate at a dose range between 4.5 to 9 g/night was the dose evaluated in most of the studies.	• Sodium oxybate • Placebo • Modafinil • One study assessed the combination of sodium oxybate and modafinil vs sodium oxybate and modafinil alone.
Inclusion Criteria	**Exclusion Criteria**
• RCTs evaluating sodium oxybate in patients with narcolepsy and cataplexy (published or unpublished)	• Non-RCTs
Primary Endpoint	**Secondary Endpoints**
• Elimination of EDS according to subjective or objective indicators.	• QoL using the SF-36 scale • CGI-C

- **Results:**
  - All of the included studies excluded patients with other sleep disorders. The percentage of females ranged from 50 to 65%. One study that assessed the effect of sodium oxybate on EDS did not include cataplexy as an enrollment criterion.
  - None of the included RCTs were assessed as having adequate sequence generation or allocation concealment. All of the studies adequately blinded participants and addressed incomplete outcome data. Five of the 6 studies were free from selective outcome reporting. All of the studies scored unclear on other biases, as they involved private-industry funding. Four of the included studies were sponsored by the manufacturer.
  - Sodium oxybate (usually 9 g/night) was superior to placebo for reducing mean weekly cataplexy attacks (n = 2 RCTs, MD -8.46, 95% CI, -15.27 to -1.64), heterogeneity: I^2 = 0%, test for overall effect: Z = 2.43 [p = 0.01]); increasing the MWT (n = 2 RCTs, MD 5.18, 95% CI, 2.59 to 7.78, I^2 = 0%, Z = 3.93 [p < 0.0001]); and reducing sleep attacks (n = 2 RCTs, MD -9.65, 95% CI, -17.72 to -1.59), I^2 = 13%, Z = 2.35 [p = 0.02]).
  - Data from 3 RCTs indicated an increase in CGI-C scores (RR 2.42, 95% CI, 1.77 to 3.32, I^2 = 0%, Z = 5.53 [p < 0.00001).
  - Sodium oxybate did not significantly increase REM sleep vs placebo (n = 2 RCTs, MD -0.49, 95% CI, -3.90 to 2.92, I^2 = 0%, Z = 0.28 [p = 0.78]).

- Patients receiving sodium oxybate (9 g per night) experienced more AEs vs placebo, including nausea (n = 3 RCTs, RR 7.74, 95% CI, 3.15 to 19.05, I^2 = 0%, Z = 4.45 [p < 0.00001]), vomiting (n = 2 RCTs, RR 2.87, 95% CI, 0.84 to 9.80, I^2 = 10%, Z = 1.69 [p = 0.09]), dizziness (n = 3 RCTs, RR 11.83, 95% CI, 1.56 to 89.43, I^2 = 0%, Z = 2.39 [p = 0.02]) and enuresis (n = 2 RCTs, RR 4.32, 95% CI, 1.14 to 16.41, I^2 = 52%, Z = 2.15 [p = 0.03]).

- **Authors' conclusion:**
  - Patients with narcolepsy on sodium oxybate showed a significant reduction in cataplexy based on diaries and significant improvement in EDS based on objective (MWT) and validated subjective (ESS) assessment methods. Sodium oxybate was well tolerated in patients with narcolepsy, and most AEs were mild to moderate in severity.
- **Study Appraisal:**
  - **Study sponsorship:**
    - This was not an industry supported study. The authors declared no financial conflicts of interest.
  - **Study rating:**
    - N/A
  - **Study strengths:**
    - All meta-analyses had minimal statistical heterogeneity (p > 0.1).
  - **Study limitations:**
    - The included trials had small sample sizes.
    - Due to the short study durations, long-term efficacy and safety could not be assessed.
    - Publication bias could not be assessed because there were too few trials in the meta-analysis.
    - In the pivotal trials of sodium oxybate, the majority of patients (80 to 85%) were receiving concomitant CNS stimulants. The high percentages of concomitant stimulant use make it impossible to assess the efficacy and safety of sodium oxybate independent of stimulant use (*Xyrem prescribing information 2018*).

Narcolepsy

Study 14. Black & Houghton, *Sleep.* 2006; 29(7):939-946

Study Objective: Evaluate the efficacy of sodium oxybate, modafinil, and the combination of the two for EDS in narcolepsy patients previously taking modafinil	
Study Design, Follow-up	**Treatment Groups** (N = 222 [ITT population])
• DB, PC, PG, MC, RCT • Visit 1: patients were evaluated for trial inclusion (1 to 2 weeks) • Visit 2: occurred 1 to 2 weeks later when overnight PSG was performed followed by the MWT; patients remained on established doses of modafinil and any other concomitant medications (14 ± 4 days) • Visit 3: included baseline PSG and MWT recordings before beginning the treatment phase according to prior DB randomization (28 ± 4 days) • Visit 4: efficacy and safety assessments were performed including PSG and MWT measurements (28 ± 4 days) • Visit 5: final efficacy and safety assessments were performed	• Placebo (n = 55) (Group 1) • Sodium oxybate (n = 50) (Group 2) • Modafinil (n = 63) (Group 3) • Modafinil + sodium oxybate (n = 54) (Group 4) • Patients randomly assigned to Groups 3 and 4 continued to receive their customary doses of modafinil in blinded fashion. Patients randomly assigned to Groups 2 and 4 received sodium oxybate at a dose of 6 g nightly, administered in 2 equally divided doses at bedtime and again 2.5 to 4 hours later for the initial 4-week period of the study. Patients in Groups 1 and 3 received an equivalent volume of placebo sodium-oxybate solution. • Patients returned to the clinic for Visit 4, 4 weeks after efficacy and safety assessments were performed. Patients continued taking modafinil or placebo modafinil at their prescribed dose; however, the dose of sodium oxybate was increased to 9 g nightly in 2 equally divided doses. Patients assigned to placebo sodium oxybate increased their dose of placebo solution by an equivalent volume. All patients continued taking their assigned drug regimen for an additional 4 weeks before returning to the clinic for final efficacy and safety assessments at Visit 5.
Inclusion Criteria	**Exclusion Criteria**
• Age ≥ 18 years • Diagnosis of narcolepsy according to the ICSD criteria • Taking a stimulant medication for the treatment of EDS for ≥ 3 months and taking stable doses of modafinil 200 to 600 mg/day for ≥ 1 month immediately prior to	• Use of sodium oxybate or any investigational therapy within the 30-day period prior to enrollment • Sleep apnea disorder • Any other cause of EDS such as periodic limb movements of sleep (PMLS)

the trial or were taking stable doses of modafinil for ≥ 6 weeks prior to trial entry	• Concurrent use of hypnotics, tranquilizers, sedating antihistamines, benzodiazepines, anticonvulsants, or clonidine • Current or recent history of a substance abuse disorder • Serum creatinine > 2.0 g/dL • Alanine aminotransferase or aspartate aminotransferase > twice the upper limit of normal (ULN) • Bilirubin > 1.5 times the ULN • History of clinically significant dysrhythmia or history of myocardial infarction within the prior 6 months • History of seizure disorder, clinically significant head trauma, or past invasive intracranial surgery • Occupation requiring variable shift work or routine night shifts
Primary Endpoint	**Secondary Endpoints**
• MWT	• ESS • CGI-S • CGI-C

- **Results:**
  - A total of 278 patients were enrolled in the study, of which 231 were randomly assigned to 1 of the 4 treatment groups. The ITT population consisted of 222 patients who received at least 1 dose of DB medication.
  - Compared with the placebo group, the other 3 treatment groups maintained significantly longer mean average daytime sleep latencies after 8 weeks of treatment, as determined by the MWT (Table 8). From the beginning of the baseline period to the end of the DB treatment period, the placebo group demonstrated a significant within-group decrease in sleep latency of 2.72 min as a consequence of withdrawal from modafinil. In contrast, neither the sodium oxybate nor the modafinil groups demonstrated within-group changes in sleep latency at the end of the trial (ie, there were no significant differences between the 2 groups). The mean average sleep latency for both groups was significantly longer than that of placebo-treated patients at the end of the trial. The sodium oxybate/modafinil group demonstrated a mean average sleep latency increase of 2.68 min, compared with baseline, representing the incremental improvement in EDS produced by the addition of sodium oxybate over the response produced by modafinil alone.
  - The sodium oxybate and sodium oxybate/modafinil groups demonstrated significant reductions in ESS scores, compared with placebo at the end of the trial (for each, $p < 0.001$) whereas the scores for the modafinil-treated patients did not significantly change and were not different from the placebo group (Table 9). In the sodium-oxybate group, following the discontinuation of modafinil, the ESS scores decreased from a median average of 15 to 12 by the end of the 8-week DB treatment phase and, similarly, from 15 to 11 in the sodium oxybate/modafinil group (for each, $p < 0.001$ compared with baseline). In contrast, the placebo group demonstrated no change in ESS scores during the same period.

Table 8. Results for MWT[a]

MWT	Placebo (n = 55)	Sodium oxybate (n = 50)	Modafinil (n = 63)	Sodium oxybate + modafinil (n = 54)
Visit 3	9.74 ± 6.57 (n = 55)	11.29 ± 6.40 (n = 49)	10.48 ± 6.03 (n = 63)	10.43 ± 6.77 (n = 54)
Visit 5	6.87 ± 6.14 (n = 53)	11.97 ± 7.21 (n = 48)	9.86 ± 5.89 (n = 62)	13.15 ± 6.91 (n = 53)
Change[b]	-2.72 ± 4.54	0.58 ± 5.68	-0.53 ± 4.36	2.68 ± 5.07
p-value[c]	--	< 0.001	0.006	< 0.001

[a]Data are presented as the mean average of 4 trials per patient ± SD, in minutes, LOCF. Visit 3 followed 2 weeks of SB modafinil at previously established doses. Visit 5 followed 4 weeks of placebo or sodium oxybate 9 g nightly and/or modafinil at previously established doses.
[b]Change from Visit 3 to Visit 5
[c]Compared with placebo

Table 9. Results for ESS[a]

ESS	Placebo (n = 55)	Sodium oxybate (n = 50)	Modafinil (n = 63)	Sodium oxybate + modafinil (n = 54)
Visit 3	16.0 (n = 54)	15.0 (n = 48)	14.0 (n = 61)	15.0 (n = 54)

Visit 4	17.0 (n = 53)	13.0 (n = 48)	15.0 (n = 62)	11.5 (n = 50)
p-value	--	< 0.001	0.071	< 0.001
Visit 5	16.0 (n = 53)	12.0 (n = 49)	15.0 (n = 63)	11.0 (n = 53)
p-value	--	< 0.001	0.767	< 0.001

[a]Data are presented as median average, in minutes, LOCF. Visit 3 followed 2 weeks of SB modafinil at previously established doses. Visit 4 followed 4 weeks of placebo or sodium oxybate 6 g nightly and/or modafinil at previously established doses. Visit 5 followed 4 weeks of placebo or sodium oxybate 9 g nightly and/or modafinil at previously established doses. Significance was as compared with placebo.

- The patients in the sodium oxybate and sodium oxybate/modafinil groups had significantly fewer weekly sleep attacks at the end of the trial, as compared with modafinil and placebo groups. In the sodium oxybate group, sleep attacks decreased from a mean of 10.05 at baseline to 7.10 after 8 weeks ($p < 0.001$) and the sodium oxybate-modafinil group demonstrated a decrease from 11.82 to 5.55 ($p < 0.001$). There was no significant difference between the modafinil- and placebo-treated groups.
- The baseline CGI-S assessment indicated that the patients enrolled in the study were considered to be markedly ill despite treatment with modafinil. At the end of the trial, the sodium oxybate group and sodium oxybate-modafinil group each demonstrated overall improvements in their clinical condition, compared with the placebo group ($p = 0.002$ and $p = 0.023$, respectively). In contrast, the placebo and modafinil groups were judged as demonstrating no significant change in disease severity.
- Based on the CGI-C, a significantly higher percentage of patients in the sodium oxybate and sodium oxybate-modafinil groups had a successful treatment response. Compared with the placebo group, 48.0% ($p = 0.002$) of the sodium oxybate group and 46.3% ($p = 0.023$) of the sodium oxybate-modafinil group were judged to be much improved or very much improved, compared with 21.8% of the placebo group and 19% of the modafinil group.
- Compared with the incidence of AEs reported in the sodium oxybate (60%), modafinil (54.0%), or placebo groups (69.6%), a somewhat greater number of AEs were reported in the sodium oxybate-modafinil group (78.9%). Among all patients, the most common TEAEs included headache (15.2%), nausea (11.7%), dizziness (9.1%), nasopharyngitis (6.1%), vomiting (6.1%), and somnolence (5.6%).
- Nausea and vomiting occurred with the highest frequency in the sodium oxybate groups (1.8% for placebo; 21.1% for sodium oxybate; 3.2% for modafinil; 21.1% for sodium oxybate-modafinil), whereas the incidence of dizziness was highest in the sodium oxybate-modafinil group (21.1% vs 5.4% for placebo, 7.3% for sodium oxybate, and 3.2% for modafinil). Statistically significant differences between treatment groups were also noted with respect to tremor (0% for placebo, 5.5% for sodium oxybate, 0% for modafinil, 14.0% for sodium-oxybate-modafinil) and paresthesia (0% for placebo, 7.3% for sodium oxybate, 0% for modafinil, 3.5% for sodium oxybate-placebo), and upper respiratory tract infections, occurring primarily in the placebo group.
- The number of patients who withdrew from the study early was highest in the sodium oxybate-modafinil group (n = 6) compared with sodium oxybate (n = 4), modafinil (n = 2), or placebo groups (n = 1).

- **Authors' conclusion:**
  - Sodium oxybate and modafinil are both effective for treating EDS in narcolepsy, producing additive effects when used together. Sodium oxybate is beneficial as both monotherapy and as adjunctive therapy for the treatment of EDS in narcolepsy.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Orphan Medical Inc.
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - The study used both objective and patient-reported validated outcome measures.
  - **Study limitations:**
    - The trial duration was short.
    - The study population was already being treated with modafinil for 3 months or longer prior to trial entry. Thus, AEs due to modafinil may have been underrepresented in these patients because only patients who were able to tolerate the medication entered the trial.
    - It is unknown whether the patients were partial responders or non-responders to modafinil prior to trial entry.

Study 15. U.S. Xyrem Multicenter Study Group. *Sleep Med*. 2004;5(2):119-123.

- Fifty-five narcoleptic patients with cataplexy who had received continuous treatment with sodium oxybate for a minimum of 6 months (range, 7 to 44 months, mean 21 months) in a long-term, OL sodium oxybate safety trial were enrolled in a DB treatment withdrawal study. Patients were previously stabilized on sodium oxybate using individualized doses providing optimum clinical effect, ranging from 3 to 9 g nightly. A 2-week SB sodium oxybate treatment phase established a baseline for the weekly occurrence of cataplexy. This was followed by a 2-week DB

phase in which patients were randomized to receive unchanged drug therapy (n = 26) or placebo (n = 29). The primary endpoint was the change in the number of weekly cataplexy attacks from the baseline to the DB treatment phase.

- In the sodium oxybate group, there was no median change in the number of cataplexy attacks between the 2-week SB baseline phase and the 2-week DB phase. In contrast, cataplexy attacks increased by a median of 21.0 in the placebo patients during the same 2-week period ($p < 0.001$); median change from baseline was 39.0 for the placebo group and 16.5 for the sodium oxybate group. The mean (SD; range) frequency of weekly cataplexy attacks over the 2-week baseline period increased from 15.8 (39.9; 0 to 197) to 46.4 (73.8; 0 to 250) at the end of the 2-week DB phase for patients receiving placebo; in patients receiving sodium oxybate, the number of cataplexy episodes was 9.9 (21.4; 0 to 93) and 12.8 (33.5; 0 to 158) at the same time points. There was no evidence of rebound cataplexy in patients who were randomized to placebo following long-term use of sodium oxybate.
- During the SB phase of the study, AEs were reported in 17 (31%) patients. During the DB phase, AEs were reported by 12 (22%) patients, including 3 patients in the sodium oxybate group, and 9 in the placebo group. No AE led to discontinuation and none were serious.
- The authors concluded that this controlled trial provides evidence supporting the long-term efficacy of sodium oxybate for the treatment of cataplexy. In contrast with antidepressant drug therapy, there is no evidence of rebound cataplexy upon abrupt discontinuation of treatment.

Pediatric Study

Study 16. Plazzi et al, *Lancet Child Adolesc Health*. 2018;2(7):483-49

Study Objective: Evaluate the safety and efficacy of sodium oxybate oral solution treatment in children and adolescents with narcolepsy with cataplexy

Study Design, Follow-up	**Treatment Groups** (N = 106)
• DB, PC, RW, MC, OL study • The study took place in 30 sites in 5 countries (U.S., Finland, France, Italy, and the Netherlands) • Randomization was balanced for age group (7 to 11 years and 12 to 17 years), previous sodium oxybate treatment (taking sodium oxybate at study entry and sodium oxybate -naive), and location (U.S. and European Union).	• Sodium oxybate in 2 divided doses (bedtime and 2.5 to 4 hours later) (n = 31) • Placebo (n = 32) • Sodium oxybate-naïve patients underwent a dose titration period of 3 to 10 weeks in which they were titrated to an effective and tolerable (optimal) dose that achieved a state of cataplexy stability. • Once an optimal dose was achieved, patients entered a stable dose period of 2 weeks. • After the screening period, patients who were taking sodium oxybate at study entry did not undergo titration and entered the stable-dose period. • During the stable dose period, sodium oxybate-naive patients remained on their established optimal dose for 2 weeks. • Patients taking sodium oxybate at entry remained on their previously established dose for 3 weeks. Efficacy assessments were based on the last 2 weeks of the stable dose period. Patients treated with stimulants or wake-promoting agents remained on the same dose during the stable-dose and DB treatment periods. • During the DB treatment period, participants randomly assigned to sodium oxybate remained on the dose and regimen used in the stable-dose period and patients randomly assigned to placebo were administered placebo at a volume and regimen equivalent to the dose and regimen of sodium oxybate taken during the stable-dose period.
Inclusion Criteria	**Exclusion Criteria**
• Patients 7 to 16 years of age at screening with primary diagnosis of narcolepsy with cataplexy as defined by either the ICSD-2 or ICSD-3 criteria, either being treated with sodium oxybate or sodium oxybate-naïve at study entry	• Previous use and discontinuation of sodium oxybate because of no efficacy or poor tolerability • Narcolepsy secondary to another medical condition • History of seizure disorder or head trauma associated with loss of consciousness

• History of ≥ 14 cataplexy attacks in a typical 2-week period, and clinically significant EDS before any narcolepsy treatment was required • If currently treated with sodium oxybate, receiving unchanged doses (twice nightly dosing ≤ 9 g/night) of sodium oxybate for at ≥ 2 months prior to screening with reported clinical improvement of cataplexy	• Clinically significant parasomnia disorder • Evidence of sleep-disordered breathing or hypoventilation • Past or current major thought disorder • Current clinically significant depression or suicidal risk • Concomitant use of sedative hypnotic or anxiolytic medications • Medications with anticataplectic effects (eg, SSRIs, or TCAs) were discontinued ≥ 1 month before study screening. Participants entering the study taking stimulant or wake-promoting medications were allowed to continue these medications.
Primary Endpoint	**Secondary Endpoints**
• Change in weekly number of cataplexy attacks from the last 2 weeks of the stable-dose period (baseline) to the 2 weeks of the DB treatment period	• Change in the Epworth Sleepiness Scale for Children and Adolescents (ESS-CHAD) score from the end of the stable dose period to the end of the DB treatment period • CGI-C for cataplexy severity • CGI-C for narcolepsy overall • Change in QoL using SF-10 Health Survey for Children

- **Results:**
  - Two sodium oxybate-naive patients did not take the study drug and discontinued from the titration period. Sixty-seven (91%) of the sodium oxybate-naive patients were titrated to an optimal dose and entered the stable-dose period. Sixty-three patients (the efficacy population) entered the DB treatment period before the protocol amendment that discontinued the placebo group.
  - Baseline demographics were similar between the sodium oxybate and placebo groups. The median age was 12 years (range, 7 to 17); 73 (69%) of the 106 enrolled patients were White and 63 (59%) were male. At study entry, 74 (70%) patients were sodium oxybate-naive, and 32 (30%) patients were treated with sodium oxybate for a median of 12 months (range, 2.0 to 52.0).
  - At study entry, the median ESS-CHAD score was 14 (moderate daytime sleepiness; range, 5 to 22), and 43 (41%) participants had ESS-CHAD scores ≥ 16. Previous stimulant or wake-promoting medications were used by 53 (50%) patients at study entry. Stimulant or wake-promoting medications were taken by 55 (56%) patients during the stable-dose period, and by 53 (56%) patients during the DB treatment period (56% of patients in the placebo group and 55% of patients in the sodium oxybate group). The median dose of sodium oxybate taken during the stable-dose period was 7.0 g per night (range, 3.0 to 9.0 g per night).
  - Results of the preplanned interim analysis of the primary endpoint (n =35) showed that efficacy was achieved (p = 0.0002). Results of the full efficacy analysis (n = 63) showed that patients who were withdrawn from sodium oxybate treatment and randomly assigned to placebo during the DB treatment period had a significant increase in the number of weekly cataplexy attacks compared with patients who were randomly assigned to continue treatment with sodium oxybate. The median change from baseline in the weekly number of cataplexy attacks was 12.7 (Q1, Q3 = 3.4, 19.8) for patients randomly assigned to placebo and 0.3 (-1.0, 2.5) for patients randomly assigned to continue treatment with sodium oxybate (p < 0.0001). Additionally, patients receiving placebo had an increased number of cataplexy attacks at week 1, which further increased at week 2.
  - Results of the CGI-C showed that patients who received placebo were rated as having worse cataplexy severity than were patients continuing sodium oxybate treatment. The mean change in CGI-C score for cataplexy severity for the placebo group was -1.5 (SD 1.2) vs -0.4 (1.1) for the sodium oxybate group (p = 0.0006).
  - The median change from baseline in ESS-CHAD scores was greater in the placebo group (3.0 [Q1, Q3 = 1.0, 5.0]), indicating increased sleepiness, compared with the sodium oxybate group (0.0 [-1.0, 2.0]; p = 0.0004).
  - Results of the CGI-C for narcolepsy overall showed a worsening of narcolepsy in patients randomly assigned to placebo (p = 0.0008), with 59% as much worse or very much worse, compared with 10% in patients continuing sodium oxybate treatment (p < 0.0001).
  - No significant difference was observed on the SF-10.
  - Generally, results of subgroup analyses by age group and by sodium oxybate status at study entry were similar to the primary analyses for weekly cataplexy attacks and CGI-C for cataplexy severity. These results showed an increased change from baseline (last 2 weeks of the stable-dose period) to the DB period in weekly cataplexy attacks and worsening CGI-C scores for cataplexy severity for patients randomly assigned to placebo; however, ESS-CHAD scores were not significantly different between treatments in the younger age group or in patients taking sodium oxybate at study entry.

- Commonly reported (> 5%) AEs were enuresis (15/72 [21%] sodium oxybate-naive patients vs 4/32 [13%] taking sodium oxybate at study entry), nausea (16 [22%] vs 2 [6%]), vomiting (15 [21%] vs 2 [6%]), headache (13 [18%] vs 4 [13%]), decreased weight (11 [15%] vs 1 [3%]), decreased appetite (8 [11%] vs none), nasopharyngitis (7 [10%] vs none), and dizziness (5 [7%] vs 1 [3%]). Two serious AEs (1 event of severe acute psychosis and 1 event of moderate suicidal ideation) were reported, and both were considered to be related to the study drug. There were no reported deaths.

- **Authors' Conclusion:**
  - The study results supported the clinical efficacy of sodium oxybate for the treatment of both EDS and cataplexy in narcolepsy in children. The safety profile of sodium oxybate was consistent with that observed in adult patients.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Jazz Pharmaceuticals
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - Concomitant stimulant or wake-promoting agents were allowed, which could be considered more representative of real-world clinical practice, in which they are commonly prescribed in addition to sodium oxybate.
  - **Study limitations:**
    - Potential participants who had tried and failed on sodium oxybate previously were excluded.
    - Patients with mild cataplexy (< 14 attacks per typical 2-week period) were excluded.
    - There were fewer patients in the younger age group (7 to 11 years) than in the older age group.
    - Efficacy during the DB, RW period might have been underestimated because of the short duration (2 weeks). Findings from subgroup analyses of ESS-CHAD in patients aged 7 to 11 years and taking sodium oxybate at entry were not significant, and there were fewer patients in these groups.
    - Subgroup analyses were limited by the small number of patients completing the DB period.
    - The study was limited to patients with narcolepsy with cataplexy.

Study 17. Xywav dossier 2020 (unpublished)

Study Objective: Evaluate the safety and efficacy of oxybate salts in adults with narcolepsy with cataplexy	
Study Design, Follow-up	**Treatment Groups**
• DB, PC, RW, MC study • The study was conducted in the U.S. and Europe. • The main study consisted of a ≤ 30-day screening period (N = 255); a 12-week, OL, optimized treatment and titration period to transition to oxybate salts from previous medications for the treatment of cataplexy (N = 201); a 2-week stable-dose period (N = 149); a 2-week DB, RW period (N = 136); and a 2-week safety follow-up. • During the screening period, patients were categorized in the following groups based on their medication use for the treatment of cataplexy at study entry: ○ Sodium oxybate only group ○ Sodium oxybate + other anticataplectics group ○ Other anticataplectics group ○ Cataplexy treatment-naïve group	• DB, RW period: ○ Oxybate salts (n = 69) ○ Placebo (n = 67) • Enrolled patients entered the 12-week, OL optimization and titration period and initiated oxybate salts treatment, with dose titration as needed to optimize efficacy and tolerability. ○ Patients treated with sodium oxybate monotherapy or in combination with other anticataplectics at screening were initiated on a g-to-g equivalent dose of oxybate salts and remained on that same dose for the first 2 weeks. ○ Patients naïve to sodium oxybate initiated oxybate salts at 4.5 g/night and titrated to an optimal dose, with a maximal increase of up to 1.5 g/night/week. ○ Patients taking other anticataplectics at study entry, with or without sodium oxybate, continued taking their other anticataplectics for the first 2 weeks, followed by a taper of other anticataplectics until discontinuation by week 10. • The OL optimized treatment and titration period was followed by a 2-week stable-dose period, during which efficacy assessments were performed while each patient received a stable dose of oxybate salts. At the end of the stable-dose period, patients were randomized 1:1 to receive placebo or to continue oxybate salts treatment.

	Randomization was stratified by treatment for cataplexy at study entry.
Inclusion Criteria	**Exclusion Criteria**
• Patients 18 to 70 years of age with a primary diagnosis of narcolepsy with cataplexy meeting ICSD-3 criteria or DSM-5 criteria and currently untreated or treated with or without anticataplectics • History of ≥ 14 cataplexy attacks in a typical 2-week period prior to receiving any narcolepsy treatment • If patients were receiving medication(s) for the treatment of cataplexy at study entry, the medication regimen was to be stable for ≥ 2 months prior to study entry; if patients were taking wake-promoting agents or stimulants at study entry, they had to be taking stable doses for ≥ 2 months prior to study entry and were to remain on the same dose and regimen throughout the duration of the study. • For patients receiving sodium oxybate at study entry, documentation of prior improvement in cataplexy and EDS with sodium oxybate treatment was required.	• Narcolepsy secondary to another medical condition (eg, CNS injury or lesion) • Restless legs syndrome requiring treatment other than iron supplementation • Uncontrolled hyperthyroidism • History of seizures (other than early childhood febrile seizures) • Head trauma associated with loss of consciousness within the past 5 years • Clinically significant parasomnias • Untreated or inadequately treated sleep-disordered breathing, and succinic semialdehyde dehydrogenase deficiency • Major depression • History of psychotic disorders • Treatment with an antidepressant for cataplexy that could not be withdrawn if considered unsafe due to prior history of depression • Positive urine screen for benzodiazepines or drugs of abuse, a positive alcohol test, a history of substance abuse, or unwillingness to refrain from consuming alcohol during the study • Abnormal ECG
Primary Endpoint	**Secondary Endpoints**
• Change in weekly number of cataplexy attacks from the time during the 2 weeks of the stable-dose period to the time during the 2 weeks of the DB, RW period (determined from patient diaries)	• Change in ESS score from the end of the stable-dose period to the end of the DB, RW period • PGI-C • CGI-C • EQ-5D

- **Results:**
  - Efficacy was assessed in 134 patients who received randomized treatment, and safety was assessed in all enrolled patients (N = 201).
  - Enrolled patients were taking a variety of medications for the treatment of cataplexy at study entry: sodium oxybate only (n = 52), sodium oxybate + other anticataplectics (n = 23), other anticataplectics (n = 36), and cataplexy treatment-naïve (n = 90). During the stable-dose period, 38.8% of patients overall were on stimulants/wake-promoting agents, and the use of stimulants/wake-promoting agents was generally similar across participants by treatment at study entry (sodium oxybate only, 44.2%; sodium oxybate + other anticataplectic, 30.4%; non-sodium oxybate anticataplectic, 47.2%; cataplexy treatment-naïve, 36.7%).
  - Of the 201 patients enrolled, 155 completed the OL optimized treatment and titration period and 149 entered the stable-dose period. Discontinuations prior to the stable-dose period (n = 52) were attributed to AEs (n = 19), protocol deviations (n = 11), withdrawal by participant (n = 6), or other reasons (n = 2).
  - Overall, in the safety population, the mean age was 37.2 years and 60.7% of the participants were female. Prior to any narcolepsy treatment, all participants experienced cataplexy (100%) and EDS (100%), and the majority of participants reported experiencing other symptoms of the narcolepsy pentad: disrupted nighttime sleep (63.2%), sleep-related hallucinations (59.7%), and sleep paralysis (59.7%).
  - Prior to randomization, the median (Q1, Q3) number of weekly cataplexy attacks did not differ in patients randomized to placebo (1.1 [0.0, 7.9]) vs those who continued oxybate salts treatment (1.0 [0.0, 4.4]). During the DB, RW period, patients randomized to continue oxybate salts experienced no change (median [IQR], mean [SD]) in the weekly frequency of cataplexy attacks, while patients randomized to discontinue oxybate salts and take placebo experienced an increase in cataplexy attacks (median [Q1, Q3]: 0.0 [-0.5, 1.7], mean [SD]: 0.12 [5.77] vs 2.4 [0.0,11.6], mean [SD]: 11.46 [24.75], respectively; treatment difference, $p < 0.0001$) (Table 10).
  - Prior to randomization, the median (Q1, Q3) ESS score did not differ in oxybate salts-treated patients who were randomized to placebo vs those who continued oxybate salts treatment (13.0 [9.0, 17.0] vs 14.0 [10.0, 19.0],

respectively). At the end of the DB, RW period, the change in median (Q1, Q3) ESS score from baseline for patients randomized to placebo vs oxybate salts was 2.0 (0.0, 5.0) vs 0.0 (-1.0, 1.0), respectively (Table 10).

Table 10. Primary and key secondary endpoints (efficacy population)

Endpoint	Placebo (N = 65)	Oxybate salts (N = 69)
Change in weekly number of cataplexy attacks from SDP to DB, RW period (primary efficacy endpoint)		
Mean (SD)	11.46 (24.751)	0.12 (5.772)
Median	2.35	0.00
Q1, Q3	0.0, 11.61	-0.49, 1.75
Location shift*	-3.308	
95% CI†; p-value‡	-6.044 to -1.500; p < 0.0001	
Change in ESS score from SDP to DB, RW period (key secondary efficacy endpoint)		
Mean (SD)	3.0 (4.68)	0.0 (2.90)
Median	2.0	0.00
Q1, Q3	0.0, 5.0	-1.0, 1.0
Location shift*	0.0, 5.0	
95% CI‡; p-value‡	-4.00 to -1.00; p < 0.0001	

Abbreviation: SDP = stable dose period
*Location shift between 2 treatment groups and asymptotic 95% CI from Hodges-Lehmann estimate (sodium oxybate-placebo).
† From a rank-based ANCOVA model including the change in average weekly number of cataplexy attacks from the 2 weeks of the SDP to the 2 weeks of the DB, RW period as response variable, prior treatment group and study treatment group as fixed effects, and average weekly number of cataplexy attacks during the 2 weeks of the SDP as covariate.
‡ From a rank-based ANCOVA model including the change in ESS total score from the end of the SDP to the end of the DB, RW period as response variable, prior treatment group and study treatment group as fixed effects, and ESS total score at the end of the SDP as covariate.

- The distribution of PGI-C ratings for narcolepsy overall demonstrated that more patients randomized to placebo experienced worsening of symptoms compared with those randomized to continue oxybate salts treatment (nominal p < 0.0001), with a greater percentage of patients randomized to placebo rating their narcolepsy overall as “much worse” or “very much worse” compared with patients randomized to continue oxybate salts treatment (44.6 vs 4.3%; post hoc nominal p < 0.0001). Similarly, the distribution of CGI-C ratings for narcolepsy overall demonstrated worsening in more participants randomized to placebo (nominal p < 0.0001), with a greater percentage of patients randomized to placebo rated by clinicians as “much worse” or “very much worse” compared with the percentage of patients randomized to continue oxybate salts treatment (60.0 vs 5.9%, respectively; post hoc nominal p < 0.0001).
- At least 1 TEAE was reported by 76.1% of patients while receiving oxybate salts. The most common TEAEs were headache (20.4%), nausea (12.9%), and dizziness (10.4%). Worsening cataplexy was reported as a TEAE by 20 (10.0%) patients; 17 of the 20 patients experienced worsening cataplexy during the tapering of other anticataplectics, and 3 were cataplexy treatment-naïve at study entry. The most common TEAEs leading to discontinuation of oxybate salts during the main study were worsening cataplexy (7/201; 3.5%), nausea (3/201; 1.5%), and anxiety, depressed mood, depression, headache, and irritability (each 2/201; 1.0%). Serious AEs were reported by 6 patients during the main study, including 3 during the OL, optimized treatment and titration period, 1 during the stable-dose period, and 2 reported the day after 2 weeks of placebo treatment in the DB, RW period.

- **Conclusion:**
  - The efficacy of oxybate salts for the treatment of cataplexy and EDS in adults with narcolepsy was demonstrated in this PC, DB, RW study. The overall safety profile of oxybate salts was consistent with sodium oxybate.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Jazz Pharmaceuticals
  - **Study rating:**
    - N/A (unpublished)
  - **Study strengths:**
    - Concomitant stimulant or wake-promoting agents were allowed, which could be considered more representative of real-world clinical practice, in which they are commonly prescribed in addition to sodium oxybate.
  - **Study limitations:**
    - The sample size was small.
    - Patients with mild cataplexy (< 14 attacks per 2-week period) were excluded.
    - Efficacy during the DB, RW period might have been underestimated because of the short duration (2 weeks).
    - The study was limited to patients with narcolepsy with cataplexy.

Solriamfetol

Narcolepsy/OSA

Study 18. Thorpy et al, *Ann Neurol.* 2019;85:359-370 (TONES 2)

Study Objective: Evaluate the safety and efficacy of solriamfetol for the treatment of narcolepsy	
Study Design, Follow-up	**Treatment Groups** (N = 239)
• 12-week, Phase 3, DB, PC, PG, MC, RCT • The study was performed at 50 study centers in the U.S. and Canada and 9 centers in Finland, France, Germany, and Italy. • Randomization was stratified on the basis of presence or absence of cataplexy.	• Solriamfetol 75 mg once daily (n = 59) • Solriamfetol 150 mg once daily (n = 55) • Solriamfetol 300 mg once daily (n = 59) • Placebo (n = 58) • Patients who were randomized to the 150 and 300 mg doses received 75 and 150 mg, respectively, on days 1 through 3 of the first week, with the full dose commencing on day 4.
Inclusion Criteria	**Exclusion Criteria**
• Adults, aged 18 to 75 years • Diagnosis of narcolepsy type 1 or type 2 according to the ICSD-3 or DSM-5 criteria ○ The DSM-5 criteria include patients who have been diagnosed with narcolepsy based on the presence of cataplexy and were applied in this study to include such patients who had been diagnosed with narcolepsy on the basis of cataplexy under ICSD-2 but who no longer meet diagnostic criteria based on a history of cataplexy under ICSD-3. • Baseline mean sleep latency < 25 minutes on the first 4 trials of a 5-trial, 40-minute MWT, baseline ESS score ≥ 10, usual nightly total sleep time ≥ 6 hours (by self-report), and a body mass index (BMI) between 18 and 45 kg/m^2	• Presence of any clinically relevant untreated medical, psychiatric, or behavioral disorder or medical condition other than narcolepsy that is associated with EDS (ie, night-time or variable shift work) • History or presence of any acutely unstable medical or psychiatric disorder, or surgical history that could affect the safety of the patient • Use of medications that could affect the evaluation of EDS or cataplexy unless prior use had stopped for > 5 half-lives of the drug and the patient had returned to baseline level of daytime sleepiness ≥ 7 days prior to the baseline visit.
Co-Primary Endpoints	**Secondary Endpoints**
• Change from baseline to week 12 in: ○ MWT mean sleep latency on the first 4 trials of the MWT ○ ESS score (see Appendix D)	• Percentage of patients who reported improvement on the PGI-C at week 12 • Change in sleep latency on each of the 5 MWT trials • Change in mean sleep latency from baseline to week 4 • Change in ESS from baseline to weeks 1, 4, and 8 • Percentage of patients who reported improvement on the PGI-C at weeks 1, 4, and 8 • Percentage of patients who reported improved at weeks 1, 4, 8, and 12 on the CGI-C • Change in the mean and median weekly number of cataplexy attacks was an exploratory endpoint among the subgroup of patients who reported the presence of cataplexy (assessed by patient diary).

- **Results:**
  - Demographic and clinical characteristics were similar across treatment groups.
  - Overall, the majority of patients (64.4%) were rated by clinicians as moderately or markedly ill and were characterized by impaired wakefulness and EDS, as indicated by baseline MWT mean sleep latency of 7.5 (SD = 5.7) min and ESS scores of 17.2 (SD = 3.2), respectively. Most patients (90.7%) had prior use of psychostimulants; prior use of sodium oxybate and antidepressants was reported for 25.8% and 34.7% of patients, respectively. Cataplexy was present in 50.8% of patients overall, with similar percentages of patients with cataplexy in each of the treatment groups.
  - The mITT population consisted of 231 patients; 1 patient randomized to placebo and 4 patients randomized to solriamfetol 150 mg did not have baseline or at least 1 post-baseline efficacy assessment of MWT and ESS.

- The discontinuation rate was highest in the solriamfetol 300 mg group (27.1%, with lack of efficacy [10.2%, n = 6] and AEs [8.5%, n = 5] as the most common reasons for discontinuation), followed by the solriamfetol 75 mg (16.9%), placebo (10.3%), and solriamfetol 150 mg (7.3%) groups.
- Solriamfetol 300 mg and 150 mg doses met the co-primary endpoints of MWT and ESS as well as the percentage of patients who reported improvement on the PGI-C (all $p < 0.0001$, Table 10). Significance was not achieved for the 75 mg dose on the MWT.
- The LS mean change from baseline at week 12 on the MWT showed an increase in mean sleep latency of 12.3 (SE = 1.4) and 9.8 (SE = 1.3) min with solriamfetol 300 mg and 150 mg, respectively, which was significant compared with 2.1 (SE = 1.3) min for placebo (both $p < 0.0001$).
- For the ESS score, the LS mean change from baseline at week 12 was -6.4 (SE = 0.7), -5.4 (SE = 0.7), and -3.8 (SE = 0.7) for the 300 mg, 150 mg, and 75 mg doses of solriamfetol, respectively, and -1.6 (SE = 0.7) with placebo.
- Improvements were observed at all solriamfetol doses at week 1 on the MWT. The magnitude of effect remained stable over the 12 weeks of the study, and the 300 and 150 mg doses differed from placebo at weeks 1 and 4. Similar patterns were observed on the ESS, with reductions in ESS score relative to placebo observed as early as week 1 with the 300 and 150 mg doses, and effects remained stable over the study duration.
- Evaluation of mean sleep latency on each of the 5 individual MWT trials at week 12 showed efficacy beginning at 1 hour after dosing through 9 hours after dosing for solriamfetol 150 and 300 mg.
- Solriamfetol increased the percentage of patients who reported improvement in their overall condition on the PGI-C. At week 12, these increases were dose-dependent and were significant for the solriamfetol 300 mg (84.7%) and 150 mg (78.2%) doses vs placebo (39.7%; both $p < 0.0001$); the 75 mg dose was nominally significant (67.8%) compared with placebo ($p = 0.0023$, but the comparison was below the hierarchical break). Effects were observed at all doses by week 1 and remained stable over the course of the study.
- On the CGI-C, all doses of solriamfetol resulted in higher percentages of patients who improved as early as week 1, with effects at 300 mg and 150 mg maintained over the study. The results of each of the sensitivity analyses across each of the endpoints (MWT, ESS, and PGI-C) yielded similar results and conclusions as the primary analyses of those endpoints.
- There was no clear effect of solriamfetol on the number of cataplexy attacks per week among patients with cataplexy, although this study was not powered or designed to rigorously evaluate the effects of solriamfetol on cataplexy (data not shown).

Table 11. Hierarchical testing of co-primary and key secondary efficacy endpoints in the mITT population

Endpoint	Solriamfetol treatment difference from placebo, LS mean (95% CI)		
	300 mg	150 mg	75 mg
MWT, min	10.14 (6.39 to 13.90) p < 0.0001	7.65 (3.99 to 11.31) p < 0.0001	2.62 (-1.04 to 6.28) p = 0.1595
ESS	-4.7 (-6.6 to -2.9) p < 0.0001	-3.8 (-5.6 to -2.0) p < 0.0001	-2.2 (-4.0 to -0.3) p = 0.0211
PGI-C, %	45.1 (29.51 to 60.67) p < 0.0001	38.5 (21.86 to 55.19) p < 0.0001	28.1 (10.80 to 45.48) p = 0.0023*

A fixed hierarchical testing procedure was used to correct for multiplicity, starting with the highest solriamfetol dose for the co-primary endpoints and followed by the key secondary endpoint; testing proceeded in that order for each subsequent lower dose, with statistical significance claimed only for those outcomes above the break in the hierarchy.
*Nominal p-value, because it is below the hierarchical break.

- Discontinuations due to AEs occurred in 8.5%, 5.1%, and 1.7% of the solriamfetol 300 mg, 150 mg, and placebo groups, respectively. Other than cataplexy, which resulted in discontinuation in 2 patients, none of the AEs leading to study discontinuation occurred in > 1 patient.
- AEs with an incidence ≥ 5% in the combined solriamfetol dose groups included headache (21.5%), nausea (10.7%), decreased appetite (10.7%), nasopharyngitis (9.0%), dry mouth (7.3%), and anxiety (5.1%).
- No patient had a TEAE of hypertension, and 2 patients had a TEAE of BP increase (1 in the 150 mg group and 1 in the 300 mg group).

- **Authors' conclusion:**
  - Once-daily oral dosing of solriamfetol 150 and 300 mg resulted in major improvements in wakefulness and reductions in EDS associated with narcolepsy together with patient- and clinician-reported global improvements. These results demonstrate that solriamfetol represents an important potential future therapeutic option for the treatment of impaired wakefulness and EDS in individuals with narcolepsy.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Jazz Pharmaceuticals

- **Study rating:**
  - Fair
- **Study strengths:**
  - The study used both objective and patient-reported validated outcome measures.
- **Study limitations:**
  - The trial had a short duration of 12 weeks.
  - Conclusions with regard to the effect of solriamfetol on cataplexy are limited by this study not being designed to rigorously evaluate effects on cataplexy. The frequency of type 2 narcolepsy (ie, without cataplexy) in approximately 50% of the study population was also somewhat higher than reported in the narcolepsy literature.
  - The study did not include modafinil or armodafinil as a comparator.

Study 19. Schweitzer et al, *Am J Respir Crit Care Med.* 2019; 199(11):1421-1431 (TONES 3)

Study Objective: Evaluate the safety and efficacy of solriamfetol for the treatment of EDS in patients with OSA with current or prior sleep apnea treatment	
Study Design, Follow-up	**Treatment Groups** (N = 476)
• 12-week, Phase 3, DB, PC, PG, MC, RCT • The study was conducted at 59 sites in the U.S., Canada, France, Germany, and the Netherlands • Randomization was stratified by adherence or non-adherence to primary OSA therapy, with adherence defined as use ≥ 4 hours per night on ≥ 70% of nights for devices from which hourly usage data could be extracted; use ≥ 70% of nights by daily diary for devices for which usage data could not be retrieved; or history of a surgical intervention for OSA. • Non-adherence was defined as usage of a primary therapy at a level that did not meet the above criteria, ie, non-use of a primary OSA therapy, or a history of a surgical intervention for OSA that was deemed by the investigator to no longer be effective at treating the obstruction.	• Solriamfetol 37.5 mg once daily (n = 58) • Solriamfetol 75 mg once daily (n = 62) • Solriamfetol 150 mg once daily (n = 117) • Solriamfetol 300 mg once daily (n = 118) • Placebo (n = 119) • Patients randomized to the 150 and 300 mg doses received 75 and 150 mg, respectively, on days 1 to 3, with the full dose commencing on day 4.
Inclusion Criteria	**Exclusion Criteria**
• Adults, aged 18 to 75 years • Diagnosis of OSA according to ICSD-3 criteria • Current or prior use of a primary OSA therapy including PAP, mandibular advancement device, or surgical intervention ○ Patients without current primary OSA therapy use or a history of a surgical intervention to treat the underlying obstruction were required to have tried to use a primary OSA therapy for at least 1 month with at least 1 documented adjustment to the therapy (eg, change in PAP pressure, change in mask, change in modality). • Baseline ESS score ≥ 10 • Baseline sleep latency < 30 min for the average of the first 4 of a 5-trial, 40-min MWT • Usual nightly sleep time of ≥ 6 hours	• Usual bedtime later than 1:00 AM • Occupation requiring nighttime shift work or variable shift work • Use of any OTC or prescription medications that could affect the evaluation of EDS; current or past (within the past 2 years) diagnosis of a moderate or severe substance use disorder according to DSM-5 criteria • Nicotine dependence that has an effect on sleep (eg, a patient who routinely awakens at night to smoke) • Any other clinically relevant medical, behavioral, or psychiatric disorder other than OSA that is associated with excessive sleepiness
Co-Primary Endpoints	**Secondary Endpoints**

• Change from baseline to week 12 in:
  ○ Mean sleep latency derived from the first 4 trials of a 5-trial, 40-min MWT
  ○ ESS score
	• Change from baseline to week 12 in sleep latency for each of the 5 individual MWT trials was tested as a pre-specified secondary endpoint for doses that were positive on both co-primary efficacy endpoints
	• Percentage of patients reporting any improvement in PGI-C at week 12

	• Percentage of patients reporting any improvement in CGI-C at week 12

- **Results:**
  - Of the 474 patients who were randomized and took at least 1 dose of study drug, representing the safety population, 404 (85.2%) completed the study.
  - Baseline demographic and clinical characteristics of the safety population were similar across treatments.
  - A history of a surgical intervention for OSA was reported in 17.6% and 13.5% of patients on placebo and solriamfetol, respectively. At baseline, primary OSA therapy was used by 69.7% of patients on placebo and 73.5% of patients on solriamfetol; of these patients, 91.6% on placebo and 92.7% on solriamfetol were using PAP, 2.4% on placebo and 1.1% on solriamfetol were using another type of device as a primary OSA therapy, and in 6.0% of patients on placebo and 6.1% on solriamfetol, the type of primary OSA therapy was not specified.
  - In the 5 treatment groups, from 69.0 to 72.9% of patients were adherent to primary OSA therapy at baseline and from 27.1 to 31.6% were non-adherent.
  - AEs were the most common reason overall for withdrawal (5.1%).
  - Those who successfully completed at least 1 follow-up visit (mITT population) comprised 459 participants.
  - Mean treatment compliance with study drug was 97.2%.
  - The co-primary endpoints of change from baseline at week 12 in MWT and ESS were met at all solriamfetol doses, and the key secondary endpoint of PGI-C was met at all doses except the 37.5 mg dose (Table 12).
    - Solriamfetol resulted in dose-dependent increases in MWT sleep latency at week 1, with LS mean changes from baseline that ranged from 4.2 to 13.3 min for the 37.5 and 300 mg doses, respectively, and that were > placebo (0.4 min). These increases were maintained across the 12 weeks of the study, and all solriamfetol doses resulted in improvements relative to placebo at weeks 4 and 12 ($p < 0.05$). At week 12, effect sizes (Cohen's d) were 0.4, 0.9, 1.1 and 1.2 for solriamfetol 37.5, 75, 150, and 300 mg, respectively. The LS mean change from baseline exceeded 10 min at all time points with solriamfetol 150 mg (11.0 to 12.2 min) and 300 mg (13.0 to 13.8 min), whereas placebo ranged from 0.2 to 1.2 min.
  - Solriamfetol treatment resulted in dose-dependent decreases in ESS score relative to placebo at week 1 that remained stable over the 12-week study duration. These decreases were greater than placebo for all doses at all time points except for the 37.5 mg dose at week 8. Effect sizes at week 12 were 0.4, 0.4, 1.0, and 1.0 for solriamfetol 37.5, 75, 150, and 300 mg, respectively. ESS scores decreased by > 7 points with the 150 and 300 mg doses at week 12 ($p < 0.0001$), whereas placebo decreased by 3.3 points.
  - Change from baseline in sleep latency on each of the 5 individual MWT trials at week 12 was significantly greater with solriamfetol 75, 150, and 300 mg doses compared with placebo, demonstrating efficacy of solriamfetol from 1 to 9 hours after dosing. The 37.5 mg dose showed a significant difference relative to placebo for trial 2 only, based on the pre-specified testing sequence.
  - At week 12, significantly higher percentages of patients on solriamfetol 75 mg (72.4%; $p < 0.05$), 150 mg (89.7%; $p < 0.0001$), and 300 mg (88.7%; $p < 0.0001$) reported overall improvement on the PGI-C relative to placebo (49.1%). These effects were dose-dependent and apparent as early as week 1. Results were generally similar on the CGI-C.
  - There were no meaningful differences in response to solriamfetol between the subgroups of patients who were adherent or non-adherent to primary OSA therapy (data not shown).

Table 12. Hierarchical testing at week 12 of co-primary and key secondary endpoints in the mITT population*

Endpoint	Difference from placebo (95% CI); p-value			
	300 mg	150 mg	75 mg	37.5 mg
MWT, LS mean difference	12.8 (10.0 to 15.6); < 0.0001	10.7 (8.1 to 13.4); < 0.0001	8.9 (5.6 to 12.1); < 0.0001	4.5 (1.2 to 7.9); 0.0086
ESS, LS mean difference	-4.7 (-5.9 to -3.4); < 0.0001	-4.5 (-5.7 to -3.2); < 0.0001	-1.7 (-3.2 to -0.2); 0.0233	-1.9 (-3.4 to -0.3); 0.0161
PGI-C, % difference	39.6 (28.7, to 50.4); < 0.0001	40.5 (29.8 to 51.3); < 0.0001	23.3 (8.6 to 38.0); 0.0035	6.2 (-9.7 to 22.2); 0.4447

*A fixed hierarchical testing procedure was used to correct for multiplicity, starting with the highest solriamfetol dose for the co-primary endpoints and followed by the key secondary endpoint; testing proceeded in that order for each subsequent lower dose, with statistical significance claimed only for those outcomes above the break in the hierarchy.

  - A higher percentage of participants (7.3%) receiving solriamfetol withdrew due to AEs compared with placebo (3.4%). AEs leading to study discontinuation in ≥ 3 patients who received solriamfetol were anxiety (n = 4), feeling jittery (n = 4), nausea (n = 3), dizziness (n = 3), and chest discomfort (n = 3).
  - In most patients, AEs were of mild or moderate severity in the placebo (93.0%) and solriamfetol (94.6%) groups.

- The most frequently reported AEs with solriamfetol, defined as occurring in ≥ 5% of participants in any treatment group, included headache (10.1%), nausea (7.9%), decreased appetite (7.6%), anxiety (7.0%), and nasopharyngitis (5.1%); most of these AEs were dose-dependent.
- Insomnia was reported in 2 patients receiving placebo (1.7%), and in 1 (1.7%), 0 (0%), 3 (2.6%), and 11 (9.3%) participants receiving solriamfetol 37.5, 75, 150, and 300 mg, respectively.
- At week 12, vital signs taken at 7 time points during the day from pre-dose to 9 hours post-dose showed small mean (95% CI) increases from baseline in BP, with the highest at the 300 mg dose of solriamfetol (2.5 [95% CI, 0.4 to 4.6] and 1.5 [0.3 to 2.7] mm Hg for systolic and diastolic, respectively) relative to minimal changes with placebo (-0.2 [95% CI, -1.7 to 1.4] mm Hg systolic; 0.0 [95% CI, -0.9 to 1.0] mm Hg diastolic). Small dose-dependent mean effects were observed on heart rate with solriamfetol 150 and 300 mg (increases of 2.2 [95% CI, 1.0 to 3.4] and 2.9 [95% CI, 1.7 to 4.1] bpm, respectively, relative to 0.1 [95% CI, -0.9 to 1.1] bpm with placebo). No apparent effects of solriamfetol on BP or heart rate were observed on predose vital sign measures at week 12.

- **Authors' conclusion:**
  - Solriamfetol 75, 150, and 300 mg resulted in objective improvements in wakefulness, subjective improvements in sleepiness, and global improvements as evaluated by participants and clinicians. The safety and tolerability profile was consistent with prior studies of solriamfetol in individuals with narcolepsy, and similar to other wake-promoting agents used in the treatment of EDS in OSA.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Jazz Pharmaceuticals
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - The study used both objective and patient-reported validated outcome measures.
    - Participants who were non-adherent to OSA therapy were included in order to study a population more representative of OSA patients in the clinical setting.
  - **Study limitations:**
    - The trial had a short duration of 12 weeks and did not assess longer-term outcomes related to safety and efficacy, including potential long-term CV consequences.
    - The study did not include modafinil or armodafinil as a comparator.

Study 20. Strollo et al, *Chest.* 2019; 155(2):364-374 (TONES 4)

Study Objective: Evaluate the maintenance of efficacy and safety of solriamfetol vs placebo for the treatment of EDS in adults with OSA	
Study Design, Follow-up	**Treatment Groups** (N = 124)
• Phase 3, DB, PC, PG, MC, RW study • After 2 weeks of clinical titration (n = 174, 75 mg once daily starting dose, titrated up or down every 3 days to 75, 150, or 300 mg) and 2 weeks of stable dose administration (n = 148), patients who reported much or very much improvement on the PGI-C and had numerical improvements on the MWT and ESS were randomly assigned to placebo or solriamfetol for 2 additional weeks. • Randomization was stratified by patients' adherence or non-adherence to a primary OSA therapy	• Solriamfetol once daily (n = 62) • Placebo (n = 62)
Inclusion Criteria	**Exclusion Criteria**
• Adults, aged 18 to 75 years • Diagnosis of OSA according to ICSD-3 criteria • Current or primary OSA therapy including CPAP, oral appliance, or surgical intervention • BMI 18 to < 45 kg/m^2 • Baseline ESS score ≥ 10 • Mean sleep latency < 30 minutes on the first 4 trials of a 5-trial, 40-min MWT • Usual nightly sleep time ≥ 6 hours	• Any disorder other than OSA associated with EDS • An occupation requiring nighttime shift work or variable shift work • Excessive caffeine use 1 week prior to the study or nicotine dependence with a reported effect on sleep • Presence of any acutely unstable medical condition, behavioral or psychiatric disorder, or surgical history that could affect patient safety or interfere with study assessments

	• Use of any OTC or prescription medications that could affect EDS evaluation within a period corresponding to at least 5 half-lives of the drug
Co-Primary Endpoints	**Secondary Endpoints**
• Changes from week 4 to week 6 in: ○ MWT mean sleep latency ○ ESS score	• Percentage of patients who reported worsening of their condition on the PGI-C from week 4 to week 6 • Percentage of patients who reported worsening of their condition on the CGI-C from week 4 to week 6 • FOSQ-10

- **Results:**
  - Of 174 patients enrolled into the titration phase, 71% (n = 124) were randomly assigned to placebo or solriamfetol in the DB RW phase. There were 17 study discontinuations (10%) during the titration phase, 6 of which were due to AEs. During the stable dose phase (n = 157), 9 patients (6%) discontinued, and 24 did not enter the RW phase, of whom 21 (13%) were for not meeting the criteria for improvement. Two patients randomly assigned to solriamfetol discontinued during the RW phase; the final mITT population consisted of 62 patients randomly assigned to placebo and 60 to solriamfetol.
  - In the stable dose phase, 14.6%, 31.8%, and 53.5% of patients received the 75, 150, and 300 mg doses of solriamfetol, respectively. Of the 62 patients randomly assigned to solriamfetol in the RW phase, 14.5%, 41.9%, and 43.5% received 75, 150, and 300 mg, respectively.
  - Analyses were performed on the mITT population, defined as patients who were randomly assigned who received ≥ 1 dose of study medication and who had an MWT or ESS assessment at week 4 and ≥ 1 assessment after week 4.
  - Baseline characteristics of the safety population (patients who received ≥ 1 dose of solriamfetol in the titration phase) and the mITT population were comparable between groups.
  - In the titration phase, 65.5% of patients were classified as moderately or markedly ill by their physicians on the CGI-C, 61.5% were male with a mean BMI of 33.3 kg/m^2, and 71.3% were using a primary OSA therapy at baseline.
  - In the mITT population, from baseline to week 4, mean MWT sleep latencies improved from 12.3 to 13.1 min to 29.0 to 31.7 min, and ESS scores improved from 15.3 to 16.0 to 5.9 to 6.4. Patient-reported EDS decreased from ~15 to 16 to ~6, which is within the normal range.
  - From weeks 4 to 6 (RW phase), solriamfetol-treated patients maintained improvements in MWT and ESS. The LS mean (SE) change in MWT mean sleep latency was -12.1 (1.3) min with placebo compared with -1.0 (1.4) min with solriamfetol; LS mean difference between solriamfetol and placebo was 11.2 minutes (95% CI, 7.8 to14.6; p < 0.0001). The LS mean changes in ESS scores were 4.5 (0.7) and -0.1 (0.7) for placebo and solriamfetol, respectively, resulting in an LS mean difference of -4.6 (95% CI, -6.4 to -2.8; p < 0.0001).
    - MWT and ESS results were similar in the subgroups of patients who were adherent or non-adherent with a primary OSA therapy, with slightly larger MD in the non-adherent subgroup.
  - During the RW phase, a statistically significant 50.0% of patients who were switched to placebo reported worsening on the PGI-C relative to 20.0% who continued using solriamfetol (-30.0; 95% CI, -46.0 to -14.0; p < 0.001). Similarly, 59.0% of patients switched to placebo worsened, as rated by the physicians on the CGI-C, vs 21.7% who continued using solriamfetol (-37.3; 95% CI, -53.50 to -21.19; p < 0.0001).
    - Results on the PGI-C and CGI-C were similar in the subgroups of patients who were adherent or non-adherent with a primary OSA therapy, with slightly larger differences from placebo in the non-adherent subgroup.
  - The FOSQ total score improved from mean baseline scores of 13.5 to 13.7 to mean scores of 17.6 to 17.8 after 4 weeks of treatment. At the end of the RW phase (week 6), mean ±SD FOSQ-10 scores were 16.4 ± 2.9 in the placebo group and 17.4 ± 3.0 with solriamfetol, resulting in LS mean (SE) changes of -1.3 (0.4) and -0.2 (0.4), respectively; the LS mean difference significantly favored solriamfetol (1.2; 95% CI, 0.2 to 2.1; p < 0.05).
  - There were no serious AEs during the study, and all withdrawals due to AEs (3.4%, n = 6) occurred during the titration phase. The most frequent AEs leading to withdrawal were headache and palpitations (each reported for 2 patients). There was a higher incidence of AEs during the titration phase (48.9%) than during the stable dose phase (10.2%) and the incidence of AEs increased by dose. The most common AEs (≥ 5%) during the titration phase included headache, (9.8%), dry mouth (6.9%), nausea (6.9%), dizziness (5.7%), and insomnia (5.7%) and the incidence of these AEs (0.6 to 1.3%) was lower during the stable dose phase.
  - During the RW phase, 29.0% of patients who continued using solriamfetol experienced any AE relative to 9.7% of those switched to placebo. Nasopharyngitis was the most frequent AE (4.8%), and there was no evidence of rebound hypersomnia or withdrawal effects after abrupt discontinuation of solriamfetol in the placebo group.
  - The mean changes in vital signs obtained before administration of the dose to 9 hours after administration of the dose on MWT days, across solriamfetol doses, were small increases from baseline to week 6 in systolic (mean ±SD change of 1.6 ± 8.7 mm Hg) and diastolic (0.8 ± 5.3 mm Hg) BP, as well as heart rate (1.0 ± 6.1 bpm). In the RW

phase, small changes in BP (1.5 ± 7.6 mm Hg for systolic and 0.5 ± 4.3 mm Hg for diastolic) and heart rate (0.2 ± 5.9 bpm) were observed in patients randomly assigned to placebo.

- **Authors' conclusion:**
  - Solriamfetol substantially increased objective wakefulness and decreased subjective EDS, with effects that were maintained in participants who continued using treatment relative to a loss of efficacy among those randomly assigned to placebo. The safety profile was consistent with those of other solriamfetol studies, and abrupt discontinuation was not associated with rebound hypersomnia or withdrawal effects.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Jazz Pharmaceuticals
  - **Study rating:**
    - N/A (RW study)
  - **Study strengths:**
    - Inclusion of non-adherent patients in the study likely reflects the characteristics of the general population of patients with OSA who may benefit from solriamfetol treatment.
  - **Study limitations:**
    - The study had a small sample size.
    - The study had a short duration.
    - The inclusion of a population enriched for treatment response, which, although customary for the RW study design, limits characterization of solriamfetol treatment effects in individuals who did not meet response criteria for random assignment.
    - Approximately 20 to 30% of patients were not using a primary OSA therapy at evaluated time points, which may have caused heterogeneity in treatment response.

Study 21. Malhotra et al, *Sleep*. 2020;43(2); Sunosi dossier 2019 (TONES 5)

Study Objective: Evaluate the long-term safety and maintenance of efficacy of solriamfetol for up to 52 weeks in the treatment of patients with narcolepsy or OSA who completed previous trials of solriamfetol	
Study Design, Follow-up	**Treatment Group**
• Phase 3, OL extension study • A 2-week titration phase was followed by a maintenance phase of up to 50 weeks. After ~6 months of OL treatment with solriamfetol, a subgroup of patients entered a 2-week PC RW phase, and the maintenance phase was resumed after RW phase completion.	• Solriamfetol (Group A, n = 519; Group B, n = 124) • Due to differences in study design as well as variable duration between prior study completion and enrollment in the long-term study, participants were enrolled into one of 2 groups. Group A included participants who completed a Phase 3, 12-week narcolepsy or OSA study, and who immediately enrolled into this long-term study; the study duration in this group was 40 weeks. Group B included participants with narcolepsy or OSA who completed one of the Phase 2 studies (or the 6-week, Phase 3 study and were subsequently enrolled into this long-term study. These participants had a study duration for 52 weeks. • During the 2-week titration phase, participants began with a once-daily dose of 75 mg and could titrate up 1 dose level every 3 days (to 150 mg/d and then a maximum dose of 300 mg/d). Participants were also able to titrate down to 75 or 150 mg at any time. • During the RW phase, patients were randomized either to placebo or to continue solriamfetol at their dose of 75 mg, 150 mg, or 300 mg for 2 weeks. • At the end of the RW phase and for the remainder of the study, participants resumed solriamfetol treatment at the same dose that they had received at the beginning of the RW phase.
Inclusion Criteria	**Exclusion Criteria**
• Patients with narcolepsy or OSA who had completed a prior Phase 2 or Phase 3 study with solriamfetol	• See above parent study descriptions
Primary Endpoint	**Secondary Endpoints**

• Change in ESS score from the beginning to the end of the 2-week RW phase	• PGI-C • CGI-C

- **Results:**
  - The overall safety population in the OL phase consisted of 643 patients (417 [64.9%] with OSA and 226 [35.1%] with narcolepsy). A total of 458 (71%) patients completed the study including 66.4% of narcolepsy participants and 73.9% of OSA participants. Patients were primarily male (52.4%) and White (78.7%), with a mean age of 49.3 years. Comorbid conditions included HTN (37.6%), hyperlipidemia (15.2%), and type 2 diabetes (14.0%). The percentages of participants who were titrated to 75, 150, and 300 mg were 10.0%, 32.2%, and 57.9%, respectively. A total of 282 patients were randomized into the RW phase, of which 280 completed this phase. One hundred-forty-one received placebo and 139 received solriamfetol, which represented the mITT population.
  - At study baseline, primary OSA therapy was used by 71.5% of OSA participants; of these participants, 93.2% were using PAP at entry into this study, 2.3% were using another type of device as a primary OSA therapy (eg, neurostimulator or mandibular advancement device), and 5.4% did not specify the type of primary OSA therapy.
  - Efficacy during the maintenance phase
    - In the overall population, mean ESS scores were 15.9 for group A and 16.2 for group B at baseline of the parent and current study, respectively. At week 2, mean ESS scores decreased to 7.6 for group A and to 7.8 for group B, and these improvements (ie, decrease in mean ESS scores) were maintained throughout the study duration. Similar patterns were observed in the individual narcolepsy and OSA populations.
    - The majority of participants (> 94%) reported improvements on the PGI-C at week 2, and these improvements were maintained at generally similar percentages at each assessment; 87.1 to 90.4% of participants in group A and 86.8 to 96.4% of participants in group B reported improvement on the PGI-C at the final assessment. Sustained improvements from the first assessment at week 2 over the study duration were also reported from the clinician perspective on the CGI-C, with good concordance with the PGI-C for the percentage of participants who improved. Similar patterns were observed in the individual narcolepsy and OSA populations.
  - Efficacy during the RW phase
    - All primary and secondary endpoints were met for the RW phase ($p < 0.0001$) in the mITT population. Participants who received solriamfetol during the RW phase maintained their improvement from the beginning of the RW phase, whereas those who were randomized to receive placebo worsened. The LS mean change (from the beginning to the end of the RW phase) for the ESS score was 1.6 with solriamfetol compared with 5.3 with placebo, resulting in an LS mean difference of -3.7 (95% CI, -4.80 to -2.65; $p < 0.0001$. In the overall population, significantly greater percentages of participants in the placebo group worsened during the RW phase compared with the solriamfetol group on both the PGI-C (64.5% vs 28.2%; $p < 0.0001$) and CGI-C (63.8% vs 28.7%; $p < 0.0001$). Similar results were observed by indication across endpoints ($p < 0.05$; data not shown).
  - Over the study duration, 482 participants (75%) had at least 1 TEAE, with similar percentages among those with narcolepsy (74.8%) and OSA (75.1%); 44% of participants (283/643) had a TEAE within the first 2 weeks whereas 12.8% had a TEAE during the second 2 weeks of treatment.
  - The most frequent TEAEs (≥ 5% in combined solriamfetol groups for any indication) were headache (11%), nausea (8.9%), insomnia (7.9%), nasopharyngitis (8.4%), dry mouth (7.3%), anxiety (7.2%), decreased appetite (5.0%), and upper respiratory tract infection (5.0%); most TEAEs were mild or moderate. With the exception of sinusitis, nasopharyngitis, and upper respiratory tract infection, the most common TEAEs occurred most often during the first 2 weeks of the study. TEAE profiles were similar in participants with OSA and narcolepsy. During the OL period, 59 (9.2%) participants had TEAEs that led to withdrawal from the study. TEAEs leading to withdrawal most frequently occurred in the system organ classes of psychiatric disorders (n = 20; 3.1%), nervous system disorders (n = 13; 2.0%), and gastrointestinal disorders (n = 8; 1.2%).TEAEs that most frequently led to withdrawal were anxiety (*n* = 7; 1.1%), headache (n = 4; 0.6%), insomnia (n = 4; 0.6%), irritability (n = 4; 0.6%), nausea (n = 4; 0.6%), depression (n = 3; 0.3%), and dry mouth (n = 3; 0.3%).
  - Serious TEAEs were reported in 27 patients (4.2%) across all phases, including 21 participants (5.0%) with OSA and 6 participants (2.7%) with narcolepsy. There was 1 death that was considered unrelated to study drug. A total of 9 participants, all with OSA, had CV or potential CV serious TEAEs: 2 participants with atrial fibrillation; 1 each with angina pectoris, chest discomfort, chest pain, noncardiac chest pain, cerebrovascular accident, pulmonary embolism; and 1 patient with acute myocardial infarction discussed previously. Of these serious TEAEs, 2 were deemed by the investigator to be related to study drug administration: atrial fibrillation in a patient whose concomitant medications included 2 types of thyroid medication, and cerebrovascular accident in a patient with a history of HTN.
  - Rebound hypersomnia, as assessed by changes on the ESS, was not observed after abrupt discontinuation of solriamfetol in the RW phase.
  - There was no pattern of withdrawal signs or symptoms based on analysis of AEs that occurred after abrupt discontinuation of long-term exposure to solriamfetol (ie, the placebo group in the RW phase).

- No clinically relevant changes in heart rate (< 1 beat per minute [bpm]) or blood pressure (< 1 mm Hg) were observed at assessed time points in group A (n = 519). However, for group B (n = 124), mean increases from baseline ranged from 1.0 to 4.3 mm Hg for systolic blood pressure, 0.8 to 2.4 mm Hg for diastolic blood pressure, and 0.6 to 4.2 bpm for heart rate across the OL extension (up to 52 weeks); these increases were generally greater for participants with narcolepsy relative to OSA. No apparent trends were observed to suggest that there were long-term increases (ie, worsening) in heart rate or blood pressure over time for participants with narcolepsy or OSA (in both group A and group B).

- **Authors' Conclusion:**
  - The long-term maintenance of efficacy with solriamfetol was demonstrated for the treatment of EDS in patients with narcolepsy or OSA. During the maintenance phase, improvements with solriamfetol were maintained for up to 1 year. The safety profile was consistent with prior PC studies of solriamfetol and there were no safety concerns that emerged with chronic administration of up to 1 year.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Jazz Pharmaceuticals
  - **Study rating:**
    - N/A (OL extension study)
  - **Study strengths:**
    - The study had a large sample size.
    - The study included patients with narcolepsy with and without cataplexy.
    - The study followed patients for up to 1 year.
  - **Study limitations:**
    - There was no placebo group for comparison, nor was solriamfetol compared with other wake-promoting agents.
    - The study did not focus on objective outcome measures such as the MWT, neurocognitive performance, or motor vehicle accident risk due to EDS but rather patient-reported outcomes.

CLINICAL GUIDELINES

AASM practice parameters for the treatment of narcolepsy and other hypersomnias of central origin (*Morgenthaler et al 2007a*) (see Appendix H for grading of evidence definitions)

- Recommendations for treatment of narcolepsy:
  - Most of the agents used to treat excessive sleepiness have little effect on cataplexy or other REM sleep associated symptoms. Conversely, most antidepressants and anticataplectics have little effect on alertness. However, some compounds act on both symptoms. Compounds should be selected depending on the diagnosis and the targeted symptoms. Co-administration of 2 or more classes of compounds may be needed in some patients to adequately address their symptoms.
  - Modafinil is effective for treatment of daytime sleepiness due to narcolepsy (Standard).
  - Sodium oxybate is effective for treatment of cataplexy, daytime sleepiness, and disrupted sleep due to narcolepsy (Standard). Sodium oxybate may be effective for treatment of hypnagogic hallucinations and sleep paralysis (Option).
  - Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for treatment of daytime sleepiness due to narcolepsy (Guideline).
  - Selegiline may be an effective treatment for cataplexy and daytime sleepiness (Option).
  - Ritanserin (not available in the U.S.) may be effective treatment of daytime sleepiness due to narcolepsy (Option).
  - Scheduled naps can be beneficial to combat sleepiness but seldom suffice as primary therapy for narcolepsy (Guideline).
  - TCAs, SSRIs, venlafaxine, and reboxetine (not available in the U.S.) may be effective treatment for cataplexy (Guideline).
  - TCAs, SSRIs, and venlafaxine may be effective treatment for treatment of sleep paralysis and hypnagogic hallucinations (Option).

AASM practice parameters for the medical therapy of OSA (*Morgenthaler et al 2006*)

- Recommendations for pharmacologic therapy of OSA:
  - Successful dietary weight loss may improve the AHI in obese OSA patients (Guideline).
  - Dietary weight loss should be combined with a primary treatment for OSA (Option).
  - Bariatric surgery may be adjunctive in the treatment of OSA in obese patients (Option).
  - SSRIs are not recommended for treatment of OSA (Standard).
  - Protriptyline is not recommended as a primary treatment for OSA (Guideline).
  - Methylxanthine derivatives (aminophylline and theophylline) are not recommended for treatment of OSA (Standard).

- Estrogen therapy (estrogen preparations with or without progesterone) is not indicated for the treatment of OSA (Standard).
- Modafinil is recommended for the treatment of residual EDS in OSA patients who have sleepiness despite effective PAP treatment and who are lacking any other identifiable cause for their sleepiness (Standard).

AASM practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders (*Morgenthaler et al 2007b*)

- Recommendations for SWD:
  - Planned napping before or during the night shift is indicated to improve alertness and performance among night shift workers (Standard).
  - Timed light exposure in the work environment and light restriction in the morning, when feasible, is indicated to decrease sleepiness and improve alertness during night shift work (Guideline).
  - Administration of melatonin prior to daytime sleep is indicated to promote daytime sleep among night shift workers (Guideline).
  - Hypnotic medications may be used to promote daytime sleep among night shift workers. Carryover of sedation to the nighttime shift with potential adverse consequences for nighttime performance and safety must be considered (Guideline).
  - Modafinil is indicated to enhance alertness during the night shift for SWD (Guideline).
  - Caffeine is indicated to enhance alertness during the night shift for SWD (Option).

EAN. Management of narcolepsy in adults (*Billiard et al 2011)* (see Appendix I for grading of evidence definitions)

- Recommendations for treatment of narcolepsy:
  - EDS and sleep attacks:
    - The first-line pharmacological treatment of EDS and sleep attacks is not unequivocal. When EDS is the most disturbing symptom, modafinil is recommended based on its efficacy, limited AEs, and dosing flexibility. Modafinil can be taken in variable doses from 100 to 400 mg/day, given as 1 dose in the morning or 2 doses, 1 in the morning and 1 early in the afternoon or tailored to individual patient needs.
    - When EDS coexists with cataplexy and poor sleep, sodium oxybate may be given, based on its well-evidenced efficacy on the 3 symptoms. However, this benefit should be balanced with its more delicate manipulation: the dose should be carefully titrated up to an adequate level over several weeks; the drug should not be used in combination with other sedatives, respiratory depressants and muscle relaxants; patient should be monitored for development of sleep-disordered breathing; and its use should be avoided in depressed patients. Sodium oxybate should be given at a starting dose of 4.5 g/night, increasing by increments of 1.5 g at 4-week intervals. AEs may require dose reduction and slow titration. The optimal response on EDS may take as long as 8 to 12 weeks. Supplementation with modafinil is generally more successful than sodium oxybate alone.
    - Methylphenidate may be an option when the response to modafinil is inadequate and sodium oxybate is not recommended. Moreover, the short-acting effect of methylphenidate may be beneficial when modafinil needs to be supplemented at a specific time of the day, or in situations where maximum alertness is required. Methylphenidate LP and mazindol (not available in the U.S.) may be useful in a limited number of cases.
    - Behavioral treatment measures are always advisable. Essentially, the studies available support on a B Level the recommendation to have regular nocturnal sleep times and to take planned naps during the day, as naps temporarily decrease sleep tendency and shorten reaction time. Because of varying performance demands and limitations on work or home times for taking them, naps are best scheduled on a patient-by-patient basis.
  - Cataplexy:
    - Based on several Class I evidence (Level A rating) studies, sodium oxybate is recommended for first-line pharmacological treatment of cataplexy at a starting dose of 4.5 g/night divided into 2 equal doses of 2.25 g/night. The dose may be increased to a maximum of 9 g/night, divided into 2 equal doses of 4.5 g/night, by increments of 1.5 g at 2-week intervals. Special considerations are noted above.
    - Second-line pharmacological treatments are antidepressants. TCAs, particularly clomipramine (10 to 75 mg), are potent anticataplectic drugs. However, they have the disadvantage of anticholinergic AEs. The starting dosage should always be as low as possible. SSRIs are slightly less active but have fewer AEs. The norepinephrine/serotonin reuptake inhibitor venlafaxine is widely used but lacks any published clinical evidence of efficacy. The norepinephrine reuptake inhibitors, such as reboxetine and atomoxetine, also lack published clinical evidence. Given the well-evidenced efficacy of sodium oxybate and antidepressants, the place for other compounds is fairly limited. There is no accepted behavioral treatment of cataplexy.
  - Hallucinations and sleep paralysis:
    - Recommendations are the same as for cataplexy.
  - Poor sleep:

- According to recent studies with sodium oxybate, this agent appears as the most appropriate to treat poor sleep (Level A). Benzodiazepine or non-benzodiazepine hypnotics may be effective in consolidating nocturnal sleep (Level C). Unfortunately, objective evidence is lacking over intermediate or long-term follow-up. The improvement in poor sleep reported by some patients once established on modafinil is noteworthy.

- Associated features:
  - OSA/hypopnea should be treated no differently in narcoleptic patients than the general population, although it has been shown that CPAP does not improve EDS in most narcolepsy patients. There is usually no need to treat PLMS in narcoleptic patients. Antidepressants and psychotherapy should be used in depressed narcoleptic patients (Level C) as in non-narcoleptic depressed patients.

SAFETY

- **Contraindications**
  - Armodafinil/modafinil
    - Known hypersensitivity to armodafinil or modafinil or its inactive ingredients
  - Pitolisant
    - Patients with severe hepatic impairment
      - Pitolisant is extensively metabolized by the liver and there is a significant increase in pitolisant exposure in patients with moderate hepatic impairment.
  - Solriamfetol
    - Concomitant use of MAOIs, or within 14 days following discontinuation of an MAOI because of the risk of hypertensive reaction
  - Sodium oxybate/oxybate salts
    - Concomitant use of sedative hypnotic agents
    - Concomitant use of alcohol
    - Diagnosis of semialdehyde dehydrogenase deficiency, a rare disorder of inborn error of metabolism variably characterized by mental retardation, hypotonia, and ataxia.
- **Warnings/precautions**
  - Armodafinil/modafinil
    - *Serious dermatologic reactions, including SJS and TEN*
      - Serious rash requiring hospitalization and discontinuation of treatment has been reported in association with the use of modafinil/armodafinil.
      - Rare cases of SJS and TEN have been reported in adults and children in worldwide postmarketing experience with armodafinil/modafinil.
      - There are no factors known to predict the risk of occurrence or the severity of rash associated with armodafinil/modafinil.
      - In cases where the time to onset was reported, serious rash occurred 1 day to 2 months after initiation of armodafinil. Nearly all cases of serious rash associated with modafinil occurred within 1 to 5 weeks after treatment initiation. However, isolated cases with either drug have been reported after prolonged treatment (eg, 3 months).
    - *DRESS/multiorgan hypersensitivity*
      - One fatal case of DRESS (also known as multiorgan hypersensitivity) that occurred in close temporal association (3 weeks) with the initiation of armodafinil treatment has been reported in the postmarketing setting. DRESS typically presents with fever, rash, lymphadenopathy, and/or facial swelling in association with other organ system involvement, such as hepatitis, nephritis, hematologic abnormalities, myocarditis, or myositis, sometimes resembling an acute viral infection. In addition, multiorgan hypersensitivity reactions, including at least 1 fatality in postmarketing experience, have occurred in close temporal association (median time to detection 13 days; range, 4 to 33) to the initiation of modafinil. Although there have been a limited number of reports, multiorgan hypersensitivity reactions may result in hospitalization or be life-threatening.
    - *Angioedema and anaphylaxis reactions*
      - Angioedema and hypersensitivity (with rash, dysphagia, and bronchospasm) were observed in patients treated with armodafinil. No such cases were observed in modafinil clinical trials. However, angioedema has been reported in postmarketing experience with modafinil. Patients should be advised to discontinue therapy and immediately report to their physician any signs or symptoms suggesting angioedema or anaphylaxis (eg, swelling of face, eyes, lips, tongue or larynx; difficulty in swallowing or breathing; hoarseness).
    - *Persistent sleepiness*
      - Patients with abnormal levels of sleepiness who take modafinil/armodafinil should be advised that their level of wakefulness may not return to normal. Patients with excessive sleepiness, including those taking modafinil/armodafinil, should be frequently reassessed for their degree of sleepiness and, if appropriate, advised to avoid driving or any other potentially dangerous activity. Prescribers should also be aware that

patients may not acknowledge sleepiness or drowsiness until directly questioned about drowsiness or sleepiness during specific activities.

- *Psychiatric symptoms*
  - Psychiatric AEs have been reported in association with the use of modafinil/armodafinil.
  - Postmarketing AEs associated with the use of modafinil/armodafinil, some of which have resulted in hospitalization, have included mania, delusions, hallucinations, suicidal ideation, and aggression. Many, but not all, patients who developed psychiatric AEs had a prior psychiatric history.
- *Known CV disease*
  - In clinical studies of modafinil, CV AEs, including chest pain, palpitations, dyspnea and transient ischemic T-wave changes on ECG were observed in 3 patients in association with mitral valve prolapse or left ventricular hypertrophy. Use of modafinil/armodafinil is not recommended in patients with a history of left ventricular hypertrophy or in patients with mitral valve prolapse who have experienced the mitral valve prolapse syndrome when previously receiving CNS stimulants.

○ Pitolisant

- Pitolisant prolongs the QT interval. The use of pitolisant should be avoided in patients with known QT prolongation or in combination with other drugs known to prolong QT interval. Pitolisant should also be avoided in patients with a history of cardiac arrhythmias, as well as other circumstances that may increase the risk of the occurrence of torsade de pointes or sudden death including symptomatic bradycardia, hypokalemia or hypomagnesemia, and the presence of congenital prolongation of the QT interval. The risk of QT prolongation may be greater in patients with hepatic or renal impairment due to higher concentrations of pitolisant. Patients with hepatic or renal impairment should be monitored for increased QTc.

○ Sodium oxybates/oxybate salts

- **Boxed warning** (sodium oxybate):
  - CNS depression
    - Xyrem is a CNS depressant, and respiratory depression can occur with sodium oxybate use.
  - Abuse and misuse
    - Sodium oxybate is the sodium salt of GHB. Abuse or misuse of illicit GHB is associated with CNS AEs, including seizure, respiratory depression, decreased consciousness, coma, and death.
- **Boxed warning** (oxybate salts)
  - CNS depression
    - Oxybate salts is a CNS depressant, and respiratory depression can occur with oxybate salts use.
  - Abuse and misuse
    - The active moiety of oxybate salts is GHB. Abuse or misuse of illicit GHB is associated with CNS AEs, including seizure, respiratory depression, decreased consciousness, coma, and death.
- *Respiratory Depression and Sleep-Disordered Breathing*
  - Sodium oxybate may impair respiratory drive, especially in patients with compromised respiratory function. In overdoses, life-threatening respiratory depression has been reported.
  - During PSG, central sleep apnea and oxygen desaturation were observed in pediatric patients with narcolepsy treated with sodium oxybate.
  - Prescribers should be aware that increased central apneas and clinically relevant desaturation events have been observed with sodium oxybate administration in adult and pediatric patients.
- *Depression and suicidality*
  - In adult clinical trials in patients with narcolepsy (n = 781), there were 2 suicides and 2 attempted suicides in patients treated with sodium oxybate, including 3 patients with a previous history of depressive psychiatric disorder. Of the 2 suicides, 1 patient used sodium oxybate in conjunction with other drugs. Sodium oxybate was not involved in the second suicide. AEs of depression were reported by 7% of 781 patients treated with sodium oxybate, with 4 patients (< 1%) discontinuing because of depression. In most cases, no change in sodium oxybate treatment was required.
  - In a controlled adult trial, with patients randomized to fixed doses of 3 g, 6 g, or 9 g per night sodium oxybate or placebo, there was a single event of depression at the 3 g per night dose. In another adult controlled trial, with patients titrated from an initial 4.5 g per night starting dose, the incidences of depression were 1 (1.7%), 1 (1.5%), 2 (3.2%), and 2 (3.6%) for the placebo, 4.5 g, 6 g, and 9 g per night doses, respectively.
  - In the pediatric clinical trial in patients with narcolepsy (n = 104), 1 patient experienced suicidal ideation while taking sodium oxybate.
- *Other Behavioral or Psychiatric Adverse Reactions*
  - During adult clinical trials in patients with narcolepsy, 3% of 781 patients treated with sodium oxybate experienced confusion, with incidence generally increasing with dose.
  - Less than 1% of patients discontinued the drug because of confusion. Confusion was reported at all recommended doses from 6 g to 9 g per night. In a controlled trial in adults where patients were randomized to

fixed total daily doses of 3 g, 6 g, or 9 g per night or placebo, a dose-response relationship for confusion was demonstrated, with 17% of patients at 9 g per night experiencing confusion. In all cases in that controlled trial, the confusion resolved soon after termination of treatment. In Trial 3 where sodium oxybate was titrated from an initial 4.5 g per night dose, there was a single event of confusion in 1 patient at the 9 g per night dose. In the majority of cases in all adult clinical trials in patients with narcolepsy, confusion resolved either soon after termination of dosing or with continued treatment.

- Anxiety occurred in 5.8% of the 874 patients receiving sodium oxybate in adult clinical trials in another population.
- Other neuropsychiatric reactions reported in adult clinical trials in patients with narcolepsy and the post-marketing setting included hallucinations, paranoia, psychosis, aggression, and agitation.
- In the pediatric clinical trial in patients with narcolepsy, neuropsychiatric reactions, including acute psychosis, confusion, and anxiety, were reported while taking sodium oxybate.

▪ *Parasomnias*

- Sleepwalking, defined as confused behavior occurring at night and at times associated with wandering, was reported in 6% of 781 patients with narcolepsy treated with sodium oxybate in adult controlled and long-term OL studies, with < 1% of patients discontinuing due to sleepwalking. Rates of sleepwalking were similar for patients taking placebo and patients taking sodium oxybate in controlled trials. It is unclear if some or all of the reported sleepwalking episodes correspond to true somnambulism, which is a parasomnia occurring during non-REM sleep, or to any other specific medical disorder. Five instances of significant injury or potential injury were associated with sleepwalking during a clinical trial of sodium oxybate in patients with narcolepsy.

▪ *Use in patients sensitive to high sodium intake (sodium oxybate)*

- Sodium oxybate has a high salt content. In patients sensitive to salt intake (eg, those with HF, HTN, or renal impairment), the amount of daily sodium intake in each dose of sodium oxybate should be considered. Table 13 provides the approximate sodium content per sodium oxybate dose.

Table 13. Approximate sodium content per total nightly dose of sodium oxybate

Sodium oxybate dose/per night	Sodium content/total nightly exposure
3 g	550 mg
4.5 g	820 mg
6 g	1100 mg
7.5 g	1400 mg
9 g	1640 mg

○ Solriamfetol

▪ *Blood pressure and heart rate increases*:

- Solriamfetol increases systolic BP, diastolic BP, and heart rate in a dose-dependent fashion.
- Epidemiological data show that chronic elevations in BP increase the risk of major adverse CV events (MACE), including stroke, heart attack, and CV death. The magnitude of the increase in absolute risk is dependent on the increase in BP and the underlying risk of MACE in the population being treated. Many patients with narcolepsy and OSA have multiple risk factors for MACE, including hypertension, diabetes, hyperlipidemia, and high BMI.
- BP should be assessed and controlled before initiation of treatment with solriamfetol. BP should be monitored regularly during treatment. New onset hypertension and exacerbations of pre-existing hypertension should be treated. Caution should be exercised when treating patients at higher risk of MACE, particularly patients with known CV and cerebrovascular disease, pre-existing hypertension, and patients with advanced age. Caution should be used with other drugs that increase BP and heart rate.
- The need for continued treatment should be periodically re-assessed. If a patient experiences increases in BP or heart rate that cannot be managed with dose reduction of solriamfetol or other appropriate medical intervention, drug discontinuation should be considered.
- Patients with moderate or severe renal impairment may be at higher risk of increases in BP and heart rate because of the prolonged half-life of solriamfetol.

▪ *Psychiatric symptoms*:

- Psychiatric AEs have been observed in clinical trials with solriamfetol, including anxiety, insomnia, and irritability.
- Solriamfetol has not been evaluated in patients with psychosis or bipolar disorders. Caution should be exercised when treating patients with solriamfetol who have a history of psychosis or bipolar disorders.
- Patients with moderate or severe renal impairment may be at a higher risk of psychiatric symptoms because of the prolonged half-life of solriamfetol.

- Patients treated with solriamfetol should be observed for the possible emergence or exacerbation of psychiatric symptoms. If psychiatric symptoms develop in association with the administration of solriamfetol, dose reduction or discontinuation of solriamfetol should be considered.

- **Adverse effects**
  - Armodafinil
    - The most common AEs (≥ 5%) vs placebo were headache (17 vs 9%), nausea (7 vs 3%), dizziness (5 vs 2%), and insomnia (5 vs 1%).
    - In PC clinical trials, 44 of the 645 patients (7%) who received armodafinil discontinued due to an AE compared to 16 of the 445 (4%) patients that received placebo. The most frequent reason for discontinuation was headache (1%).
  - Modafinil
    - The most common AEs (≥ 5%) vs placebo were headache (34 vs 23%), nausea (11 vs 3%), nervousness (7 vs 3%), rhinitis (7 vs 6%), diarrhea (6 vs 5%), back pain (6 vs 5%), anxiety (5 vs 1%), insomnia (5 vs 1%), dizziness (5 vs 4%), and dyspepsia (5 vs 4%).
    - In PC clinical trials, 74 of the 934 patients (8%) who received modafinil discontinued due to an AE compared to 3% of patients that received placebo. The most frequent reasons for discontinuation that occurred at a higher rate for modafinil than placebo patients were headache (2%), nausea, anxiety, dizziness, insomnia, chest pain, and nervousness (each < 1%).
  - Pitolisant
    - In the PC clinical trials conducted in patients with narcolepsy with or without cataplexy, the most common AEs (occurring in ≥ 5% of patients and at twice the rate of placebo) with the use of pitolisant were insomnia (6%), nausea (6%), and anxiety (5%).
  - Sodium oxybate
    - The most common AEs in adults (≥ 2% and more frequently than placebo) were nausea (8 to 20% vs 3%), dizziness (9 to 15% vs 4%), vomiting (2 to 11% vs 1%), somnolence (1 to 8% vs 4%), enuresis (3 to 7% vs 1%), and tremor (2 to 5% vs 0%).
    - The overall AE profile in the pediatric clinical trials was similar to that seen in the adult clinical trial program. The most common AEs of sodium oxybate in pediatric patients (≥ 5%) were enuresis (18%), nausea (17%), headache (16%), vomiting (16%), weight decreased (12%), decreased appetite (8%), and dizziness (6%).
    - Of the 398 patients with narcolepsy treated with sodium oxybate, 10.3% of patients discontinued because of AEs compared with 2.8% of patients receiving placebo. The most common AE leading to discontinuation was nausea (2.8%). The majority of AEs leading to discontinuation began during the first few weeks of treatment.
  - Oxybate salts
    - The most common AEs in the adult study (incidence ≥ 5% of oxybate salts-treated patients) were headache, nausea, dizziness, decreased appetite, parasomnia, diarrhea, hyperhidrosis, anxiety, and vomiting.
    - AEs observed in clinical studies with sodium oxybate (≥ 2%), but not in the adult oxybate salts study, and which may be relevant for oxybate salts included pain, feeling drunk, pain in extremity, cataplexy, disturbance in attention, sleep paralysis, and disorientation.
  - Solriamfetol
    - The most common AEs (≥ 5% and greater than placebo) in either the narcolepsy or OSA populations vs placebo were headache (16 vs 7%), nausea (7 vs 4%), decreased appetite (9 vs 1%), insomnia (5 vs 4%), and anxiety (6 vs 1%).
    - In the 12-week PC clinical trials, 11 of the 396 patients (3%) who received solriamfetol discontinued because of an AE compared to 1 of the 226 patients (< 1%) who received placebo. The AEs resulting in discontinuation that occurred in more than 1 solriamfetol-treated patient and at a higher rate than placebo were: anxiety (2/396; < 1%), palpitations (2/396; < 1%), and restlessness (2/396; < 1%).
    - Drug abuse and dependence
      - Abuse
        - Solriamfetol has potential for abuse. Abuse is the intentional non-therapeutic use of a drug, even once, to achieve a desired psychological or physiological effect. The abuse potential of solriamfetol 300 mg, 600 mg, and 1200 mg (2, 3, and 4 times the maximum recommended dose, respectively) was assessed relative to phentermine, 45 mg and 90 mg, (a Schedule IV controlled substance) in a human abuse potential study in individuals (N = 43) experienced with the recreational use of stimulants. Results from this clinical study demonstrated that solriamfetol produced Drug Liking scores similar to or lower than phentermine. In this XO study, elevated mood was reported by 2.4% in the placebo group, 8 to 24% in the solriamfetol group, and 10 to 18% in the phentermine group. A “feeling of relaxation” was reported in 5% of the placebo group, 5 to 19% of the solriamfetol group, and 15 to 20% of the phentermine group (*Carter et al 2018, Solriamfetol prescribing information 2019*).

- Physicians should carefully evaluate patients for a recent history of drug abuse, especially those with a history of stimulant (eg, methylphenidate, amphetamine, or cocaine) or alcohol abuse, and follow such patients closely, observing them for signs of misuse or abuse of solriamfetol (eg, incrementation of doses, drug-seeking behavior).

- Dependence
  - In a long-term safety and maintenance of efficacy study, the effects of abrupt discontinuation of solriamfetol were evaluated following at least 6 months of solriamfetol use in patients with narcolepsy or OSA. The effects of abrupt discontinuation of solriamfetol were also evaluated during the 2-week safety follow-up periods in the Phase 3 studies. There was no evidence that abrupt discontinuation of solriamfetol resulted in a consistent pattern of AEs in individual patients that was suggestive of physical dependence or withdrawal.

- **Drug Interactions**
  - Modafinil/armodafinil
    - *Effects on CYP3A4/5 substrates*
      - The clearance of drugs that are substrates for CYP3A4/5 (eg, steroidal contraceptives, cyclosporine, midazolam, and triazolam) may be increased by modafinil/armodafinil via induction of metabolic enzymes, which results in lower systemic exposure. Dosage adjustment of these drugs should be considered when these drugs are used concomitantly with modafinil/armodafinil.
      - The effectiveness of steroidal contraceptives may be reduced when used with armodafinil/modafinil and for 1 month after discontinuation of therapy. Alternative or concomitant methods of contraception are recommended for patients taking steroidal contraceptives (eg, ethinyl estradiol) when treated concomitantly with modafinil/armodafinil and for 1 month after discontinuation of modafinil/armodafinil treatment.
      - Blood levels of cyclosporine may be reduced when used with modafinil/armodafinil. Monitoring of circulating cyclosporine concentrations and appropriate dosage adjustment for cyclosporine should be considered when used concomitantly with modafinil/armodafinil.
    - *Effects on CYP2C19 substrates*
      - Elimination of drugs that are substrates for CYP2C19 (eg, phenytoin, diazepam, propranolol, omeprazole, and clomipramine) may be prolonged by modafinil/armodafinil via inhibition of metabolic enzymes, with resultant higher systemic exposure. In individuals deficient in the CYP2D6 enzyme, the levels of CYP2D6 substrates which have ancillary routes of elimination through CYP2C19, such as TCAs and SSRIs, may be increased by co-administration of modafinil/armodafinil. Dose adjustments of these drugs and other drugs that are substrates for CYP2C19 may be necessary when used concomitantly with modafinil/armodafinil.
    - *Warfarin*
      - More frequent monitoring of prothrombin times/international normalized ratio (INR) should be considered whenever modafinil/armodafinil is co-administered with warfarin.
    - *MAOIs*
      - Caution should be used when concomitantly administering MAOIs and modafinil/armodafinil.
  - Pitolisant
    - Drugs having clinically important interactions with pitolisant:

Table 14. Clinically significant drug interactions with pitolisant

Effect of Other Drugs on pitolisant	
Strong CYP2D6 Inhibitors	
Clinical implication:	Concomitant administration of pitolisant with strong CYP2D6 inhibitors increases pitolisant exposure by 2.2-fold.
Prevention or management:	Reduce the dose of pitolisant by half.
Examples:	paroxetine, fluoxetine, bupropion
Strong CYP3A4 Inducers	
Clinical implication:	Concomitant use of pitolisant with strong CYP3A4 inducers decreases exposure of pitolisant by 50%.
Prevention or management:	Assess for loss of efficacy after initiation of a strong CYP3A4 inducer. For patients stable on pitolisant 8.9 mg or 17.8 mg once daily, increase the dose of pitolisant to reach double the original daily dose (ie, 17.8 mg or 35.6 mg, respectively) over 7 days. If concomitant dosing of a strong CYP3A4 inducer is discontinued, decrease pitolisant dosage by half.
Examples:	rifampin, carbamazepine, phenytoin
Histamine-1 (H_1) Receptor Antagonists	

Clinical implication:	Pitolisant increases the levels of histamine in the brain; therefore, H_1 receptor antagonists that cross the blood-brain barrier may reduce the effectiveness of pitolisant.
Prevention or management:	Avoid centrally acting H_1 receptor antagonists.
Examples:	pheniramine maleate, diphenhydramine, promethazine (antihistamines) imipramine, clomipramine, mirtazapine (tri or tetracyclic antidepressants)
QT interval prolongation	
Clinical implication:	Concomitant use of drugs that prolong the QT interval may add to the QT effects of pitolisant and increase the risk of cardiac arrhythmia.
Prevention or management:	Avoid the use of pitolisant in combination with other drugs known to prolong the QT interval.
Examples:	Class 1A antiarrhythmics: quinidine, procainamide, disopyramide Class 3 antiarrhythmics: amiodarone, sotalol Antipsychotics: ziprasidone, chlorpromazine, thioridazine Antibiotics: moxifloxacin
Sensitive CYP3A4 Substrates	
Clinical implication:	Pitolisant is a borderline/weak inducer of CYP3A4. Therefore, reduced effectiveness of sensitive CYP3A4 substrates may occur when used concomitantly with pitolisant.
Prevention or management:	The effectiveness of hormonal contraceptives (eg, ethinyl estradiol) may be reduced when used with pitolisant and effectiveness may be reduced for 21 days after discontinuation of therapy.
Examples:	midazolam, hormonal contraceptives, cyclosporine

- Drugs having no clinically important interactions with pitolisant:
  - A clinical study was conducted to evaluate the concomitant use of pitolisant with modafinil or sodium oxybate. This study demonstrated no clinically relevant effect of modafinil or sodium oxybate on the PK of pitolisant and no effect of pitolisant on the PK of modafinil or sodium oxybate.
  - A clinical study showed that strong CYP3A4 inhibitors (eg, ketoconazole, grapefruit juice) have no effect on the PK of pitolisant.

- Sodium oxybate/oxybate salts
  - *Alcohol, sedative hypnotics, and CNS depressants*
    - Sodium oxybate/oxybate salts are contraindicated in combination with alcohol or sedative hypnotics. Use of other CNS depressants may potentiate the CNS-depressant effects of sodium oxybate/oxybate salts.
  - *Divalproex sodium*
    - Concomitant use of sodium oxybate with divalproex sodium results in an increase in systemic exposure to GHB, which was shown to cause a greater impairment on some tests of attention and working memory in a clinical study. A similar increase in exposure is expected with concomitant use of oxybate salts and divalproex sodium; therefore, an initial dose reduction of oxybate salts is recommended when used concomitantly with divalproex sodium. Prescribers are advised to monitor patient response closely and adjust dose accordingly if concomitant use of oxybate salts and divalproex sodium is warranted.
- Solriamfetol
  - *MAOIs*
    - Solriamfetol should not be administered concomitantly with MAOIs or within 14 days after discontinuing MAOI treatment. Concomitant use of MAOIs and noradrenergic drugs may increase the risk of a hypertensive reaction. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure.
  - *Drugs that increase BP and/or heart rate*
    - Concomitant use of solriamfetol with other drugs that increase BP and/or heart rate has not been evaluated, and such combinations should be used with caution.
  - *Dopaminergic drugs*
    - Dopaminergic drugs that increase levels of dopamine or that bind directly to dopamine receptors might result in pharmacodynamic interactions with solriamfetol. Interactions with dopaminergic drugs have not been evaluated with solriamfetol. Caution should be used when concomitantly administering dopaminergic drugs with solriamfetol.

- **Risk Evaluation and Mitigation Strategy (REMS)**
  - Sodium oxybate/oxybate salts

- Sodium oxybate/oxybate salts are available only through a REMS program called the Xywav and Xyrem REMS program because of the risks of CNS depression and abuse and misuse.
- Notable requirements of the Xywav and Xyrem REMS program include:
  - Healthcare Providers who prescribe Xyrem and Xywav are specially certified.
  - Xywav and Xyrem will be dispensed only by the central pharmacy that is specially certified.
  - Xywav and Xyrem will be dispensed and shipped only to patients who are enrolled in the Xywav and Xyrem REMS Program with documentation of safe use.

DOSAGE AND ADMINISTRATION

- **Armodafinil**
  - Narcolepsy/OSA
    - The recommended dosage of armodafinil for patients with OSA or narcolepsy is 150 mg to 250 mg taken orally once a day as a single dose in the morning.
    - In patients with OSA, doses up to 250 mg/day, given as a single dose, have been well tolerated, but there is no consistent evidence that these doses confer additional benefit beyond that of the 150 mg/day dose.
  - SWD
    - The recommended dosage of armodafinil for patients with SWD is 150 mg taken orally once a day as a single dose approximately 1 hour prior to the start of their work shift.
  - Hepatic impairment
    - The dosage of armodafinil should be reduced in patients with severe hepatic impairment.
- **Modafinil**
  - Narcolepsy/OSA
    - The recommended dosage of modafinil for patients with narcolepsy or OSA is 200 mg taken orally once a day as a single dose in the morning.
  - SWD
    - Doses up to 400 mg/day, given as a single dose, have been well tolerated, but there is no consistent evidence that this dose confers additional benefit beyond that of the 200 mg/day dose.
  - Hepatic impairment
    - In patients with severe hepatic impairment, the dose of modafinil should be reduced to one-half of that recommended for patients with normal hepatic function.
- **Pitolisant**
  - Recommended dosage
    - The recommended dosage of pitolisant is 17.8 to 35.6 mg administered orally once daily in the morning upon wakening. The dose should be titrated as follows:
      - Week 1: Initiate with a dosage of 8.9 mg (two 4.45 mg tablets) once daily
      - Week 2: Increase dosage to 17.8 mg (one 17.8 mg tablet) once daily
      - Week 3: May increase to the maximum recommended dosage of 35.6 mg (two 17.8 mg tablets) once daily
    - Dose may be adjusted based on tolerability.
    - If a dose is missed, patients should take the next dose the following day in the morning upon wakening.
    - It may take up to 8 weeks for some patients to achieve a clinical response.
  - Hepatic impairment
    - In patients with moderate hepatic impairment, pitolisant should be initiated at 8.9 mg once daily and increased after 14 days to a maximum dosage of 17.8 mg once daily.
    - Pitolisant is contraindicated in patients with severe hepatic impairment. Pitolisant has not been studied in patients with severe hepatic impairment.
  - Renal impairment and ESRD
    - In patients with moderate and severe renal impairment, pitolisant should be initiated at 8.9 mg once daily and increased after 7 days to a maximum dosage of 17.8 mg once daily.
    - Pitolisant is not recommended in patients with ESRD.
  - Concomitant use with strong CYP2D6 inhibitors and strong CYP3A4 inducers
    - Coadministration with strong CYP2D6 inhibitors
      - For patients receiving strong CYP2D6 inhibitors, pitolisant should be initiated at 8.9 mg once daily and increased after 7 days to a maximum dosage of 17.8 mg once daily.
      - For patients on a stable dose of pitolisant, the pitolisant dose should be reduced by half upon initiating strong CYP2D6 inhibitors.
    - Coadministration with strong CYP3A4 inducers
      - Concomitant use of pitolisant with strong CYP3A4 inducers decreases pitolisant exposure by 50%.
      - Patients should be assessed for loss of efficacy after initiation of a strong CYP3A4 inducer.

- For patients stable on pitolisant 8.9 mg or 17.8 mg once daily, the dose of pitolisant should be increased to double the original daily dose (ie, 17.8 mg or 35.6 mg, respectively) over 7 days.
- If concomitant dosing of a strong CYP3A4 inducer is discontinued, the pitolisant dosage should be decreased by half.

○ Patients who are known CYP2D6 poor metabolizers
- In patients known to be poor CYP2D6 metabolizers, pitolisant should be initiated at 8.9 mg once daily and titrated to a maximum dose of 17.8 mg once daily after 7 days.

• **Sodium oxybate/oxybate salts**

○ Adult dosing
- The recommended starting dose of sodium oxybate/oxybate salts is 4.5 g per night administered orally, divided into 2 doses: 2.25 g at bedtime and 2.25 g taken 2.5 to 4 hours later (see Table 15). The dosage should be increased by 1.5 g per night at weekly intervals (additional 0.75 g at bedtime and 0.75 g taken 2.5 to 4 hours later) to the effective dosage range of 6 g to 9 g per night orally. Doses higher than 9 g per night have not been studied and should not ordinarily be administered.

Table 15. Recommended adult sodium oxybate/oxybate salts dose regimen

If a patient's total nightly dose is:	Take at bedtime:	Take 2.5 to 4 hours later:
4.5 g	2.25 g	2.25 g
6 g	3 g	3 g
7.5 g	3.75 g	3.75 g
9 g	4.5 g	4.5 g

○ Pediatric dosing
- Sodium oxybate/oxybate salts are administered orally twice nightly. The recommended starting pediatric dosage, titration regimen, and maximum total nightly dosage are based on patient weight, as specified in Table 16. The dosage may be gradually titrated based on efficacy and tolerability.

Table 16. Recommended pediatric sodium oxybate/oxybate salts dosage for patients ≥ 7 years of age*

Patient weight	Initial Dosage		Maximum Weekly Dosage Increase		Maximum Recommended Dosage	
	Take at bedtime:	Take 2.5 to 4 hours later:	Take at bedtime:	Take 2.5 to 4 hours later:	Take at bedtime:	Take 2.5 to 4 hours later:
< 20 kg†	There is insufficient information to provide specific dosing recommendations for patients who weigh < 20 kg.					
20 to < 30 kg	≤ 1 g	≤ 1 g	0.5 g	0.5 g	3 g	3 g
30 to < 45 kg	≤ 1.5 g	≤ 1.5 g	0.5 g	0.5 g	3.75 g	3.75 g
≥ 45 kg	≤ 2.25 g	≤ 2.25 g	0.75 g	0.75 g	4.5 g	4.5 g

*For patients who sleep > 8 hours per night, the first dose may be given at bedtime or after an initial period of sleep.
†In patients ≥ 7 years of age who weigh < 20 kg, a lower starting dosage, lower maximum weekly dosage increases, and lower total maximum nightly dosage should be considered.
Note: Unequal dosages may be required for some patients to achieve optimal treatment.

○ Important administration instructions
- The first dose of sodium oxybate/oxybate salts should be taken at least 2 hours after eating.
- Both doses should be prepared prior to bedtime. Prior to ingestion, each dose should be diluted with approximately one-fourth cup (approximately 60 mL) of water in the empty pharmacy containers provided. Patients should take both doses while in bed and lie down immediately after dosing as oxybate/oxybate salts may cause them to fall asleep abruptly without first feeling drowsy. Patients will often fall asleep within 5 minutes of taking oxybate/oxybate salts, and will usually fall asleep within 15 minutes, though the time it takes any individual patient to fall asleep may vary from night to night. Patients should remain in bed following ingestion of the first and second doses, and should not take the second dose until 2.5 to 4 hours after the first dose. Patients may need to set an alarm to awaken for the second dose. Rarely, patients may take up to 2 hours to fall asleep.
- If the second dose is missed, that dose should be skipped and the drug should not be taken again until the next night. Both doses should never be taken at one time.

○ Patients transitioning from sodium oxybate to oxybate salts
- On the first night of dosing with oxybate salts, treatment should be initiated at the same dose (g for g) and regimen as sodium oxybate. The dose should be titrated as needed based on efficacy and tolerability.

○ Hepatic impairment

- The recommended starting dosage of sodium oxybate/oxybate salts in patients with hepatic impairment is one-half of the original dosage per night administered orally, divided into 2 doses.

○ Dose adjustment with co-administration of divalproex sodium
- When initiating divalproex sodium in patients receiving a stable dosage of sodium oxybate/oxybate salts, a reduction of the sodium oxybate/oxybate salts dosage by at least 20% is recommended with initial concomitant use. When initiating sodium oxybate/oxybate salts in patients already taking divalproex sodium, a lower starting dosage of sodium oxybate/oxybate salts is recommended. Subsequently, the dosage can be adjusted based on individual clinical response and tolerability.

• **Solriamfetol**
○ Solriamfetol should be administered upon awakening with or without food. Patients should avoid taking solriamfetol within 9 hours of planned bedtime because of the potential to interfere with sleep if taken too late in the day.
○ Solriamfetol 75 mg tablets are functionally scored tablets that can be split in half (37.5 mg) at the score line.
○ Narcolepsy
- Solriamfetol should be initiated at 75 mg once daily in adults with narcolepsy. The recommended dose range is 75 to 150 mg once daily. Based on efficacy and tolerability, the dosage of solriamfetol may be doubled at intervals of at least 3 days. The maximum recommended dose is 150 mg once daily. Dosages above 150 mg daily do not confer increased effectiveness sufficient to outweigh dose-related AEs.

○ OSA
- Solriamfetol should be initiated at 37.5 mg once daily in adults with OSA. The recommended dosage range is 37.5 to 150 mg once daily. Based on efficacy and tolerability, the dosage of solriamfetol may be doubled at intervals of at least 3 days. The maximum recommended dosage is 150 mg once daily. Dosages above 150 mg daily do not confer increased effectiveness sufficient to outweigh dose-related AEs.

○ Renal impairment
- Moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 59 mL/min/1.73 m^2): dosing should be initiated at 37.5 mg once daily. Based on efficacy and tolerability, the dose may be increased to a maximum of 75 mg once daily after at least 7 days.
- Severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2): a dose of 37.5 mg should be administered daily. The maximum recommended dose is 37.5 mg.
- ESRD (eGFR < 15 mL/min/1.73 m^2): solriamfetol is not recommended for use in patients with ESRD.

SPECIFIC POPULATIONS

• **Geriatrics**
○ Armodafinil
- In elderly patients, elimination of armodafinil and its metabolites may be reduced as a consequence of aging. Therefore, consideration should be given to the use of lower doses and close monitoring in this population.

○ Modafinil
- In clinical trials, experience in a limited number of modafinil-treated patients who were > 65 years of age showed an incidence of AEs similar to other age groups. In elderly patients, elimination of modafinil and its metabolites may be reduced as a consequence of aging. Therefore, consideration should be given to the use of lower doses and close monitoring in this population.

○ Pitolisant
- Limited PK data are available in healthy elderly patients. A PK study that compared 12 elderly patients (68 to 82 years of age) to 12 healthy adults (18 to 45 years of age) did not reveal any significant differences in drug exposure.
- Of the total number of patients with narcolepsy in clinical studies of pitolisant, 14 patients (5%) were ≥ 65 years of age. No overall differences in safety or effectiveness were observed between these patients and younger patients in these clinical trials, but greater sensitivity of some older individuals cannot be ruled out.

○ Sodium oxybate/oxybate salts
- Clinical studies of sodium oxybate/oxybate salts in patients with narcolepsy did not include sufficient numbers of patients ≥ 65 years of age to determine whether they respond differently from younger patients. In controlled trials of sodium oxybate in another population, 39 (5%) of 874 patients were ≥ 65 years of age. Discontinuations of treatment due to AEs were increased in the elderly compared to younger adults (20.5% vs 18.9%). Frequency of headaches was markedly increased in the elderly (39% vs 19%). The most common AEs were similar in both age categories.

○ Solriamfetol
- Of the total number of patients in the narcolepsy and OSA clinical studies treated with solriamfetol, 13% (123/930) were 65 years of age or over.
- No clinically meaningful differences in safety or efficacy were observed between elderly and younger patients.

- Solriamfetol is predominantly eliminated by the kidney. Because elderly patients are more likely to have decreased renal function, dosing may need to be adjusted based on eGFR in these patients. Consideration should be given to the use of lower doses and close monitoring in this population.

- **Pediatrics**
  - Armodafinil
    - Safety and efficacy in pediatric patients have not been established.
  - Modafinil
    - Safety and efficacy in pediatric patients have not been established.
  - Pitolisant
    - The safety and effectiveness of pitolisant in pediatric patients have not been established.
    - Limited PK data from 24 pediatric patients with narcolepsy (7 to < 18 years of age) receiving a single dose of pitolisant suggested that pediatric patients have higher exposure to pitolisant than adults. The exposure (C_{max} and AUC) of pitolisant was 2-fold higher in pediatric patients 12 to < 18 years and 3-fold higher in pediatric patients 7 to < 12 years compared to adults.
  - Sodium oxybate/oxybate salts
    - The safety and effectiveness of sodium oxybate in the treatment of cataplexy or EDS in pediatric patients ≥ 7 years of age with narcolepsy have been established in a DB, PC, RW study.
    - The safety and effectiveness of oxybate salts for the treatment of cataplexy or EDS in pediatric patients ≥ 7 years of age with narcolepsy have been established. Oxybate salts has not been studied in a pediatric clinical trial. Use of oxybate salts in pediatric patients ≥ 7 years of age with narcolepsy is supported by evidence from the RW study of sodium oxybate, a study in adults showing a treatment effect of oxybate salts similar to that observed with sodium oxybate, PK data of sodium oxybate from adult and pediatric patients, and PK data of oxybate salts from healthy adult volunteers.
    - Safety and effectiveness of sodium oxybate and oxybate salts in pediatric patients < 7 years of age have not been established.
  - Solriamfetol
    - Safety and efficacy in pediatric patients have not been established. Clinical studies of solriamfetol in pediatric patients have not been conducted.
- **Renal dysfunction**
  - Pitolisant
    - The PK of pitolisant in patients with ESRD (eGFR of < 15 mL/minute/1.73 m^2) is unknown.
    - See dosing section above.
  - Solriamfetol
    - See dosing section above.
- **Hepatic dysfunction**
  - Armodafinil
    - See dosing section above.
  - Modafinil
    - See dosing section above.
  - Pitolisant
    - Pitolisant is contraindicated in patients with severe hepatic impairment (Child Pugh C) as it has not been studied in this population. Pitolisant is extensively metabolized by the liver and there is a significant increase in pitolisant exposure in patients with moderate hepatic impairment.
    - See dosing section above for patients with moderate hepatic impairment.
    - Patients with mild hepatic impairment (Child Pugh A) should be monitored. No dosage adjustment of pitolisant is recommended in patients with mild hepatic impairment.
  - Sodium oxybate/oxybate salts
    - See dosing section above.
- **Pregnancy and nursing**
  - Armodafinil
    - There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to armodafinil during pregnancy. Healthcare providers are encouraged to register pregnant patients, or pregnant women may enroll themselves in the registry by calling 1-866-404-4106.
    - Limited available data on armodafinil use in pregnant women are insufficient to inform a drug associated risk of adverse pregnancy outcomes.
    - There are no data on the presence of armodafinil or its metabolites in human milk, the effects on the breastfed infant, or the effect of this drug on milk production. Modafinil was present in rat milk when animals were dosed during the lactation period. The developmental and health benefits of breastfeeding should be considered along

with the mother's clinical need for armodafinil and any potential AEs on the breastfed child from armodafinil or from the underlying maternal condition.

- Modafinil
  - A pregnancy registry has been established to collect information on the pregnancy outcomes of women exposed to modafinil. Healthcare providers are encouraged to register pregnant patients, or pregnant women may enroll themselves in the registry by calling 1-866-404-4106.
  - There are no adequate and well-controlled studies of modafinil in pregnant women.
  - It is not known whether modafinil or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when modafinil is administered to a nursing woman.
  - A pregnancy registry reported an elevated rate of major congenital anomalies (17%) and cardiac anomalies (4%) among women in the U.S. exposed to modafinil and/or armodafinil (some took additional drugs). Based on these data, Health Canada issued a warning that modafinil is contraindicated in women who are pregnant or may become pregnant in June 2019 (*Eichler et al 2019*).
- Pitolisant
  - There is a pregnancy exposure registry that monitors pregnancy outcomes in women who are exposed to pitolisant during pregnancy. Patients should be encouraged to enroll in the pitolisant pregnancy registry if they become pregnant. To enroll or obtain information from the registry, patients can call 1-800-833-7460.
  - Available case reports from clinical trials and postmarketing reports with pitolisant use in pregnant women have not determined a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes.
  - There are no data on the presence of pitolisant in human milk, the effects on the breastfed infant, or the effect of this drug on milk production.
  - Pitolisant is present in the milk of lactating rats. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for pitolisant and any potential AEs on the breastfed child from pitolisant or from the underlying maternal condition.
- Sodium oxybate/oxybate salts
  - There are no adequate data on the developmental risk associated with the use of sodium oxybate or oxybate salts in pregnant women.
  - GHB is excreted in human milk after oral administration of sodium oxybate. There is insufficient information on the risk to a breastfed infant, and there is insufficient information on milk production in nursing mothers. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for sodium oxybate/oxybate salts and any potential AEs on the breastfed infant from sodium oxybate or from the underlying maternal condition.
- Solriamfetol
  - Pregnancy Exposure Registry There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to solriamfetol during pregnancy. Healthcare providers are encouraged to register pregnant patients, or pregnant women may enroll themselves in the registry by calling 1-877-283-6220 or contacting the company at *www.SunosiPregnancyRegistry.com*.
  - Available data from case reports are not sufficient to determine drug-associated risks of major birth defects, miscarriage, or adverse maternal or fetal outcomes.
  - There are no data available on the presence of solriamfetol or its metabolites in human milk, the effects on the breastfed infant, or the effect of this drug on milk production.
  - Solriamfetol is present in rat milk. When a drug is present in animal milk, it is likely that the drug will be present in human milk. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for solriamfetol and any potential AEs on the breastfed child from solriamfetol or from the underlying maternal condition.

APPENDICES

Appendix A. Definitions of terms (*Freedman 2019*)

- Epoch: An epoch is a standard 30-second interval of a PSG to which a sleep stage is assigned. In special situations, an epoch can be longer or shorter.
- Sleep onset: The recommended definition for sleep onset for the MWT is 3 consecutive epochs of stage 1 sleep or 1 epoch of any other stage of sleep.
- Sleep latency: Sleep latency is the duration from lights out to the onset of sleep.
- Mean sleep latency: The mean sleep latency is the average of the sleep latencies determined during a test.

Appendix B. Multiple Sleep Latency Test (MSLT) (*American Sleep Association Web site, Thorpy 1992*)

- The MSLT is a diagnostic tool that measures the time it takes an individual to fall asleep in ideal quiet conditions during the day. It objectively measures daytime sleepiness. Colloquially known as the daytime nap study, the MSLT is also a standard tool used to diagnose idiopathic hypersomnia and narcolepsy.
- The MSLT is based on the fact that the more tired an individual is, the faster they will fall asleep. In addition to assessing for narcolepsy and idiopathic hypersomnia, the MSLT is used to evaluate insomnia, OSA, circadian rhythm sleep disorders, and response to treatment following effective therapy for disorders that cause sleepiness.
- For correct interpretation, the MSLT must be performed following an all-night PSG.
- The MSLT consists of 5 nap opportunities to determine both severity of sleepiness and presence of 2 or more sleep onset REM periods for the diagnosis of narcolepsy. A shorter 4-nap test may be performed for determination of excessive sleepiness, but this test is not reliable for the diagnosis of narcolepsy unless at least 2 sleep onset REM periods (SOREMPs) have occurred.
- The absence of sleep on any nap opportunity is recorded as a sleep latency of 20 minutes.
- Mean sleep latency times (min) are interpreted as follows:
  - 0 to 5: severe sleepiness
  - 5 to 10: moderate sleepiness
  - 10 to 15: mild sleepiness

Appendix C. Maintenance of Wakefulness Test (MWT) (*Freedman 2019*)

- The MWT objectively measures the ability of an individual to remain awake for a defined period of time. It is based on the premise that individuals with a greater degree of sleepiness are less likely to remain awake than individuals with less sleepiness.
- The MWT is primarily used in a research setting to assess an intervention's ability to improve alertness. Some commercial driving companies utilize the MWT to assess a driver's ability to operate a vehicle safely, although the utility of the MWT in clinical practice is limited by the test's inability to accurately predict safety in real world settings.
- MWT Protocol:
  - The MWT should be performed following a standard protocol. Using a protocol minimizes the variables that can impact sleep latency, the test's primary measure. Several acceptable protocols exist including the following, which was endorsed by a task force from the AASM:
    - Patients should maintain their normal routine prior to the test. Upon arrival, they should be questioned to determine whether their sleep prior to the test was adequate in quality and quantity, and whether they feel alert. The MWT should be delayed if the patient reports suboptimal sleep or not feeling alert. A PSG on the prior night is not necessary. Urine drug testing may be indicated to ensure that the result is not influenced by substances other than prescribed medications and is usually performed on the morning of the MWT or as directed by the sleep clinician.
    - The MWT begins 1.5 to 3 hours after the patient's usual wake-up time. The patient is placed in a room with little or no external light. The only light source should be dim, slightly behind the patient's head, and just out of the patient's field of vision. The room temperature is based on the patient's comfort level. The patient sits upright in bed, with their back and head supported, and is instructed to try to stay awake as long as possible. Monitoring includes electroencephalography (EEG), electrooculography, mental or submental electromyography, and electrocardiography.
    - A session is ended after unequivocal sleep, or after 40 minutes if sleep does not occur. Sleep is considered unequivocal after 3 consecutive epochs of stage 1 sleep or 1 epoch of any other stage of sleep. For each session, the sleep latency is recorded. It is documented as being 40 minutes if the patient does not fall asleep.
    - This is repeated every 2 hours, until the patient has completed 4 sessions.
- Interpretation of MWT:
  - The primary measure from the MWT is the mean sleep latency. There are few data regarding what constitutes a normal mean sleep latency, as measured by the MWT. Among healthy individuals who complete the 4 session, 40-minute protocol described above, the mean sleep latency is approximately 30 minutes, with > 97% of individuals having a mean sleep latency ≥ 8 minutes. As a result, a mean sleep latency < 8 minutes is generally considered abnormal. Staying awake for at least 40 minutes during all 4 sessions is strong objective evidence that an individual can stay awake. A mean sleep latency between 8 and 40 minutes has uncertain significance.

Appendix D. Epworth Sleepiness Scale (ESS) (*Johns 1991*)

- The ESS is a self-administered questionnaire that provides a measurement of an individual's general level of daytime sleepiness.
- Patients are asked to rate on a scale of 0 to 3 how likely they would be to doze off or fall asleep in 8 situations that involve low levels of stimulation, relative immobility, and relaxation based on their usual way of life in recent times. The following question is rated for each situation using a scale of 0 to 3 as defined below:

- How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently, try to work out how they would have affected you. Use the following scale to choose the most appropriate number for each situation:
  - 0 = would never doze
  - 1 = slight chance of dozing
  - 2 = moderate chance of dozing
  - 3 = high chance of dozing
- The 8 situations include:
  - Sitting and reading
  - Watching TV
  - Sitting, inactive in a public place (eg, a theater or a meeting)
  - As a passenger in a car for an hour without a break
  - Lying down to rest in the afternoon when circumstances permit
  - Sitting and talking to someone
  - Sitting quietly after a lunch without alcohol
  - *In a car, while stopped for a few minutes in the traffic*
- Interpretation of ESS scoring (range, 1 to 24):
  - 1 to 6 points: normal sleep
  - 7 to 8 points: average sleepiness
  - 9 to 24 points: abnormal (possibly pathologic) sleepiness

Appendix E. Karolinska Sleepiness Scale (KSS) (*Akerstedt & Gillberg 1990*)

- The KSS is a 9-point Likert scale often used when conducting studies involving self-reported, subjective assessment of an individual's level of drowsiness at the time. The KSS scores are defined as follows:
  - 1 = extremely alert
  - 3 = alert
  - 5 = neither alert nor sleepy
  - 7 = sleepy, no difficulty remaining awake
  - 9 = extremely sleepy, fighting sleep
    - The steps in between have a scale value but no verbal label.

Appendix F. Stanford Sleepiness Scale (SSS) (*upenn.edu Web site*)

- The SSS is a subjective measure of sleepiness, frequently used for both research and clinical purposes. Whereas an instrument like the ESS examines general experiences of sleepiness over the course of an entire day, the SSS evaluates sleepiness at specific moments in time. Consisting of only 1 item, the scale requires respondents to select 1 of 7 statements best representing their level of perceived sleepiness. As a single-item measure, the scale is best suited for repeated use over the course of a research study or treatment intervention. The rating scale is as follows:
  - 1 = feeling active, vital, alert, or wide awake
  - 2 = functioning at high levels, but not at peak; able to concentrate
  - 3 = awake, but relaxed; responsive but not fully alert
  - 4 = somewhat foggy, let down
  - 5 = sleepy, woozy, fighting sleep; prefer to lie down
  - 6 = no longer fighting sleep, sleep onset soon; having dream-like thoughts
  - 7 = asleep

Appendix G. Sustained Attention to Response Task (SART) (*Fronczek et al 2006*)

- A number from 1 to 9 is shown to the patient 225 times in white on a black computer screen over a 4.3-minute period in a quiet room with dimmed lights. Each of the 9 numbers is shown 25 times in random order. The font size is chosen at random from 26, 28, 36, or 72 points. The numbers are presented in a predetermined and quasirandom way so that identical numbers were not clustered. Each number is presented for 250 milliseconds, followed by a blank screen for 900 milliseconds. Patients have to respond to the appearance of each number by pressing a small button, except when the number is a 3. Patients have to press the button before the next number appears and are instructed that accuracy is more important than speed. A complete SART takes 4 minutes and 20 seconds to perform. The SART error score consists of the total number of errors, expressed as the sum of the times a key was pressed when a 3 was presented, and the times when no key was pressed when it should have been.

Appendix H. AASM grading of evidence (*Morgenthaler et al 2007a*)

Classification of evidence

Evidence levels	Study design

I	Randomized, well-designed trials with low alpha and beta error,* or meta-analyses of RCTs with homogeneity of results
II	Randomized trials with high alpha and beta error, methodologic problems, or high-quality cohort studies*
III	Nonrandomized concurrently controlled studies (case-control studies)
IV	Case-control or cohort studies with methodological problems, or case series
V	Expert opinion, or studies based on physiology or bench research

*Alpha (type I error) refers to the probability that the null hypothesis is rejected when in fact it is true (generally acceptable at 5% or less, or $p < 0.05$). Beta (Type II error) refers to the probability that the null hypothesis is mistakenly accepted when in fact it is false (generally, trials accept a beta error of 0.20). The estimation of Type II error is generally the result of a power analysis. The power analysis takes into account the variability and the effect size to determine if sample size is adequate to find a difference in means when it is present (power generally acceptable at 80 to 90%).

Levels of recommendation

Term	Definition
Standard	This is a generally accepted patient-care strategy that reflects a high degree of clinical certainty. The term standard generally implies the use of level 1 evidence, which directly addresses the clinical issue, or overwhelming level 2 evidence.
Guideline	This is a patient-care strategy that reflects a moderate degree of clinical certainty. The term guideline implies the use of level 2 evidence or a consensus of level 3 evidence.
Option	This is a patient-care strategy that reflects uncertain clinical use. The term option implies either inconclusive or conflicting evidence or conflicting expert opinion.

Appendix I. EAN grading of evidence (*Brainin et al 2004*)

Evidence classification scheme for a therapeutic intervention

Evidence levels	Definition
Class I	An adequately powered prospective, randomized, controlled clinical trial with masked outcome assessment in a representative population or an adequately powered systematic review of prospective randomized controlled clinical trials with masked outcome assessment in representative populations. The following are required: (a) randomization concealment (b) primary outcome(s) is/are clearly defined (c) exclusion/inclusion criteria are clearly defined (d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias (e) relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences
Class II	Prospective matched-group cohort study in a representative population with masked outcome assessment that meets a through e above or an RCT in a representative population that lacks 1 criteria (a) through (e)
Class III	All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment
Class IV	Evidence from uncontrolled studies, case series, case reports, or expert opinion

Evidence classification scheme for a diagnostic measure

Evidence levels	Definition
Level A	Established as effective, ineffective, or harmful) requires at least 1 convincing class I study or at least 2 consistent, convincing class II studies
Level B	Probably effective, ineffective, or harmful) requires at least 1 convincing class II study or overwhelming class III evidence
Level C	Possibly effective, ineffective, or harmful) rating requires at least 2 convincing class III studies

Appendix J. Micromedex recommendation, efficacy, and evidence ratings (*Micromedex Web site 2019*)

Strength of recommendation

Class I	Recommended	The given test or treatment has been proven to be useful, and should be performed or administered
Class IIa	Recommended in most cases	The given test, or treatment is generally considered to be useful, and is indicated in most cases.
Class IIb	Recommended in some cases	The given test, or treatment may be useful, and is indicated in some, but not most, cases.
Class III	Not recommended	The given test, or treatment is not useful, and should be avoided.
Class indeterminate	Evidence inconclusive	

Strength of evidence	
Category A	Category A evidence is based on data derived from: Meta-analyses of RCTs with homogeneity with regard to the directions and degrees of results between individual studies. Multiple, well-done randomized clinical trials involving large numbers of patients.
Category B	Category B evidence is based on data derived from: Meta-analyses of RCTs with conflicting conclusions with regard to the directions and degrees of results between individual studies. RCTs that involved small numbers of patients or had significant methodological flaws (eg, bias, drop-out rate, flawed analysis, etc.). Nonrandomized studies (eg, cohort studies, case-control studies, observational studies).
Category C	Category C evidence is based on data derived from: Expert opinion or consensus, case reports or case series.
No evidence	

Efficacy		
Class I	Effective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is effective.
Class IIa	Evidence favors efficacy	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion favors efficacy.
Class IIb	Evidence is inconclusive	Evidence and/or expert opinion is conflicting as to whether a given drug treatment for a specific indication is effective, but the weight of evidence and/or expert opinion argues against efficacy.
Class III	Ineffective	Evidence and/or expert opinion suggests that a given drug treatment for a specific indication is ineffective.

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Publication date: 12/2/2020

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 2019, asthma affected an estimated 20 million adults and 5.1 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] 2021, 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] 2021*).
  - Control medications include:
    - Corticosteroids (inhaled corticosteroids [ICSs], or oral corticosteroids for severe exacerbations)
    - Long-acting beta$_2$-agonists (LABAs)
    - Leukotriene receptor antagonists (LTRAs) in select patients
    - Methylxanthines (ie, theophylline) in select patients
    - 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 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 for relief of acute symptoms and if needed before exercise
    - 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 2021, Fasenra 2021, Nucala 2020*) or with oral corticosteroid dependent asthma (*Dupixent prescribing information 2021*). Additionally, tiotropium, long used for COPD, is FDA-approved for the maintenance treatment of asthma (*Spiriva Respimat prescribing information 2020*).
  - ICSs are the most effective and most commonly recommended long-term control medications used for the treatment of asthma. The updated 2021 GINA Report on Global Strategy for Asthma Management and Prevention recommends initial treatment based on a patient's presenting symptoms. The preferred track for Step 1 and Step 2 therapy in adults and adolescents is low dose combination ICS-formoterol as needed. (*GINA 2021*).
  - LABAs should not be used as monotherapy for the management of asthma due to an increased risk for serious adverse events, including death; however, they are part of combination ICS-formoterol therapy and can be used as adjunctive therapy in patients who are not adequately controlled with an ICS alone (*GINA 2021*).
  - The preferred reliever medication recommended by GINA is low dose ICS-formoterol. SABA-only treatment is not recommended for the treatment of asthma in adults or adolescents. Children can be managed with as needed SABA or ICS-formoterol. (*GINA 2021*).
  - 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 but

are not recommended. An additional controller option is LTRAs. Add-on options for severe asthma include tiotropium, low dose macrolides, and biologic agents for severe allergic or severe Type 2 asthma (*GINA 2021*).

- 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] 2021*).
  - COPD affects 6.4% of the U.S. population and is a major contributor to mortality from chronic lower respiratory diseases, the third leading cause of death in the U.S. (*CDC 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 2021*).
  - 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 2021*).
  - Patients with COPD may experience exacerbations, which are periods of acute worsening of respiratory symptoms (*GOLD 2021*).
  - 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 clinical trial evidence that COPD medications modify the long-term decline in lung function characteristics of COPD (*GOLD 2021*).
  - Pharmacologic options for COPD treatment comprise several classes, including beta$_2$-agonists, anticholinergics, methylxanthines, various combination products (including bronchodilators with ICSs), 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 2021*).
  - 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 2021*).
  - 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. Arcapta Neohaler (indacaterol) was previously available but was discontinued in March 2020 (*FDA Drug Shortages 2020*).
  - 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)	✔
metaproterenol syrup	✔
terbutaline, oral tablets and injection	✔
Long-acting beta$_2$-agonists (LABAs) (inhaled)	
Brovana (arformoterol) solution for nebulization	✔

Drug	Generic Availability
Perforomist (formoterol) solution for nebulization‡	✔
Serevent Diskus (salmeterol) inhalation powder	-
Striverdi Respimat (olodaterol) inhalation spray	-

Abbreviation: HFA = hydrofluoroalkane
* AB-rated generics have been approved by the FDA for Proventil HFA and ProAir HFA, but no A-rated generics are approved for Ventolin HFA. Authorized generics are available for these products. 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.
‡ Formoterol was previously available as a dry powder inhaler (Foradil Aerolizer); however, this formulation is no longer marketed.

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

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			✔	
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 2020, albuterol tablets 2020, albuterol extended-release tablets 2015, Brovana 2019, metaproterenol syrup 2019, Perforomist 2019, ProAir HFA 2020, ProAir Digihaler 2020, ProAir RespiClick 2021, Proventil HFA 2018, Serevent Diskus 2020, Striverdi Respimat 2020, terbutaline injection 2011, terbutaline tablets 2018, Ventolin HFA 2021, 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 2020*).

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*).
- 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 versus 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 versus 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}]) versus 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 [no longer available]) 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.

- A 2020 focused update of the 2007 NAEPP guideline provided updated recommendations on the use of intermittent ICSs and the use of LAMAs as add-on therapy (*Cloutier et al 2020*). The update did not address use of ICS-formoterol as an option for intermittent asthma. For mild, persistent asthma, the use of as needed concomitant ICS and SABA was added as an alternative to daily low-dose ICS with as needed SABA for management of mild, persistent asthma. Additionally, ICS-formoterol in a single inhaler used as both a daily controller and reliever therapy in moderate to severe persistent asthma was recommended over the use of a higher-dose ICS-LABA therapy with a SABA as needed. Finally, the addition of a LAMA can be considered for patients who have uncontrolled, persistent asthma despite ICS-LABA therapy.

- The 2021 GINA report also provides a stepwise approach to asthma management. Treatment recommendations are based on 2 tracks stratified by the choice of reliever. Track 1 includes ICS-formoterol as the reliever, and it is the preferred approach for most patients because it reduces the risk of severe exacerbations. Track 2 uses a SABA as the reliever. Treatment in adults and adolescents with a SABA only is not recommended. For Step 1 and 2 therapy, the preferred (track 1) approach is low dose ICS-formoterol as needed for symptom relief or if needed for exercise for patients with mild asthma. For Step 3, the preferred treatment is low dose ICS-formoterol as both maintenance and reliever therapy. Preferred therapy for Step 4 is a medium dose ICS-formoterol with as needed low dose ICS-formoterol as the reliever therapy. For patients with persistent symptoms or exacerbations despite Step 4 therapy, referral to a specialist with expertise in severe asthma management is recommended. Treatment options may include any of the following options: high dose ICS-LABA therapy, add-on LAMA (tiotropium or triple combination [ICS/LABA/LAMA] inhaler), azithromycin, low-dose oral corticosteroids, and biologic agents for severe allergic or severe Type 2 asthma (*GINA 2021*).
  - The 2021 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 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. Vaccination for COVID-19 is recommended for people with asthma (*GINA 2021*).
- Recommendations have also been made for stepping down therapy among patients with asthma that has been well-controlled for an extended period of time. Reasons for stepping down therapy include reducing excess drug exposure (and potential adverse effects), improving adherence by simplifying a treatment regimen, and reducing cost (*Chipps et al 2019, GINA 2021*). Prior to stepping down therapy, patients need to be assessed for risk of asthma exacerbation, lung function, symptom control, and adherence to current therapy. Recommendations for step-to-step reductions include decreasing dose or frequency of ICS with concurrent use of LABA, switching to an oral agent (ie, an LTRA such as montelukast), or use of ICS-formoterol as needed, depending on the current step of therapy. During step-down therapy, patients need to be evaluated for asthma symptoms, use of rescue medications, and lung function.
- 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 2021 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. Historically, "asthma-COPD overlap" was addressed, but they are now recognized as separate unique disease states with some similar signs and symptoms. Key recommendations from the GOLD guidelines are as follows (*GOLD 2021*):
  - 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 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.

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

- American Thoracic Society clinical practice guidelines recommend the following pharmacologic treatment for patients with COPD (Strong to conditional Strength of Recommendation/moderate Level of Evidence) (*Nici et al 2020*):
  - Those who complain of dyspnea or exercise intolerance: LAMA/LABA combination therapy is recommended over LABA or LAMA monotherapy.
  - Those who complain of dyspnea or exercise intolerance despite dual therapy with LAMA/LABA: use of triple therapy with LAMA/LABA/ICS is recommended over dual therapy with LAMA/LABA in those patients with a history of ≥ 1 exacerbation(s) in the past year requiring antibiotics or oral steroids or hospitalization.
  - Those receiving triple therapy (LAMA/LABA/ICS): it is suggested that the ICS can be withdrawn if the patient has had no exacerbations in the past year.

- No recommendation is made for or against ICS as an additive therapy to long-acting bronchodilators in patients with COPD and blood eosinophilia, except for those patients with a history of ≥ 1 exacerbation(s) in the past year requiring antibiotics or oral steroids or hospitalization, for whom ICS as an additive therapy is suggested.

- 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 do 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, and terbutaline injection 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	The ProAir Digihaler inhalation device is a digital dry powder inhaler with built-in sensors to detect when it is used and to measure inspiratory flow. It is designed to be used with a companion mobile app.
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.
formoterol	Solution for nebulization	Inhalation	Twice 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	

Generic Name	Available Formulations	Route	Usual Recommended Frequency	Comments
			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 olodaterol, which is 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. Use of maintenance and as-needed combination ICS-formoterol is the preferred treatment approach for adults and adolescents.
- 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. For most patients with COPD, LAMAs are recommended as they have a greater effect on exacerbation reduction compared to LABAs.
- 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 30, 2021

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

Therapeutic Class Overview
Bile Acid Sequestrants

INTRODUCTION

- Cholesterol is a fat-like substance (lipid) that is present in cell membranes and is a precursor of bile acids as well as steroid hormones. The bile acid sequestrants work to modify lipids by binding to bile acids in the intestine through anion exchange, which ultimately causes an interruption of their reabsorption. This reduction leads to feedback regulation to increase the conversion of cholesterol to bile acids. The major action of these agents is to reduce low density lipoprotein cholesterol (LDL-C) specifically. The overall reduction in cholesterol causes intrahepatic cholesterol to be reduced, which in turn enhances LDL receptor expression. The receptors then bind LDL-C from the plasma causing a further reduction in blood cholesterol. Through a different mechanism, the bile acid sequestrants cause a minimal increase in high density lipoprotein cholesterol (HDL-C). The actions of bile acid sequestrants also have the potential to increase serum triglycerides (TG) *(Grundy et al 2019)*.
- There are 3 available bile acid sequestrants: cholestyramine (Prevalite, Questran, and Questran Lite), colesevelam (Welchol), and colestipol (Colestid, Flavored Colestid). Cholestyramine and colestipol are both available as powders to be mixed with water or juice, and are typically administered once or twice daily with meals. Colestipol is also available as a tablet, and the powder formulation is available in 2 flavors: tasteless and orange flavored. Colesevelam is available as a powder and tablet and is typically administered once or twice daily.
- Bile acid sequestrants are generally recommended as optional secondary agents when other second-line agents cannot be used (eg, intolerance to ezetimibe or intolerance to higher doses of statins) for further reduction of LDL-C. When administered as monotherapy, reductions in LDL-C with bile acid sequestrants have ranged from 10% to 30%, depending on the dose administered *(Grundy et al 2019)*.
- In 2018, the American College of Cardiology (ACC)/American Heart Association (AHA) and a variety of other organizations released a 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 in a newly defined “very high risk of atherosclerotic cardiovascular disease [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 medication, such as ezetimibe or a proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor, to a maximally tolerated statin. Bile acid sequestrants may also be used in patients taking maximally tolerated statins (with or without ezetimibe), including patients with intermediate ASCVD risk in whom high-intensity statins are advisable but not accepted or tolerable. However, the clinical utility of bile acid sequestrants is limited due to the absence of ASCVD outcomes data when used in combination with statins. Bile acid sequestrants can increase TG levels and should therefore be avoided in patients with high TG levels or familial dysbetalipoproteinemia *(Grundy et al 2019)*.
- This review will focus on cholestyramine, colesevelam hydrochloride, and colestipol.
- Medispan class: Bile Acid Sequestrants

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Colestid (colestipol hydrochloride)	✔
Questran, Questran Lite†, Prevalite* (cholestyramine)	✔
Welchol (colesevelam hydrochloride)	✔ (tablet and powder for oral suspension only) ‡

* Prevalite is a branded generic of Questran/Questran Lite.

† Questran and Questran Lite were FDA-approved by a new drug application (NDA), but the products were discontinued by BMS in 2013. Par Pharmaceuticals markets both Questran and Questran Lite branded generics and cholestyramine and cholestyramine lite.

‡ The chewable bar formulation of Welchol was FDA-approved in April 2019, but is not available and is noted as discontinued by the FDA.

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 2. FDA Approved Indications

Indication	Cholestyramine	Colesevelam	Colestipol
Adjunctive therapy to diet for the reduction of elevated serum cholesterol in patients with primary hypercholesterolemia who do not respond adequately to diet	✔ *		✔ †
Adjunct to diet and exercise to reduce elevated LDL-C in adults with primary hyperlipidemia		✔	
Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM)		✔	
To reduce LDL-C levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia (HeFH) who are unable to reach LDL-C target levels despite an adequate trial of dietary therapy and lifestyle modification		✔	
Relief of pruritus associated with partial biliary obstruction‡	✔		

* May be useful to lower LDL-C levels in patients who also have hypertriglyceridemia, but it is not indicated where hypertriglyceridemia is the abnormality of most concern.
† For the reduction of elevated serum total cholesterol and LDL-C.
‡ Has been shown to have a variable effect on serum cholesterol in these patients. Patients with primary biliary cirrhosis may exhibit elevated cholesterol as part of their disease.

(Prescribing information: Colestid & Flavored Colestid granule 2018, Colestid tablets 2017, Prevalite 2020, Questran 2016, Welchol 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

- Clinical trial data consistently demonstrate the superiority of the bile acid sequestrants over placebo for the management of hyperlipidemia *(Bays et al 2006, Blankenhorn et al 1987, Brown et al 1990, Davidson et al 2001, Huijgen et al 2010, Hunninghake et al 2001, Insull et al 2001, Knapp et al 2001, Stein et al 2010, Rosenson et al 2006).*
- Clinical trial data demonstrate that the addition of a bile acid sequestrant to another lipid-lowering agent has the potential to produce further reductions in lipid levels compared to monotherapy with either of the agents *(Ballantyne et al 2004, Blankenhorn et al 1987, Brown et al 1990, Davidson et al 2001, Eriksson et al 1998, Huijgen et al 2010, Hunninghake et al 2001, Knapp et al 2001).*
- The Lipid Research Clinical Coronary Primary Prevention trial (LRC-CPPT) demonstrated that compared to placebo, treatment with cholestyramine reduced the risk of coronary heart disease death and/or nonfatal myocardial infarction by 19% ($p < 0.05$) in asymptomatic males with primary hypercholesterolemia *(LRC-CPPT 1984).*
- Several clinical trials have demonstrated the safety and efficacy of colesevelam as adjunct therapy in adults with T2DM. Compared to placebo, the addition of colesevelam resulted in modest, but statistically significant reductions in glycosylated hemoglobin (HbA1c) levels *(Bays et al 2008, Fonseca et al 2008, Goldberg et al 2008, Goldberg et al 2012, Goldfine et al 2010, Jialal et al 2009, Rigby et al 2010, Rosenstock et al 2010, Zieve et al 2007).* A meta-analysis of 17 trials evaluating colesevelam and colestimide (not available in the U.S.) estimated that addition of a bile acid sequestrant lowered HbA1c levels by a mean difference of −0.55% in patients with T2DM *(Hansen et al 2017).*

- One meta-analysis evaluated the effects of bile acid sequestrants (colesevelam, colestimide, and cholestyramine) on lipid and blood glucose profiles *(Mazidi et al 2017)*. Based on data from 15 clinical trials (as pooled estimates [weighted mean difference]), bile acid sequestrants were reported to increase serum TG levels by 0.54 mg/dL, with total cholesterol reduced by 1.18 mg/dL and LDL-C by 0.24 mg/dL vs placebo. The reduction in HbA1c was 0.83%.

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 2021, Cosentino et al 2020, Grundy et al 2019, Handelsman et al 2020, Knuuti et al 2020, Mach et al 2020, Newman et al 2020, Rosenzweig et al 2019*).
  - Statin intolerance: In patients with mild statin-associated adverse effects, rechallenge with a statin should be considered to achieve a maximal LDL-C lowering by using a 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 randomized controlled trial-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, colesevelam, bempedoic acid, or PCSK9 inhibitor should be considered. Ezetimibe can be used in combination with statins to further reduce both LDL-C and ASCVD risk (*Garber et al 2020, Handelsman et al 2020*).

- **American Heart Association (AHA)/American College of Cardiology (ACC): Guideline on the Management of Blood Cholesterol** *(Grundy et al 2019)*
  - Among lipid-lowering drugs, statins are the cornerstone of therapy, in addition to healthy lifestyle interventions.
  - Other LDL-lowering drugs include ezetimibe, bile acid sequestrants, and PCSK9 inhibitors.
    - Ezetimibe is the most commonly used non-statin agent. It lowers LDL-C levels by 13% to 20% and has a low incidence of adverse effects.
    - Bile acid sequestrants reduce LDL-C levels by 15% to 30% depending on the dose. Bile acid sequestrants are not absorbed and do not cause systemic adverse effects, but they are associated with gastrointestinal complaints (eg, constipation) and can cause severe hypertriglyceridemia when fasting TGs are ≥ 300 mg/dL.
    - PCSK9 inhibitors are powerful LDL-lowering drugs. They generally are well tolerated, but long-term safety remains to be proven.
  - When administered to patients with severe hypercholesterolemia who are taking maximally tolerated statins with or without ezetimibe, bile acid sequestrants have demonstrated LDL-C lowering efficacy. However, the clinical utility of bile acid sequestrants is limited by the absence of ASCVD outcomes data when used in combination with statins, as well as twice-daily dosing, high pill burden, the absence of well-tolerated generic formulations, drug interactions, and the potential for TG elevation. Nonetheless, in patients with very severe hypercholesterolemia, adding bile acid sequestrants to otherwise maximal cholesterol-lowering therapy in patients who are not eligible for a PCSK9 inhibitor may be considered.

- **American Heart Association (AHA): Cardiovascular Risk Reduction in High-Risk Pediatric Patients** *(de Ferranti et al 2019)*
  - Treatment for HeFH should include statins, a low-saturated-fat diet high in fiber, adequate physical activity, and a smoke-free environment.
  - If a 50% reduction of LDL-C is not achieved or if there are adverse effects to multiple statins (rare), then ezetimibe or a bile acid binding resin can be added as a second-line agent.

- **American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE): Consensus Statement on the Comprehensive T2DM Management Algorithm** *(Garber et al 2020)*

- For glycemic control, colesevelam is among the second-line agents that may be utilized after metformin. However, glucagon-like peptide-1 receptor agonists (GLP-1RAs), sodium-glucose cotransporter-2 inhibitors (SGLT2i), dipeptidyl-peptidase 4 inhibitors (DPP-4i), thiazolidinediones, and basal insulin are preferred over colesevelam in the suggested hierarchy of usage.
- Colesevelam lowers glucose modestly, does not cause hypoglycemia, and decreases LDL-C. A perceived modest efficacy for both HbA1c and LDL-C lowering as well as gastrointestinal intolerance (constipation and dyspepsia, which occurs in 10% of users), may contribute to limited use. In addition, colesevelam can increase TG levels in individuals with pre-existing TG elevations, but this is somewhat preventable by concomitant statin use.
- For T2DM patients with dyslipidemia, lifestyle modifications are followed by first-line therapy with statins. If the desirable LDL-C goal is not reached with a statin, second-line options to lower LDL-C include statin intensification or the addition of ezetimibe, a PCSK9 inhibitor, colesevelam, or niacin.

- **National Lipid Association (NLA) for Patient-Centered Management of Dyslipidemia Part 1** (*Jacobson et al 2015*)
  - The NLA guideline recommends non-statin drug therapy (cholesterol absorption inhibitors, bile acid sequestrants, fibric acids, long-chain omega-3 fatty acid concentrates, and nicotinic acid) may be considered for patients with contraindications for, or intolerance to, statin therapy. Combination drug therapy with a statin plus a second (or third) agent that further lowers non-HDL-C and LDL-C may be considered for patients who have not attained their treatment goals for atherogenic cholesterol levels after the maximum tolerated statin dosage has been reached and for those who have contraindications or are intolerant to statin therapy.

- **American Association for the Study of Liver Diseases (AASLD): Primary Biliary Cholangitis Practice Guidance** *(Lindor et al 2018)*
  - Ursodeoxycholic acid (UDCA) is recommended for patients with primary biliary cholangitis who have abnormal liver enzyme values regardless of histologic stage.
  - For patients requiring bile acid sequestrants, UDCA should be given at least 1 hour before or 4 hours after the bile acid sequestrant.
  - Cholestyramine, colestipol, and colesevelam are nonabsorbable, highly positively charged resins that bind to negatively charged anions such as bile acids. It is not known which substance in the gut they may be binding to that leads to improved cholestatic itching, and clinical trials proving their efficacy are limited, but they have a long track record of clinical use.
  - Colestipol and colesevelam are available as pills and are preferred by some patients over the powder preparation of cholestyramine.
  - Colesevelam was not effective in a single placebo-controlled trial that enrolled patients with cholestatic pruritus who had already failed other resins.

SAFETY SUMMARY

- Contraindications
  - Cholestyramine is contraindicated in patients with complete biliary obstruction.
  - Colesevelam is contraindicated in patients with serum TG concentrations > 500 mg/dL, a history of hypertriglyceridemia-induced pancreatitis, or a history of bowel obstruction.
- Warnings and precautions
  - Bile acid sequestrants have been reported to increase serum TG concentrations and should be used with caution in patients with hypertriglyceridemia.
  - Bile acid sequestrants may produce or severely worsen pre-existing constipation. Use is not recommended in patients with gastroparesis, other gastrointestinal motility disorders, and in those who have had major gastrointestinal tract surgery and who may be at risk for bowel obstruction.
  - Bile acid sequestrants may decrease the absorption of fat-soluble vitamins A, D, E, and K.
    - Chronic use of colestipol may be associated with an increased bleeding tendency due to hypoprothrombinemia from vitamin K deficiency.
  - Bile acid sequestrants may reduce the absorption of other drugs. It is generally advised that other medications be taken at least 1 hour before or 4 to 6 hours after the administration of bile acid sequestrants.
  - Powder formulations of bile acid sequestrants contain phenylalanine, which may be harmful to patients with phenylketonuria.

- Colestipol hydrochloride is a chloride form of an anion exchange resin; thus, prolonged use may lead to the development of hyperchloremia acidosis.

- Adverse effects
  - Bile acid sequestrants are not well absorbed from the gut; they are generally regarded as safe with limited systemic side effects. However, they may cause problems in the gastrointestinal tract, such as constipation, diarrhea, and flatulence.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
cholestyramine (Prevalite, Questran)	Powder	Oral	Twice daily	Powder should be mixed with fluids prior to administration May be administered in 1 to 6 doses per day
colesevelam (Welchol)	Powder Tablet	Oral	Powder: Once daily Tablets: Once or twice daily	Powder should be mixed with fluids prior to administration Take with a meal
colestipol (Colestid)	Granules Tablet	Oral	Once or twice daily	Granules should be mixed with fluids prior to administration

See the current prescribing information for full details

CONCLUSION

- The major function of the bile acid sequestrants class of medications is to decrease LDL-C levels. In general, these agents work by binding to bile acids in the intestine through anion exchange causing an interruption of the reabsorption of bile acids. This reduction in bile acids leads to feedback regulation on the conversion of cholesterol to bile acids. Currently, there are 3 bile acid sequestrants available: cholestyramine, colesevelam, and colestipol. All agents are typically administered once or twice daily, and are available generically.
- The bile acid sequestrants are all FDA-approved for adjunctive treatment in patients with hypercholesterolemia. Cholestyramine is also FDA-approved for relief of pruritus associated with partial biliary obstruction. In addition, colesevelam is FDA-approved as monotherapy in children 10 to 17 years of age for the treatment of HeFH and as adjunct therapy to diet and exercise to improve glycemic control in adults with T2DM.
- Clinical trial data consistently demonstrate the superiority of the bile acid sequestrants over placebo for the management of hyperlipidemia.
- The addition of a bile acid sequestrant to another lipid-lowering agent has the potential to produce further reductions in LDL-C levels compared to monotherapy with either of the agents.
- In the LRC-CPPT trial, treatment with cholestyramine demonstrated a mortality benefit in reducing the risk of coronary heart disease death and/or nonfatal myocardial infarction in asymptomatic males with primary hypercholesterolemia.
- Trials have also demonstrated that as add-on therapy to existing antidiabetic regimens, colesevelam achieved modest reductions in HbA1c compared to placebo.
- Lifestyle changes, including diet, exercise and smoking cessation, remain an essential modality in the management of patients with hypercholesterolemia. When pharmacologic therapy to lower LDL-C is required, initial treatment with a statin is recommended.
- The 2018 AHA/ACC guidelines recommend that cholesterol absorption inhibitors, bile acid sequestrants, and PCSK9 inhibitors are all options in patients who do not achieve therapeutic goals with statins alone *(Grundy et al 2019)*.

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Publication Date: June 17, 2021

Annual Review - Established Drug Classes

Therapeutic Class Overview
Cystic Fibrosis – Inhaled Antibiotics

INTRODUCTION

- Cystic fibrosis (CF) is the most common fatal genetic disease, affecting approximately 30,000 patients in the United States (U.S.) (*National Institutes of Health 2013*). It is caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene, which encodes for the CFTR protein. This protein acts as an ion channel regulating salt and fluid homeostasis, and defects are associated with thickened secretions, obstruction, and damage to several organs (*Ong et al 2016*). Respiratory manifestations are a significant feature of the disease, and respiratory failure is the most common cause of death in patients who do not receive a lung transplant (*Elborn 2016*).
  - CF is an autosomal recessive disorder; 2 copies of an abnormal gene must be present for the disease to develop (*Elborn 2016*). Patients may have 2 copies of the same mutation (homozygous) or 2 different mutations (heterozygous) (*Ong et al 2016*). Approximately 2000 mutations have been identified in the *CFTR* gene, of which more than 300 have been confirmed to cause CF (*CFTR2 2019*, *Quon and Rowe 2016*). In general, these mutations either reduce the amount of CFTR protein that reaches the cell membrane surface or reduce the function of CFTR as a chloride channel (*Egan 2016*).
  - There are 6 known classes of mutations that can cause CF. Classes I through III are associated with minimal CFTR function and most patients with these mutations have a severe CF phenotype (pancreatic insufficient and more severe lung disease). In contrast, class IV and V mutations are associated with some residual CFTR function and a milder phenotype (pancreatic sufficient and improved pulmonary outcomes and survival). Reports on the risk level for class VI mutations vary (*Egan 2016, Elborn 2016, Sosnay et al 2016*).
- Treatment of CF has traditionally been limited to addressing disease manifestations in specific organs (*Quon and Rowe 2016*).
  - Inhaled antibiotics have been commonly used to treat persistent airway infection with *Pseudomonas aeruginosa*, which contributes to lung damage in patients with CF; a reduction of bacterial load in the lungs decreases inflammation and the deterioration of lung function (*Smith et al 2018a*).
    - The 2013 CF Foundation (CFF) guidelines recommend chronic inhaled antibiotics, including tobramycin and aztreonam, for patients > 6 years of age with mild to severe disease with persistent colonization of *P. aeruginosa* to improve lung function, improve quality of life, and/or reduce exacerbations (*Mogayzel et al 2013*).
  - Inhaled dornase alfa, hypertonic saline, and mannitol have been used to enhance airway mucociliary clearance, while oral macrolide antibiotics and high-dose ibuprofen have been used to reduce inflammation (*Quon and Rowe 2016*).
  - More recently, CFTR modulators have been made available that act on the basic defect(s) in CFTR function; these include Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), Symdeko (tezacaftor/ivacaftor), and Trikafta (elexacaftor/tezacaftor/ivacaftor) (*Drugs@FDA 2020, Elborn 2016*). Eligibility for CFTR modulator therapy depends on the patient's age and CF-causing mutation(s), and these products are used in conjunction with traditional therapies in patients who are eligible.
- This review includes the inhaled aminoglycoside antibiotic tobramycin and the inhaled monobactam antibiotic aztreonam.
  - Inhaled tobramycin is indicated for the management of CF patients with *P. aeruginosa*, is available in a variety of formulations, and may be administered via nebulization or dry powder inhalation.
  - Inhaled aztreonam is indicated to improve respiratory symptoms in CF patients with *P. aeruginosa* and may be administered via inhaled nebulization.
- Medispan classes: Anti-Infective Agents – Aminoglycosides (tobramycin); Anti-Infective Agents – Miscellaneous (aztreonam)

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Tobramycin inhaled agents	
Bethkis (tobramycin) 300 mg/4 mL inhalation solution	-
Kitabis Pak (tobramycin) 300 mg/5 mL inhalation solution co-packaged with a Pari LC Plus reusable nebulizer	-
Tobi (tobramycin) 300 mg/5 mL inhalation solution	✔
Tobi Podhaler (tobramycin) 28 mg inhalation capsule	-
Aztreonam inhaled agent	
Cayston (aztreonam) 75 mg inhalation solution	-

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Inhaled tobramycin agents*				Inhaled aztreonam agent*
	Bethkis (tobramycin)	Kitabis Pak (tobramycin)	Tobi (tobramycin)	Tobi Podhaler (tobramycin)	Cayston (aztreonam)
Management of CF patients with *P. aeruginosa* in patients ≥ 6 years of age†	✔	✔	✔	✔	
To improve respiratory symptoms in CF patients with *P. aeruginosa* in patients ≥ 7 years of age†					✔

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

(*Prescribing information: Bethkis 2019, Cayston 2019, Kitabis Pak 2019, Tobi 2018, Tobi Podhaler 2015*)

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

CLINICAL EFFICACY SUMMARY

- A systematic review and meta-analysis of 18 trials (N = 3042), including 12 trials with tobramycin and 2 trials with aztreonam, evaluated the effects of long-term inhaled antibiotic therapy in patients with CF on clinical outcomes, quality of life, and adverse events (*Smith et al 2018a*).
  - There was no subgroup analysis of individual drugs or combinations due to the small number of trials, different duration of trials, different methods of expressing outcome results, and absence of variance in results.
  - Results showed that treatment with inhaled antibiotics improved lung function (4 trials; n = 814) and reduced the frequency of exacerbations (3 trials; n = 946) vs placebo. There were insufficient data to determine an effect on nutritional outcomes, survival, or quality of life.
    - Of the 8 trials that compared different inhaled antibiotics, 1 trial (N = 273; *Assael et al 2013*) demonstrated that aztreonam improved lung function significantly more than tobramycin inhalation solution, but the method of defining the outcome was different vs the remaining trials, and patients were exposed to tobramycin for a long period. No significant differences were found in the remaining trials with regard to lung function.
  - Important adverse events related to the treatment were uncommon, but were less common with tobramycin vs other antibiotics.

- Overall, the analysis determined that treatment with inhaled anti-pseudomonal antibiotics likely improved lung function and reduced exacerbation rates; however, the pooled estimates of the level of benefit were very limited. The best evidence was for inhaled tobramycin.

- A systematic review of 4 randomized controlled trials (N = 167) was conducted to determine if treatment of pulmonary exacerbations with inhaled antibiotics in patients with CF improved quality of life, reduced time off school or work and improved long-term survival (*Smith et al 2018b*). Data on the effectiveness of inhaled antibiotics for long-term suppression of respiratory infection has suggested there may also be benefit for treatment of exacerbations, with the strongest evidence supporting inhaled tobramycin. However, the review found little useful high-level evidence to support the use of inhaled antibiotics for the treatment of pulmonary exacerbations, as the included trials were inadequate for a valid analysis.
  - An inhaled aminoglycoside may be useful when an intravenous aminoglycoside is contraindicated due to renal impairment or risk of drug-induced hearing loss.
- A systematic review of 7 trials (N = 744) evaluated whether antibiotic treatment of early *P. aeruginosa* infection in patients with CF resulted in clinical improvements, and whether treatment with any particular antibiotic strategy (ie, combinations of inhaled, oral or intravenous antibiotics) was superior compared to other strategies or placebo (*Langton Hewer et al 2017*).
  - Most trials included inhaled tobramycin as a comparator.
  - The analysis determined that nebulized antibiotics, alone or in combination with oral antibiotics, were better vs no treatment for early infection with *P. aeruginosa*, and eradication may be sustained for up to 2 years.
  - There was insufficient evidence to determine whether antibiotic treatment for the eradication of early *P. aeruginosa* decreased mortality or morbidity, improved quality of life, or was associated with adverse events vs placebo or standard treatment.
  - Overall, there was insufficient evidence to state which antibiotic strategy should be used for the eradication of early *P. aeruginosa* infection in patients with CF.
- A network meta-analysis of 11 randomized controlled trials evaluated the effectiveness of inhaled antibiotics, including Bethkis, Tobi, tobramycin inhalation powder, and aztreonam, for the treatment of chronic *P. aeruginosa* lung infection in patients with CF (*Littlewood et al 2012*).
  - The analysis concluded that the studied antibiotics had comparable efficacies for the treatment of chronic *P. aeruginosa* lung infection in CF, as measured by improvements in change from baseline in percent predicted forced expiratory volume in 1 second ($ppFEV_1$), *P. aeruginosa* sputum density, and acute exacerbations.
  - The analyses suggested that all treatments improved clinical outcomes vs placebo. Treatment with the inhaled tobramycin formulations provided potentially clinically meaningful improvement in lung function over inhaled aztreonam, but differences were not statistically significant.
  - Prior exposure to an active drug was identified as a key factor affecting outcomes, yet this was not typically reported in trials as a predictive factor. Most trials involved the first use of the active drug, and therefore had a population who was naïve to the active drug.
- Multiple clinical trials have shown that the efficacy of tobramycin inhalation solution was significantly better vs placebo, as demonstrated by improved FEV_1, reduced sputum *P. aeruginosa* density, decreased relative risk of hospitalization for respiratory and other reasons, and decreased use of other antibiotics (*Chuchalin et al 2007, Lenoir et al 2007, Máiz et al 2013, Mazurek et al 2011, Murphy et al 2004, Ramsey et al 1999, Quittner and Buu 2002*).
  - Reported improvements in health-related quality of life (HRQoL) were significantly more likely in patients treated with tobramycin inhalation solution vs placebo, and $ppFEV_1$ was a significant predictor of HRQoL improvement (*Quittner and Buu 2002*).
  - A safety and efficacy trial determined that treatment with Bethkis inhalation solution 300 mg/4 mL demonstrated similar improvement in $ppFEV_1$ over 8 weeks of treatment compared with Tobi 300 mg/5 mL inhalation solution (*Mazurek et al 2014*). Lung function improvement with Bethkis continued throughout a 48-week extension phase, and was also associated with a favorable tolerability profile.
- Tobramycin inhalation powder delivered via the Tobi Podhaler has been shown to have similar efficacy vs the tobramycin inhalation solution; long-term safety and efficacy studies have shown that treatment with tobramycin inhalation powder was well tolerated with no unexpected adverse events and had sustained efficacy in patients with CF (*Hamed et al 2017, Máiz et al 2013, Sommerwerck et al 2016*).
  - The Phase 3 EVOLVE and EDIT clinical trials demonstrated that treatment with Tobi Podhaler significantly improved $ppFEV_1$ vs placebo at 28 days, and also reduced sputum *P. aeruginosa* density, respiratory-related hospitalizations,

and antipseudomonal antibiotic use (*Galeva et al 2013, Konstan et al 2011a*). Improvements in lung function and a decrease in sputum *P. aeruginosa* density from baseline were sustained in patients treated with up to 7 cycles of tobramycin inhalation powder over a period of at least 1 year (*Hamed et al 2017, Konstan et al 2016*).
  - The Phase 3 open-label EAGER trial demonstrated similar increases in $ppFEV_1$ and mean reduction in sputum *P. aeruginosa* density over 24 weeks (3 cycles) of treatment with tobramycin inhalation powder vs tobramycin inhalation solution (*Konstan et al 2011b*).
- Multiple clinical trials, including 3 pre-approval studies and 7 post-approval trials, have demonstrated that inhaled aztreonam is a safe and effective antimicrobial treatment for the eradication of newly acquired *P. aeruginosa* and long-term suppressive therapy of chronic endobronchial infection among patients with CF (*Elson et al 2019*).
  - Two Phase 3, double-blind, placebo-controlled, randomized-controlled trials (AIR-CF1, N = 164; AIR-CF2, N = 211) demonstrated improvements in lung function, decreased pulmonary exacerbations, reduced sputum *P. aeruginosa* density, and improvement in respiratory symptoms compared with placebo when aztreonam was administered in 28-day cycles as suppressive therapy (*McCoy et al 2008, Retsch-Bogart et al 2009*).
  - A long-term, 18-month, open-label study (AIR-CF3, N = 274) in patients who completed these 2 trials demonstrated that aztreonam use was also associated with consistent, sustained weight gain among CF patients (*Oermann et al 2010*).

CLINICAL GUIDELINES

- **Cystic Fibrosis Foundation (CFF) – CF pulmonary guidelines: chronic medications for maintenance of lung health** (*Mogayzel et al 2013*)
  - This guideline provided several new recommendations when published in 2013, in addition to reaffirming several recommendations from a previous (2007) version of the guideline.
  - For these guidelines, the severity of lung disease is defined by $ppFEV_1$ as follows: normal, > 90% predicted; mildly impaired, 70 to 89% predicted; moderately impaired, 40 to 69% predicted; and severely impaired, < 40% predicted.
  - The level of evidence and strength of recommendations are based on the U.S. Preventive Services Task Force system.
  - Recommendations specific to inhaled antibiotics and treatment of *P. aeruginosa* are included in Table 3.

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

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

	ceftazidime, colistin, gentamicin) to improve lung function and quality of life, or reduce exacerbations.			
Oral antipseudomonal antibiotics	For individuals with CF, ≥ 6 years of age, with *P. aeruginosa* persistently present in cultures of the airways, the CFF concludes that the evidence is insufficient to recommend for or against the routine use of chronic oral antipseudomonal antibiotics to improve lung function and quality of life, or reduce exacerbations.	Low	--	I
2013 new or modified recommendations				
Inhaled aztreonam – moderate-to-severe disease	For individuals with CF, ≥ 6 years of age, with moderate-to-severe lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CFF strongly recommends the chronic use of inhaled aztreonam to improve lung function and quality of life.	High	Substantial	A
Inhaled aztreonam – mild disease	For individuals with CF, ≥ 6 years of age, with mild lung disease and *P. aeruginosa* persistently present in cultures of the airways, the CFF recommends the chronic use of inhaled aztreonam to improve lung function and quality of life.	Moderate	Moderate	B

* **A**: The committee strongly recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is substantial. **B**: The committee recommends that clinicians routinely provide this therapy. There is high certainty that the net benefit is moderate, or there is moderate certainty that the net benefit is moderate to substantial. **I**: The committee concludes that the current evidence is insufficient to assess the balance of benefits and harms of the service. Evidence is lacking, of poor quality, or conflicting, and the balance of benefits and harms cannot be determined.

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

Table 4. CFF recommendations for inhaled antibiotics in preschoolers 2 to 5 years of age with CF

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

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

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

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

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

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

SAFETY SUMMARY

Tobramycin inhaled agents

- The inhaled tobramycin agents are contraindicated in patients with hypersensitivity or allergy to components of the product(s).
- Key warnings and precautions are similar among the inhaled tobramycin products, and generally include:
  - Bronchospasm: Can occur with inhalation of tobramycin.
  - Ototoxicity: Tinnitus and hearing loss have been reported in patients receiving tobramycin inhalation.
  - Nephrotoxicity: Has been associated with aminoglycosides as a class.
  - Neuromuscular disorders: Aminoglycosides may aggravate muscle weakness because of a potential curare-like effect on neuromuscular function.
  - Embryo-fetal toxicity: Aminoglycosides can cause fetal harm when administered to a pregnant woman.
- Adverse events associated with the inhaled tobramycin agents include:
  - Common adverse events (> 5%) occurring more frequently in Bethkis-treated patients: decreased FEV, rales, increased red blood cell sedimentation rate, and dysphonia.
  - Common adverse events (> 5%) in patients treated with Kitabis Pak and Tobi inhalation solution: cough, pharyngitis, and increased sputum.
  - Common adverse events (≥ 10%) in patients treated with Tobi Podhaler: cough, lung disorder, productive cough, dyspnea, pyrexia, oropharyngeal pain, dysphonia, hemoptysis, and headache.
    - Cough was the most common adverse event and was reported more frequently with Tobi Podhaler vs nebulized tobramycin (48% vs 31%, respectively) in clinical trials.

Aztreonam inhaled agent

- Inhaled aztreonam is contraindicated in patients with a known allergy to aztreonam.
- Key warnings and precautions for aztreonam include risk of allergic reactions, bronchospasm, decreases in FEV_1 after a 28-day treatment cycle, and development of drug-resistant bacteria.
- Common adverse events (> 5%) with aztreonam include cough, nasal congestion, wheezing, pharyngolaryngeal pain, pyrexia, chest discomfort, abdominal pain and vomiting.

DOSING AND ADMINISTRATION

Table 6. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments*
Bethkis (tobramycin)	Inhalation solution: 300 mg/4 mL ampules	Oral inhalation	Twice daily in repeated cycles of 28 days on drug, followed by 28 days off	• Dose should be administered using the hand-held Pari LC Plus Reusable Nebulizer with a Pari Vios air compressor.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments*
Kitabis Pak (tobramycin)	Inhalation solution: 300 mg/5 mL ampules	Oral inhalation	Twice daily in repeated cycles of 28 days on drug, followed by 28 days off	• Dose should be administered using the hand-held Pari LC Plus Reusable Nebulizer. • Kitabis Pak is a co-packaging of tobramycin inhalation solution with a Pari LC Plus Reusable Nebulizer.
Cayston (aztreonam)	Inhalation solution: 75 mg single-use vials of lyophilized powder packaged with sterile saline diluent	Oral Inhalation	Three times daily in repeated cycles of 28 days on drug, followed by 28 days off	• Dose should be reconstituted with 1 mL of sterile diluent. • Dose should be administered over an approximate 2 to 3 minute period using the Altera Nebulizer System. • Patients should use a bronchodilator before administration.
Tobi (tobramycin)	Inhalation solution: 300 mg/5 mL ampules	Oral inhalation	Twice daily in repeated cycles of 28 days on drug, followed by 28 days off	• Dose should be administered using the hand-held Pari LC Plus Reusable Nebulizer and DeVilbiss PulmoAide compressor.
Tobi Podhaler (tobramycin)	Inhalation powder: 28 mg capsules	Oral inhalation	4 capsules twice daily in repeated cycles of 28 days on drug, followed by 28 days off	• Capsules are for use with the Podhaler device only. • The contents of each capsule are administered through a deep inhalation with a single breath; the patient must inhale 2 times from each of the 4 capsules (ie, a total of 8 breath-activated inhalations)

* Doses for all agents should be administered as close to 12 hours apart as possible; but not less than 6 hours apart for tobramycin agents and not < 4 hours apart for aztreonam; dose is not adjusted for age or weight.

See the current prescribing information for full details

- In general, aerosolized antibiotics require a compressor and nebulizer, and approximately 15 minutes per dose for administration of tobramycin and 2 to 3 minutes for aztreonam. Nebulizers require regular cleaning after each use to prevent device contamination; lack of regular cleaning may potentially lead to transport of pathogens to the lower airways (*Blau et al 2007, Lester et al 2012*).
- Phase 1 and Phase 3 studies of treatment with tobramycin administered via the Tobi Podhaler reported an administration time of 4 to 6 minutes in patients with CF (*Geller et al 2007, Konstan et al 2011a*). The Tobi Podhaler device does not require disinfection (*Hamed et al 2017, Vazquez-Espinosa et al 2016*).

CONCLUSION

- Inhaled antibiotics are commonly used to treat persistent airway infection with *P. aeruginosa*, which contributes to lung damage in patients with CF. Treatment with inhaled antibiotics reduces bacterial load in the lungs, and decreases inflammation and the deterioration of lung function.
- Current clinical evidence supports the efficacy of the various inhaled tobramycin formulations and inhaled aztreonam for the management of CF patients with *P. aeruginosa*. Efficacy appears comparable among agents, and data are limited regarding which antibiotic strategy may be more effective in improvement in lung function, reduction of exacerbation rates, and eradication of *P. aeruginosa* infection.

- Guidelines recommend chronic use of inhaled tobramycin or aztreonam in patients with CF 6 years of age and older, with mild or moderate-to-severe lung disease and *P. aeruginosa*, to improve lung function and quality of life, and reduce exacerbations.
  - Inhaled antibiotic therapy is strongly recommended for initial or new growth of *P. aeruginosa*, with inhaled tobramycin as the favored regimen.
  - Inhaled tobramycin agents are indicated in patients ≥ 6 years of age, while inhaled aztreonam is indicated in patients ≥ 7 years of age.
- Safety concerns with inhaled tobramycin agents include bronchospasm, ototoxicity, nephrotoxicity, and neuromuscular disorders.
  - In clinical trials, cough was reported more frequently with the Tobi Podhaler inhalation powder vs nebulized tobramycin or placebo.
- Safety concerns with inhaled aztreonam include bronchospasm, decreases in FEV_1, and development of drug-resistant bacteria.
- All inhaled tobramycin agents are administered twice daily. Bethkis, Kitabis Pak, and Tobi inhalation solution are administered via a 15-minute nebulization. In contrast, tobramycin inhalation powder administered via the Tobi Podhaler takes approximately 4 to 6 minutes to administer via a total of 8 breath-activated inhalations (2 inhalations of the contents of 4 dry powder capsules).
- Inhaled aztreonam is administered 3 times daily via a 2 to 3 minute nebulization; patients should use a bronchodilator before administration.
- Use of a nebulizer requires additional steps for set-up and regular cleaning after each use to prevent device contamination, while the Tobi Podhaler device does not require disinfection.

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Publication Date: January 17, 2020

Therapeutic Class Overview
Immunomodulators

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: Abrilada (adalimumab-afzb), Cyltezo (adalimumab-adbm), Hadlima (adalimumab-bwwd), Hulio (adalimumab-fkjp), Hyrimoz (adalimumab-adaz), Erelzi (etanercept-szzs), Eticovo (etanercept-ykro), Avsola (infliximab-axxq), Inflectra (infliximab-dyyb), 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, 3 biosimilar products have been approved: Truxima (rituximab-abbs), Ruxience (rituximab-pvvr), and Riabni (rituximab-arrx). Oral agents on the market, Xeljanz/Xeljanz XR/Xeljanz oral solution (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. Tremfya is additionally indicated for PsA.
- Certain rare conditions for which immunomodulators are indicated are mentioned in this review but not discussed in detail. These include:
  - Ilaris for the treatment of 1) cryopyrin-associated periodic syndromes (CAPS), specifically the subtypes familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS); 2) TNF receptor associated periodic syndrome (TRAPS); 3) hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD); 4) familial Mediterranean fever (FMF); and 5) adult-onset Still's disease.
  - Kineret for the treatment of deficiency of interleukin-1 receptor antagonist (DIRA) and CAPS, specifically neonatal-onset multisystem inflammatory disease (NOMID).
  - Actemra for giant cell arteritis (GCA) and cytokine release syndrome (CRS).
  - Cimzia, Cosentyx, and Taltz 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 2020*). Arcalyst (rilonacept), an interleukin-1 blocker indicated for CAPS, is also not included in this review (*Arcalyst prescribing information 2020*).
- Although FDA-approved, the launch plans for the biosimilar drugs Abrilada (adalimumab-afzb), Erelzi (etanercept-szzs), Eticovo (etanercept-ykro), Cyltezo (adalimumab-adbm), Hadlima (adalimumab-bwwd), Hulio (adalimumab-fkjp), and Hyrimoz (adalimumab-adaz) are pending and may be delayed; therefore, these agents are not currently included in this review. Ixifi (infliximab-qbtx) was FDA-approved as a biosimilar to infliximab, but the manufacturer to date does not have

plans to launch Ixifi in the United States; Ixifi is listed as discontinued in the FDA Purple Book. Amjevita (adalimumab-atto) was approved as an adalimumab biosimilar but never launched; it is listed as discontinued in the FDA Purple Book (*Purple Book: Database of Licensed Biological Products 2021*).

- 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
Avsola (infliximab-axxq)	N/A†	TNFα inhibitor
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
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/Xeljanz oral solution (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), Cyltezo (adalimumab-adbm), Hadlima (adalimumab-bwwd), Hulio (adalimumab-fkjp), and

Hyrimoz (adalimumab-adaz) have been FDA-approved as biosimilars to Humira (adalimumab). Further information on Erelzi, Eticovo, Abrilada, Cyltezo, Hadlima, Hulio, and Hyrimoz will be included in this review after these products have launched. None of these agents is FDA-approved as an interchangeable biologic.
†Inflectra (infliximab-dyyb), Renflexis (infliximab-abda), and Avsola (infliximab-axxq) have been FDA-approved as biosimilar agents to Remicade (infliximab). Truxima (rituximab-abbs), Ruxience (rituximab-pvvr), and Riabni (rituximab-arrx) have been FDA-approved as biosimilar agents to Rituxan (rituximab), but Ruxience (rituximab-pvvr) and Riabni (rituximab-arrx) are only approved for adult patients with NHL, CLL, and GPA/MPA. None of these agents is FDA-approved as an interchangeable biologic.

(Drugs@FDA, 2021; Purple Book: Database of Licensed Biological Products 2021; Prescribing information: Actemra 2020; Avsola 2019; Cimzia 2019; Cosentyx 2020; Enbrel 2020; Entyvio 2020; Humira,2020; Ilaris 2020; Ilumya 2021; Inflectra 2019; Kevzara 2018; Kineret 2020; Olumiant 2020; Orencia 2020; Otezla 2020; Remicade 2020; Renflexis 2020; Rinvoq 2020; Rituxan 2020; Siliq 2020; Simponi 2019; Simponi Aria 2021; Skyrizi 2020; Stelara 2020; Taltz 2020; Tremfya 2020; Truxima 2020; Xeljanz/Xeljanz XR/Xeljanz oral solution 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.

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)	✔ *		✔ **	✔ **						
Avsola (infliximab-axxq)	✔ ⊥	✔ ⌐⌐			✔ ‡‡‡	✔	✔	✔ ⊥⊥		
Cimzia~~ (certolizumab)	✔	✔			✔ ‡	✔	✔			
Cosentyx~~ (secukinumab)					✔ ‡	✔	✔			
Enbrel (etanercept)	✔ †			✔ **	✔ ‡	✔ †	✔			
Entyvio (vedolizumab)		✔						✔		

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)
Humira (adalimumab)	✔ ‡‡	✔ ⌐		✔ ∫	✔ ‡	✔ ∫∫	✔	✔	✔ ↑	✔ ▼
Ilaris" (canakinumab)			✔ **							
Ilumya (tildrakizumab-asmn)					✔ ‡					
Inflectra (infliximab-dyyb)	✔ ⊥	✔ ⌐⌐			✔ ‡‡‡	✔	✔	✔ ⊥⊥		
Kevzara (sarilumab)	✔ *									
Kineret▼▼ (anakinra)	✔ ∞									
Olumiant (baricitinib)	✔ *									

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)
Orencia (abatacept)	✔ ∞∞			✔ ⌂		✔				
Otezla~~~ (apremilast)					✔ ‡	✔				
Remicade (infliximab)	✔ ⊥	✔ ⌐⌐			✔ ‡‡‡	✔	✔	✔ ⊥⊥		
Renflexis (infliximab-abda)	✔ ⊥	✔ ⌐⌐			✔ ‡‡‡	✔	✔	✔ ⊥⊥		
Rinvoq (upadacitinib)	✔ †									
Rituxan‴ (rituximab)	✔ ⫩									
Siliq (brodalumab)					✔ ⫩					

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 (golimumab)	✔┤					✔┤┤	✔	✔˜		
Simponi Aria (golimumab)	✔┤			✔**		✔**	✔			
Skyrizi (risankizumab-rzaa)					✔‡					
Stelara (ustekinumab)		✔⌐⌐⌐			✔‡	✔		✔		
Taltz˜˜ (ixekizumab)					✔‡	✔	✔			
Tremfya (guselkumab)					✔‡	✔				
Truxima (rituximab-abbs)''''	✔╪									

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)
Xeljanz/ Xeljanz XR/Xeljanz oral solution (tofacitinib)	✔‡‡‡			✔ **		✔		✔		

ϒActemra is also indicated for treatment of giant cell arteritis in adults and chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome in adults and pediatric patients ≥ 2 years.
*Patients with moderately to severely active RA who have had an inadequate response (or intolerance [Kevzara]) to ≥ 1 Disease-Modifying Anti-Rheumatic Drugs (DMARDs) 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, Taltz, which is indicated for the treatment of patients 6 years and older with moderate-to-severe PsO who are candidates for systemic therapy or phototherapy, and Stelara, which is indicated for the treatment of patients 6 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), and for the treatment of deficiency of interleukin-1 receptor antagonist (DIRA).
"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; familial Mediterranean fever (FMF) in adult and pediatric patients; and adult-onset Still's disease.
∞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, Avsola).
'''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 ≥ 1 TNF 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, Cosentyx, and Taltz 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.
''''Truxima is also indicated for adults with NHL, CLL, GPA (Wegener's Granulomatosis) and MPA.
***Ruxience is indicated for NHL, CLL, GPA (Wegener's Granulomatosis) and MPA.
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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 2018).*
- 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)*. A network meta-analysis of the SELECT trials found that upadacitinib plus MTX was more effective than MTX alone, and upadacitinib 15 mg plus MTX was most likely to achieve the best ACR 20 response rate (followed by upadacitinib 30 mg plus MTX, adalimumab 40 mg plus MTX, upadacitinib 30 mg, upadacitinib 15 mg, and MTX, in order) (*Song and Lee 2020*).
- A 24-week, phase 3, double-blind trial explored the efficacy of upadacitinib compared with abatacept in 612 patients with RA. The mean change in the Disease Activity Score for 28 joints based on C-reactive protein (DAS28-CRP) was -2.52 in the upadacitinib group and -2.00 in the abatacept group from baseline to week 12 (difference, -0.52 points; 95% CI, -0.69 to -0.35; $p < 0.001$ for noninferiority; $p < 0.001$ for superiority). Additionally, 30% of patients in the upadacitinib group and 13.3% of patients in the abatacept group achieved remission (difference, 16.8%; 95% CI, 10.4 to 23.2; $p <$ 0.001 for superiority) (*Rubbert-Roth et al 2020*).
- 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*).
- Avsola (infliximab-axxq) was evaluated and compared to Remicade (infliximab) in 558 patients in a double-blind, multicenter, randomized equivalence trial (*Genovese et al 2020*). The primary endpoint, ACR 20 at week 22, was achieved by 68.1% and 59.1% of patients in the Avsola and Remicade groups, respectively (TD, 9.37%; 90% CI, 2.67% to 15.96%). The upper bound exceeded the pre-specified equivalence criteria by 0.96% such that superiority could not be ruled out statistically. In a post hoc analysis with adjustment for imbalances in baseline factors, the CI was narrowed (90% CI, 0.75% to 13.62%). Secondary endpoints were also very similar between the 2 groups.
- 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).
- Truxima (rituximab-abbs) was evaluated and compared to Rituxan (rituximab) in 372 patients in a double-blind, multicenter, randomized phase 3 trial (*Park et al 2018*). The primary efficacy endpoint, change from baseline in DAS28 based on C-reactive protein (CRP) at week 24, was -2.13 and -2.09 for Truxima and Rituxan, respectively (TD, -0.04; 95% CI, -0.29 to 0.21). Equivalence was demonstrated between the 2 products. Secondary endpoints were also very similar between the 2 groups.
  - In an extension of this study, 330 patients received a second 24-week course of their assigned study drug (Truxima or Rituxan) (*Suh et al 2019*). Mean change in DAS28-CRP from baseline to week 48 was similar between groups (-2.7 and -2.6 for Truxima and Rituxan, respectively). ACR 20/50/70 responses were also similar between groups at week 48.
  - After week 48, 295 patients entered a second extension phase that continued until week 72; during this extension phase, patients who were previously receiving Truxima or Rituxan (European Union formulation) received Truxima,

while patients who were previously receiving Rituxan (United States formulation) were randomized 1:1 to continue receiving Rituxan (United States formulation) or switch to Truxima (*Shim et al 2019*). All patients experienced similar improvements in disease activity parameters, including DAS28 and ACR response rates. Switching from Rituxan to Truxima did not result in any clinically meaningful efficacy differences.

- 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).

- A Bayesian network meta-analysis of 5 randomized trials (n = 1,547) examined the efficacy and safety of tofacitinib, baricitinib, upadacitinib, filgotinib (not approved in the U.S.) and peficitinib (not approved in the U.S.) in patients with RA. The ranking probability based on SUCRA revealed the following agents with the highest probability to achieve the ACR 20 response rate: perficitinib 150 mg (highest probability) followed by peficitinib 100 mg, filgotinib 200 mg, filgotinib 100 mg, tofacitinib 5 mg, upadacitinib 15 mg, baricitinib 4 mg, and placebo *(Ho Lee et al 2020)*.
- A meta-analysis of 20 randomized trials (n = 8,982) assessed the efficacy of tofacitinib, baricitinib, and upadacitinib in patients with RA. Tofacitinib 10 mg (RR, 2.48; 95% CI, 1.97 to 3.14; p < 0.001) had to the highest ACR20 response rates followed by tofacitinib 5 mg (RR, 2.16; 95% CI, 1.81 to 2.58; p < 0.001). Tofacitinib displayed higher ACR 20 response rates compared with baricitinib and upadacitinib (*Wang et al 2020*).
- 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.
- A network meta-analysis of individual patient data from 38 randomized controlled trials compared various MTX-biologic combinations for RA in patients with an inadequate response to MTX alone (*Janke et al 2020*). Anakinra plus MTX showed relatively less benefit than other combinations in terms of clinical remission or low disease activity, and certolizumab plus MTX showed relatively higher rates of serious adverse events or infections; however, differences between combinations were generally minor.
- 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, including 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 ASAS 40 response seen at week 16 was sustained through week 52 in both trials (*Dougados et al 2020*).
- 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; 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).
- The approval of Simponi Aria (IV golimumab) for polyarticular JIA was based on an open-label phase 3 study (n = 127). Children 2 to < 18 years of age with active polyarticular course JIA and inadequate response to MTX were enrolled. The primary endpoints were pharmacokinetic exposure and model-predicted steady-state area under the curve (AUC_{ss}) over an 8-week dosing interval at weeks 28 and 52. Other endpoints included ACR response rates. The ACR 30, 50, 70, and 90 response rates were 84%, 80%, 70%, and 47%, respectively, at week 28. Golimumab serum concentrations and AUC_{ss} were 0.40 mcg/mL and 399 mcg•day/mL at week 28. ACR response rates, serum concentrations, and AUC_{ss} were maintained at week 52 (*Ruperto et al 2021*).
- The approval of Xeljanz/Xeljanz oral solution (tofacitinib) for polyarticular JIA was based on a 44-week study (n = 225) that enrolled patients 2 to 17 years old with polyarticular course JIA and inadequate responses to at least 2 DMARDs. The primary endpoint was the occurrence of disease flare at week 44. Compared with patients receiving placebo, patients receiving tofacitinib experienced significantly fewer disease flares (31% with tofacitinib vs 55% with placebo; difference in proportions -25% [95% CI, -39% to -10%]; p = 0.0007) (*Xeljanz prescribing information 2020*).

- 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.

- Otezla (apremilast) has additionally been studied in patients with moderate to severe PsO of the scalp in the phase IIIb, double-blind, randomized, placebo-controlled STYLE trial. In this trial, 303 patients with moderate to severe scalp PsO who had an inadequate response to 1 or more topical scalp therapies were randomized 2:1 to receive apremilast 30 mg twice daily (with a titration period) or placebo for 16 weeks. The primary endpoint was the proportion of patients achieving ScPGA response (score of 0 or 1 with a ≥ 2-point reduction from baseline) at week 16. Patients receiving apremilast were more likely to achieve ScPGA response at week 16 (43.3% vs 13.7%; $p < 0.0001$) (*Van Voorhees et al 2020*).
- 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). After week 52, patients receiving ustekinumab or placebo were switched to brodalumab and treatment was continued to week 120 (*Puig et al 2020*). At 120 weeks, 84.4%, 75.6%, and 61.1% of patients achieved PASI 75, PASI 90, and PASI 100, respectively, with brodalumab treatment.
  - 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 2018*). 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 ≤ 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) and Taltz (ixekizumab) in pediatric patients (age 6 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.
- An open-label, single arm, multicenter, phase 3 trial evaluated the efficacy and safety of ustekinumab in patients 6 to < 12 years of age with moderate to severe PsO (*Philipp et al 2020*). A total of 44 patients received weight-based ustekinumab at weeks 0 and 4, then every 12 weeks through week 40. At week 12, 77% of patients achieved PGA 0 or 1, 84% achieved PASI 75, and 64% achieved PASI 90. No new safety concerns were identified.
- The IXORA-PEDS study (n = 171) evaluated the efficacy of Taltz (ixekizumab) in pediatric patients aged 6 to < 18 years with moderate to severe PsO (*Paller et al 2020*). At week 12, weight-based ixekizumab every 4 weeks was superior to placebo for the co-primary endpoints of proportion of patients achieving PASI 75 (89% vs 25%; $p < 0.001$) and proportion of patients achieving PGA 0 or 1 (81% vs 11%; $p < 0.001$). Responses were sustained or further improved through week 48.

- 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 2015*). 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.
- A network meta-analysis of 41 randomized clinical trials (N = 19,248) assessed the proportion of patients with moderate-to-severe PsO who achieved PASI 100, PASI 90, and PASI 75 at weeks 10, 12, and 16 while using agents such as infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, risankizumab or guselkumab. The results revealed higher rates of PASI 100 and PASI 90 with brodalumab, ixekizumab, and risankizumab (*Tada et al 2020*).

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 response 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]*).
- An additional open-label extension of the SPIRIT-P1 trial followed patients through week 156. The ACR 20, ACR 50, and ACR 70 response rate for the every 2 weeks and every 4 weeks groups were 62.5% and 69.8%, 56.1% and 51.8%, and 43.8% and 33.4%, respectively (*Chandran et al 2020*).

- SPIRIT-H2H is a 52-week multicenter, open-label study comparing ixekizumab with adalimumab in patients with PsA and without prior use of biologic DMARDs. At week 52, a higher proportion of patients treated with ixekizumab achieved the combined ACR 50 and PASI 100 response (39% vs 26%, $p < 0.001$) and PASI 100 response (64% vs 41%, $p < 0.001$) compared with the patients treated with adalimumab. Both agents yielded similar outcomes for ACR 50 (49.8% vs 49.8%, $p = 0.924$) (*Smolen et al 2020[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*).
- Tremfya (guselkumab) received FDA approval for the treatment of PsA based on 2 randomized, double-blind, placebo controlled trials (*Deodhar et al 2020[c], Mease et al 2020*). The DISCOVER-1 trial randomized 381 patients with active PsA despite standard therapies to receive guselkumab 100 mg every 4 weeks, guselkumab 100 mg at weeks 0, 4, then every 8 weeks, or placebo. At week 24, ACR 20 response rates for guselkumab every 4 weeks and every 8 weeks were 59% and 52%, respectively, which was significantly greater than the ACR 20 response rate with placebo (22%; $p < 0.0001$) (*Deodhar et al 2020[c]*). The DISCOVER-2 trial randomized 741 biologic-naïve patients with PsA to receive guselkumab 100 mg every 4 weeks, guselkumab 100 mg at weeks 0, 4, then every 8 weeks, or placebo. At week 24, ACR 20 response rates for guselkumab every 4 weeks and every 8 weeks were 64% and 64%, respectively, which was significantly greater than the ACR 20 response rate with placebo (33%; $p < 0.0001$) (*Mease et al 2020*).
- 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.
- The multicenter, randomized, double-blind EXCEED study compared Cosentyx (secukinumab) to Humira (adalimumab) in 853 biologic-naïve patients with active PsA and an inadequate response to DMARDs (*McInnes et al 2020*). The ACR 20 response rates at week 52 were 67% with secukinumab and 62% with adalimumab ($p = 0.0719$). Secukinumab did not show statistical superiority over adalimumab.
- 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[b]*). 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.
- A network meta-analysis of 30 randomized trials (N = 10,191) compared the efficacy of infliximab, apremilast, adalimumab, tofacitinib, ustekinumab, golimumab, abatacept, secukinumab, certolizumab, brodalumab, etanercept, and ixekizumab in PsA (*Qiu et al 2020*). Direct and indirect comparisons were performed. In direct comparisons, most agents were better than placebo in terms of ACR 20 response rate (except adalimumab, tofacitinib, and abatacept), and no agent was significantly different from placebo in terms of serious adverse events. In the network meta-analysis, etanercept and infliximab were more effective than golimumab for ACR 20 response, and infliximab was more effective than certolizumab for PASI 75 response. Etanercept and infliximab were ranked as the most effective treatments.
- A network meta-analysis of 30 randomized trials (only 12 randomized trials for peripheral arthritis outcome) assessed the efficacy of adalimumab, etanercept, infliximab, golimumab, certolizumab, ustekinumab, secukinumab, ixekizumab, guselkumab, brodalumab, risankizumab, and tildrakizumab on peripheral arthritis by using ACR 70 criteria and on skin by reporting PASI 100 (*Torres et al 2021*). Secukinumab and ixekizumab had the highest probability for reaching both ACR 70 and PASI 100 responses.
- A meta-analysis of 11 randomized studies (N = 5382) revealed that TNF inhibitors, IL inhibitors, and abatacept are more likely to achieve radiographic non-progression compared with placebo (*Wu et al 2020*). Ixekizumab and adalimumab had a similar proportion of non-progressors.

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.
- A Cochrane review examined the evidence for oral JAK inhibitors in the maintenance of UC remission (*Davies et al 2020*). Only 1 randomized controlled trial met criteria for inclusion. In this trial, tofacitinib was superior to placebo for maintenance of clinical and endoscopic remission in patients with moderate to severe UC. The authors concluded that further studies are required to assess long-term effectiveness and safety of tofacitinib as maintenance therapy.

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, DIRA, 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 2020*). 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 Kineret (anakinra) for DIRA was evaluated in a long-term natural history study of 9 patients (ages 1 months to 9 years) with genetically-confirmed DIRA who were treated with anakinra for up to 10 years. All patients achieved inflammatory remission (defined as CRP ≤ 5 mg/dL and absence of pustulosis, inflammatory bone disease, or glucocorticosteroid use) (*Kineret prescribing information 2020*).
- 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 Taltz (ixekizumab) were evaluated in NRAS in the 52 week, randomized, double-blind, placebo-controlled, parallel-group, multicenter COAST-X trial (*Deodhar et al 2020[a]*). In COAST-X, 303 adults with NRAS 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.
- The efficacy and safety of Cosentyx (secukinumab) were evaluated in NRAS in the randomized, double-blind, placebo-controlled, phase 3 PREVENT study (*Deodhar et al 2020[b]*). In this trial, 555 adults with NRAS were randomized to receive secukinumab with a loading dose, secukinumab without a loading dose, or placebo (secukinumab was dosed as 150 mg at weeks 0, 1, 2, and 3, then every 4 weeks starting at week 4). The primary analyses were performed in TNF inhibitor-naïve patients (n = 501). Both primary endpoints were met. At week 16, more patients in the secukinumab plus loading dose group achieved ASAS 40 compared with placebo (41.5% vs 29.2%; p < 0.05). At week 52, more patients in the secukinumab without loading dose group achieved ASAS 40 compared with placebo (39.8% vs 19.9%; p < 0.05).
- The efficacy and safety of Ilaris (canakinumab) has been evaluated for the treatment of CAPS, TRAPS, HIDS/MKD, FMF, and adult-onset Still's disease.
  - 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 2020*). 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*).
  - Efficacy and safety in adult-onset Still's disease were evaluated in a randomized, double-blind, placebo-controlled study of 36 patients with adult-onset Still's disease and active joint involvement. The primary endpoint, proportion of patients achieving a significant reduction in DAS28 at week 12, was achieved in 67% of canakinumab-treated patients and 41% of placebo-treated patients (p = 0.18). Proportions of patients achieving the secondary endpoints of ACR 30, 50, and 70 were significantly greater in the canakinumab group (61%, 50%, and 28% with canakinumab vs 20%, 6.7%, and 0% with placebo; p = 0.033, 0.009, and 0.049 for canakinumab vs placebo, respectively). The study was terminated prematurely due to recruitment difficulties (*Kedor et al 2020*).
- 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 2020*). 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.

- A systematic literature review of 38 studies determined that anakinra, canakinumab, and etanercept are the most commonly studied biologics for treating familial Mediterranean fever, while studies with adalimumab, tocilizumab, rilonacept, and infliximab remain limited (*Kuemmerle-Deschner et al 2020*). The available evidence suggests that anakinra and canakinumab are effective in treating familial Mediterranean fever.

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 spring 2021.
  - EULAR guidelines for RA management were recently updated (*Smolen et al 2020[a]*). 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*).
  - The ACR/Arthritis Foundation guidelines for the management of osteoarthritis of the hand, hip, and knee strongly recommends against the use of biologics (eg, TNF inhibitors, IL-1 receptor antagonists) for any form of osteoarthritis (*Kolasinski et al 2020*).
- JIA:
  - According to the 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 summer 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:
  - Joint guidelines from the American Academy of Dermatology (AAD)/National Psoriasis Foundation (NPF) state that topical medications (eg, corticosteroids, vitamin D analogues) are the most common agents used to treat mild to moderate PsO. They are commonly used as adjunctive therapy to phototherapy, systemic agents, and biologics (*Elmets et al 2021).* Phototherapy is viewed as a reasonable and effective treatment option for patients requiring more than topical medications and/or those wishing to avoid systemic medications (*Elmets et al 2019*). Although biologic therapies have changed the treatment landscape, non-biologic systemic agents (eg, methotrexate) either as monotherapy or in combination with biologics, are still widely used due to benefit
  - for widespread disease, comparatively low cost, increased availability, and ease of administration (*Menter et al 2020[a])*.
  - Joint guidelines from the AAD/NPF 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*).
  - The AAD/NPF guideline on PsO in pediatric patients states that etanercept, adalimumab, and ustekinumab are effective biologic therapies for moderate to severe pediatric psoriasis. Infliximab can be recommended as monotherapy or in combination with MTX for use in pediatric patients with severe plaque or pustular psoriasis that is unresponsive to other systemic medications, rapidly progressive, unstable, and/or life threatening (*Menter et al 2020[b]*).
  - EULAR 2019 PsA guidelines recommend biologic DMARDs in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, such as MTX. For patients with peripheral arthritis, an inadequate response to at least 1 synthetic DMARD, and relevant skin involvement, biologics targeting IL-12/23 or IL-17 pathways may be considered. In patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD and at least one biologic DMARD, JAK inhibitors may be considered; JAK inhibitors may also be considered in patients for whom biologic DMARD therapy is not appropriate. Apremilast is considered a treatment option in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, in whom biologics and JAK inhibitors are not appropriate (*Gossec et al 2020, Kerschbaumer et al 2020*).
  - 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.
  - For the management of GCA, EULAR recommendations state that tocilizumab (or methotrexate as an alternative) should be used as an adjunctive therapy in patients who have refractory or relapsing disease or who are at an increased risk of glucocorticoid-related adverse effects or complications (*Hellmich et al 2020*).
  - No recent guidelines were identified for CAPS, CRS, DIRA, HIDS/MKD, TRAPS, or Still's disease.

SAFETY SUMMARY

- Contraindications:
  - Actemra (tocilizumab), Avsola (infliximab-axxq), 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), Avsola (infliximab-axxq), 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), Avsola (infliximab-axxq), 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/Xeljanz oral solution (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, Avsola (infliximab-axxq), 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/Xeljanz XR/Xeljanz oral solution (tofacitinib) have warnings for increased risk of thrombosis and death, including sudden cardiovascular 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) and Truxima (rituximab-abbs) 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/Xeljanz oral solution (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)
  - Infusion-related and hypersensitivity reactions with Entyvio (vedolizumab)
  - Diarrhea, nausea, and vomiting with Otezla (apremilast)
  - Depression with Otezla (apremilast)
  - Gastrointestinal perforations with Xeljanz/Xeljanz XR/Xeljanz oral solution (tofacitinib), Olumiant (baricitinib), Actemra (tocilizumab), Kevzara (sarilumab), Rituxan (rituximab), and Truxima (rituximab-abbs)
  - 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)
  - Macrophage activation syndrome with Ilaris (canakinumab)
  - Posterior reversible encephalopathy syndrome (PRES) with Stelara (ustekinumab)
  - 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) vs placebo (0 events in 1070 patients) (*Taylor et al 2019*).

- PsO
  - A total of 3,117 patients treated with at least 1 dose of Stelara (ustekinumab) for moderate to severe PsO were evaluated for long-term safety. At least 4 years of ustekinumab exposure was seen in 1,482 patients (including 838 patients with ≥ 5 years of exposure). The most commonly reported AEs were nasopharyngitis, upper respiratory tract infection, headache and arthralgia. Infections, malignancies and cardiac disorders were the most commonly reported serious AEs. Twenty deaths were reported through year 5. The causes of death were considered related to cardiovascular events (n = 5), malignancy (n = 5), infection (n = 3) and other causes (n = 7). The observed mortality rate among ustekinumab-treated patients was consistent with that expected in the general U.S. population (SMR = 0.36; 95% CI, 0.22 to 0.55). From year 1 to year 5, rates of overall AEs, and AEs leading to discontinuation generally decreased. Serious AE rates demonstrated year-to-year variability with no increasing trend. The results of this long-term study of AEs are similar to reports of shorter-term studies (*Papp et al 2013*).
  - In a 5-year extension study, a total of 2510 patients on etanercept for the treatment of PsO were evaluated for long-term safety and efficacy (*Kimball et al 2015*). Serious AEs were reported as a cumulative incidence of the entire 5-year observation period. The following incidences were reported: serious infections (6.5%, 95% CI, 5.4 to 7.7%); malignancies excluding nonmelanoma skin cancer (3.2%, 95% CI, 2.3 to 4.1%); nonmelanoma skin cancer (3.6%, 95% CI, 2.7 to 4.1%); coronary artery disease (2.8%, 95% CI, 2 to 3.6%); PsO worsening (0.7%, 95% CI, 0.3 to 1.2%); CNS demyelinating disorder (0.2%, 95%CI, 0 to 0.4%); lymphoma and tuberculosis each (0.1%, 95% CI, 0 to 0.3%); and opportunistic infection and lupus each (0.1%, 95%CI, 0 to 0.2%). A total of 51% of patients reported clear/almost clear rating at month 6 and remained stable through 5 years.
  - In a ≥ 156-week extension study, a total of 1,184 patients treated with apremilast in ESTEEM 1 and 2 were evaluated for long-term safety and tolerability (*Crowley et al 2017*). Serious AEs (≥ 2 patients) were coronary artery disease (n = 6), acute myocardial infarction (n = 4), osteoarthritis (n = 4), and nephrolithiasis (n = 4). The exposure-adjusted incidence rate for major cardiac events was 0.5/100 patients years, for malignancies was 1.2/100 patient years, for serious infections was 0.9/100 patient-years, and for suicide attempts was 0.1/100 patient-years.
  - A multicenter registry called Psoriasis Longitudinal Assessment and Registry (PSOLAR) evaluated the risk of serious infections in patients with PsO (*Kalb et al 2015*). Patients were followed for up to 8 years with a total of 11,466 patients with PsO enrolled, 74.3% of whom were from the U.S. A total of 22,311 patient-years of data were collected. Ustekinumab, infliximab, adalimumab, and etanercept as well as traditional DMARDs were included in the data analysis. During the follow-up period, 323 serious infections were reported. The rates of serious infections per 100 patient-years were 0.83 (secukinumab), 1.47 (etanercept), 1.97 (adalimumab), and 2.49 (infliximab). The most commonly reported serious infection was cellulitis. Risk factors for serious infections were increasing age, diabetes mellitus, smoking, and history of significant infections prior to registry entry. Exposure to infliximab (hazard ratio, 2.51; 95% CI, 1.45 to 4.33; $p < 0.001$) and adalimumab (hazard ratio, 2.13; 95% CI, 1.33 to 3.41; $p = 0.002$) during the registry were independently associated with the risk of serious infections whereas use of ustekinumab or etanercept were not.
- PsA
  - Subcutaneous golimumab for patients with active PsA demonstrated safety and efficacy over 5 years in the long-term extension of the randomized, placebo-controlled GO-REVEAL study (*Kavanaugh et al 2014b*). Approximately one-half of patients also took MTX concurrently. No new safety signals were observed.
- AS
  - A meta-analysis of 25 randomized controlled studies with 2,403 patients with AS or non-radiographic axial spondyloarthritis treated with agents such as adalimumab, certolizumab, etanercept, golimumab, infliximab, sarilumab, tocilizumab, and secukinumab showed no significant increase in the risk of serious infections with biologic agents compared to controls (OR, 1.42; 95% CI, 0.58 to 3.47) (*Wang et al 2018*).
  - Another meta-analysis of 14 randomized controlled trials with 2,032 patients with AS that were treated with adalimumab, certolizumab, etanercept, golimumab, or infliximab revealed no significant difference between TNF inhibitors and placebo for overall serious adverse events (OR, 1.34; 95% CI, 0.87 to 2.05), risk of serious infections (OR, 1.59; 95% CI, 0.63 to 4.01), risk of malignancy (OR, 0.98; 95% CI, 0.25 to 3.85), and discontinuation due to adverse events (OR, 1.55; 95% CI, 0.95 to 2.54) (*Hou et al 2018*).
- Multiple indications
  - One study looked at 23,458 patients who were treated with Humira (adalimumab) for RA, JIA, AS, PsA, PsO and CD. Patients received adalimumab for up to 12 years. No new safety signals were observed from this analysis. Rates of malignancies and infections were similar to the general population and also similar to rates reported in other shorter-term trials for anti-TNF therapies (*Burmester et al 2013b*).

- Pooled data from 5 Phase 3 trials of SQ golimumab over at least 3 years demonstrated a safety profile consistent with other TNF inhibitors (*Kay et al 2015*). A total of 1,179 patients with RA, PsA or AS were treated for at least 156 weeks. Rates of AEs up to week 160 for placebo, golimumab 50 mg and golimumab 100 mg, respectively, were as follows: 0.28, 0.30, 0.41 for death; 5.31, 3.03, 5.09 for serious infection; 0, 0.17, 0.35 for tuberculosis; 0, 0.13, 0.24 for opportunistic infection; 0, 0, 0.12 for demyelination; and 0, 0.04, 0.18 for lymphoma.
- A total of 18 multicenter, placebo-controlled, randomized controlled trials evaluated the safety profile of certolizumab pegol monotherapy or in combination with DMARDs in RA, CD, AS, PsA and PsO (*Capogrosso Sansone et al 2015).* All but 1 trial was conducted in a double-blind manner. The overall pooled risk ratios for all doses of certolizumab pegol were reported as follows: AEs (defined as AE reported but not evaluated for causality) 1.09 (95% CI, 1.04 to 1.14), serious AEs 1.50 (95% CI, 1.21 to 1.86), ADRs (defined as an AE possibly related to drug treatment by investigators) 1.20 (95% CI, 1.13 to 1.45), infectious AEs 1.28 (95% CI, 1.13 to 1.45), infectious serious AEs 2.17 (95% CI, 1.36 to 3.47), upper respiratory tract infections 1.34 (95% CI, 1.15 to 1.57), neoplasms 1.04 (95% CI, 0.49 to 2.22), and tuberculosis 2.47 (95% CI, 0.64 to 9.56). Rare AEs may not have been captured by the studies due to limiting the reporting of most AEs to those occurring in > 3 to 5%.
- The safety of ustekinumab was examined in a pooled analysis of 12 trials in patients with PsO, PsA, and CD. A total of 5584 patients were evaluated, equating to 4521 PYs. Respective incidences per 100 PY of infections (125.4 vs 129.4), major cardiovascular adverse events (0.5 vs 0.3), malignancies (0.4 vs 0.2), and death (0.1 vs 0.0) were similar between ustekinumab and placebo, respectively (*Ghosh et al 2019*).
- Several 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/Xeljanz oral solution (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 enroll in the program.
    - Pharmacies must be certified with the program and must only dispense to patients who are enrolled in the program.

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	**RA:** IV: 4 mg/kg IV every 4 weeks. May increase to 8 mg/kg IV every 4 weeks. Maximum dose = 800	**RA:** Can give with MTX or other DMARDs.	Give as a single 60-minute intravenous infusion. <30 kg, use a 50 mL infusion bag.

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

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
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 Single-dose vial: 25 mg/0.5 mL	**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 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	**RA, AS, PsA**: 40 mg SQ every other week. For RA, may increase to 40 mg every week or 80 mg every other week if not on MTX. **PJIA or pediatric uveitis:** 10 kg to <15 kg: 10 mg SQ every other week; 15 kg to <30 kg: 20 mg SQ every other week; ≥30 kg, 40 mg SQ every other week **CD 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. **HS:** 160 mg SQ on Day 1 (given in 1 day or split	**RA, AS, PsA:** MTX, other non-biologic DMARDS, glucocorticoids, NSAIDs, and/or analgesics may be continued. **JIA:** NSAIDs, MTX, analgesics, and/or glucocorticoids, may be continued. **CD and UC:** aminosalicylates and/or corticosteroids may be continued. Azathioprine, 6-MP or MTX may be continued if necessary. Needle cover of the syringe contains dry rubber (latex).	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 temperature prior to injecting.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		over 2 consecutive days), followed by 80 mg SQ 2 weeks later (Day 15). Two weeks later (Day 29), begin 40 mg weekly or 80 mg 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; maintenance dose is 40 mg every week.		

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Ilaris (canakinumab)	Single-dose vial: 150 mg injection solution	**SJIA and adult-onset Still's disease:** ≥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 weeks.	**RA:** give with MTX. **CD:** If no response by week 14, consider discontinuation.	Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion. Infuse over 2 hours. Do not administer with other drugs.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Kevzara (sarilumab)	Prefilled syringe: 150 mg/1.14 mL 200 mg/1.14 mL Prefilled pen: 150 mg/1.14 mL 200 mg/1.14 mL	**RA:** 200 mg SQ every 2 weeks.	**RA:** give with or without MTX or other conventional DMARDs Reduce dose for neutropenia, thrombocytopenia, and elevated liver enzymes.	Patients may be taught to self-inject. Bring to room temperature (30 minutes [pre-filled syringe] or 60 minutes [pre-filled pen]) prior to injecting. Rotate injection sites.
Kineret (anakinra)	Prefilled syringe: 100 mg/0.67 mL	**RA:** 100 mg SQ once daily. **CAPS (NOMID) and DIRA:** 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 infusion and every 4		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
		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 mg/kg.	**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.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		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.		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 1000 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. **Aria (PJIA):** 80 mg/m^2 IV at weeks 0 and 4, and 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	**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. In pediatric patients, it is recommended that Stelara be administered by a

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		later, followed by 90 mg every 12 weeks. **PsO (≥ 6 years):** <60 kg, 0.75 mg/kg (injection volume based on weight) 60 to 100 kg, 45 mg >100 kg, 90 mg; administer recommended dose initially, 4 weeks later, than every 12 weeks. **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).	healthcare provider. Stelara for IV infusion must be diluted, prepared and infused by a healthcare professional; it is diluted in 0.9% sodium chloride or 0.45% sodium chloride for a final volume of 250 mL and infused 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. **PsO (6 to <18 years old):** <25 kg, 40 mg SQ at week 0 then 20 mg every 4 weeks; 25 to 50 kg, 80 mg SQ at week 0 then 40 mg every 4 weeks; >50 kg, 160 mg SQ at week 0, then 80 mg every 4 weeks. **PsA, AS:** 160 mg by SQ injection at week 0, followed by 80 mg every 4 weeks. **NRAS:** 80 mg by SQ injection every 4 weeks.		Patients weighing >50 kg may be taught to self-inject with either the prefilled syringe or the autoinjector. Bring to room temperature prior to injecting. Rotate injection sites. Doses for patients weighing ≤50 kg must be administered by a healthcare professional. Contents of a prefilled syringe should be transferred to a sterile vial, and the appropriate dose drawn out of the vial into a new syringe.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		NOTE: For patients with PsA with coexistent moderate-to-severe PsO, use dosing regimen for PsO.		
Tremfya (guselkumab)	Prefilled syringe or single-dose patient-controlled autoinjector: 100 mg/mL	**PsO, PsA:** 100 mg by SQ injection at week 0, week 4, and then every 8 weeks	For PsA, Tremfya may be used alone or in combination with MTX.	Patients may be taught to self-inject. Bring to room temperature (30 minutes) prior to injecting.
Truxima (rituximab-abbs)	Vial: 100 mg/10 mL 500 mg/50 mL	**RA:** Two 1000 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.
Xeljanz/Xeljanz XR (tofacitinib)	Tablet: 5 mg, 10 mg Extended-release Tablet: 11 mg, 22 mg Oral solution: 1 mg/mL	**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 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	Patients may switch from Xeljanz 5 mg twice daily to Xeljanz XR 11 mg once daily the day following the last dose of Xeljanz 5 mg. 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. Xeljanz XR is not interchangeable or substitutable with Xeljanz oral solution. Use as monotherapy or in combination with MTX or other nonbiologic DMARDs in RA.	May take with or without food. Swallow Xeljanz XR tablets whole; do not crush, split, or chew. Xeljanz oral solution should not be initiated in patients with absolute lymphocyte count < 500 cells/mm^3, absolute neutrophil count < 1000 cells/mm^3, or hemoglobin < 9 g/dL. Administer Xeljanz oral solution with the included press-in bottle adapter and oral dosing syringe.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		considered and limited to the shortest duration. **PJIA:** 3.2 mg (3.2 mL oral solution) twice daily if weight ≥ 10 kg but < 20 kg, 4 mg (4 mL oral solution) twice daily if weight ≥ 20 kg but < 40 kg, and 5 mg (tablet or 5 mL oral solution) twice daily if weight ≥ 40 kg.	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; DIRA=deficiency of interleukin-1 receptor antagonist; 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.
Avsola (infliximab-axxq)	Frequency of serious infection is greater in ≥65 years. Use caution.	Not recom-mended in children <6 years 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.
Cimzia (certolizumab)	The number of subjects ≥65 years in clinical trials was not sufficient to determine	Safety and effectiveness have not been established.	No data	No data	Unclassified† Limited data from ongoing pregnancy

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	whether they responded differently from younger subjects. Use caution.				registry not sufficient to inform risks. Minimal excretion 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)	The number of patients ≥65 years in clinical trials was not sufficient to determine whether they responded differently from younger subjects. Use caution.	Not studied in children <2 years with PJIA or <4 years with PsO.	No data	No data	Unclassified† Available studies do not reliably support association with major birth defects. Present in low levels in breast milk; consider risks and benefits.
Humira (adalimumab)	Frequency of serious infection and malignancies is greater in ≥65 years. Use caution.	Only studied in PJIA, pediatric uveitis (ages 2 years and older), CD (6 years and older), and HS	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
		(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.
Kineret (anakinra)	Use caution as there is a higher	For NOMID, has been used in all	CrCl <30 mL/min: give	No data	Unclassified†

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	incidence of infections in the elderly in general.	ages. For DIRA, has been used in ages from 1 month to 9 years. Safety and efficacy have not been established in pediatric patients with juvenile RA. Not possible to give a dose <20 mg.	dose every other day.		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 and efficacy have not been established.	The dose of Otezla should be reduced to 30 mg once	No dosage adjustment necessary.	Unclassified† Available data have not established a

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	safety profile of elderly patients.		daily in patients with severe renal impairment (CrCl<30 mL/min).		drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Unknown whether excreted in breast milk; consider risks and benefits.
Remicade (infliximab)	Frequency of serious infection is greater in ≥65 years. Use caution.	Not recom-mended in <6 years in children with CD or UC.	No data	No data	Unclassified† Available data do not report clear association with adverse outcomes. Present in low levels in breast milk; systemic exposure thought to be low; consider risks and benefits.
Renflexis (infliximab-abda)	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 do not report clear association with adverse outcomes. Unknown whether excreted in breast milk; consider risks and benefits.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
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.
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	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.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	in clinical trials was insufficient to determine any differences in response.				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 established for PJIA and PsA in pediatric patients 2 years and older but not established for other conditions (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. Unknown whether excreted in breast milk; consider risks and benefits.
Stelara (ustekinumab)	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 been established in children 6 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	Safety and effectiveness have been	No data	No data	Unclassified†

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	patients; however, the number of patients ≥65 years in clinical trials was not sufficient to determine differences.	established in children 6 to <18 years with moderate to severe PsO; safety and effectiveness not established in children <6 years with PsO or children of any age with PsA, AS, or NRAS.			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.
Truxima (rituximab-abbs)	Rates of serious infections, malignancies, and cardiovascular events were higher in older patients.	Safety and efficacy have not been established.	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.

Xeljanz/Xeljanz XR (tofacitinib)	Frequency of serious infection is greater in ≥65 years. Use caution.	Safety and effectiveness established for PJIA in pediatric patients 2 years to 17 years old but not established for other conditions.	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. Patients with PJIA on Xeljanz tablets or oral solution should reduce dosing to once daily if taking 3.2 mg, 4 mg, or 5 mg twice daily. For patients on hemodialysis, administer	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. Patients with PJIA on Xeljanz tablets or oral solution should reduce dosing to once daily if taking 3.2 mg, 4 mg, or 5 mg twice daily. Not recom-mended in	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.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
			doses after the dialysis session. Do not take supplemental doses if a dose was taken before dialysis.	severe hepatic impairment.	

AS=ankylosing spondylitis; CLL=chronic lymphocytic leukemia; CrCl=creatinine clearance; CD=Crohn's disease; CAPS=cryopyrin-associated periodic syndromes; CRS=cytokine release syndrome; DIRA=deficiency of interleukin-1 receptor antagonist; 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; NRAS=non-radiographic axial spondyloarthritis; 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.
†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, upadacitinib was superior to abatacept for changes in the DAS28-CRP and the achievement of remission (*Rubbert-Roth et al 2020*).
  - 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*).
- In the SPIRIT-H2H study, ixekizumab led to a higher proportion of patients with PsA achieving the combined ACR 50 and PASI 100 and PASI 100 alone compared with adalimumab (*Smolen et al 2020[b]*)
- 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[a]*). 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*).
- EULAR 2019 PsA guidelines recommend biologic DMARDs in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, such as MTX (*Gossec et al 2020, Kerschbaumer et al 2020*). For patients with peripheral arthritis, an inadequate response to at least 1 synthetic DMARD, and relevant skin involvement, biologics targeting IL-12/23 or IL-17 pathways may be considered. In patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD and at least one biologic DMARD, JAK inhibitors may be considered; JAK inhibitors may also be considered in patients for whom biologic DMARD therapy is not appropriate. Apremilast is considered a

treatment option in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, in whom biologics and JAK inhibitors 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 AAD/NPF on the treatment of PsO 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 ACR/NPF 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[bj]*).
- 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[bj]*). 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: March 15, 2021

INTRODUCTION

Multiple Sclerosis

- 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 2021)*. Multiple sclerosis is characterized by inflammation, demyelination, and degenerative changes in the CNS. 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])*.
- An estimated 1 million adults in the United States (U.S.) 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 (*Montalban et al 2018, Rae-Grant et al 2018*). These therapies may delay the progression from CIS to clinically definite MS (CDMS) *(Armoiry et al 2018, Miller et al 2012)*. 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 with MS. Its approval was based on the PARADIGMS trial (*Chitnis et al 2018*).
- 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 (*Bafiertam prescribing information 2021*).

Ulcerative Colitis

- Ulcerative colitis is a form of inflammatory bowel disease (IBD) that 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 and Kane 2020, Rubin et al 2019).*
- Precise incidence and prevalence estimates of ulcerative colitis have been limited by a lack of gold standard criteria for diagnosis, inconsistent case ascertainment, and disease misclassification. The existing data suggest that the U.S. incidence rate of ulcerative colitis varies between 2.2 to 19.2 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] 2020).*
- Current pharmacotherapy for ulcerative colitis includes 5-aminosalicylic acid (5-ASA) derivatives, glucocorticoids, immunomodulators (azathioprine, 6-mercaptopurine [6-MP], and methotrexate), and biologic agents (eg, infliximab, Humira [adalimumab]) *(Micromedex 2021, Bernstein et al 2015).* These agents are discussed in separate class reviews.
- Zeposia (ozanimod) is the first sphingosine 1-phosphate (S1P) receptor modulator that is approved for moderate to severe ulcerative colitis in adults in addition to its approval for MS *(Zeposia prescribing information 2021).*
- 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)	-
Kesimpta (ofatumumab)§	-
Lemtrada (alemtuzumab)	-
Mavenclad (cladribine)‖	-
Mayzent (siponimod)	-
mitoxantrone	✔‡
Ocrevus (ocrelizumab)	-
Plegridy (peginterferon β-1a)	-
Ponvory (ponesimod)	-
Rebif (interferon β-1a)	-
Tecfidera (dimethyl fumarate)	✔
Tysabri (natalizumab)	-
Vumerity (diroximel fumarate)	-

Drug	Generic Availability
Zeposia (ozanimod)	-

†Glatopa by Sandoz is an FDA-approved generic for Copaxone (glatiramer acetate).
‡Although brand Novantrone has been discontinued, generic mitoxantrone remains available.
§Ofatumumab was originally approved as an IV formulation for treatment of chronic lymphocytic leukemia as a different product (Arzerra). Only clinical data for ofatumumab use in MS are included in this review.
‖Cladribine injection is indicated for the treatment of active hairy-cell leukemia. This oncology indication is not related to the treatment of MS and will not be discussed in this review.

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

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 in adults	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	Moderately to severely active ulcerative colitis in adults	Moderately to severely active Crohn's disease in adults
Ampyra (dalfampridine)	✔ *	-	-	-	-	-	-
Aubagio (teriflunomide)	-	✔	-	-	-	-	-
Avonex (interferon β-1a)	-	✔	-	-	-	-	-
Bafiertam (monomethyl fumarate)	-	✔	-	-	-	-	-
Betaseron/Extavia (interferon β-1b)	-	✔	-	-	-	-	-
Copaxone (glatiramer acetate)	-	✔	-	-	-	-	-
Gilenya (fingolimod)	-	✔ †	-	-	-	-	-
Kesimpta (ofatumumab)		✔					
Lemtrada (alemtuzumab)	-	-	✔ ‡	-	-	-	-
Mavenclad (cladribine)	-	-	✔ §	-	-	-	-
Mayzent (siponimod)	-	✔	-	-	-	-	-
mitoxantrone	-	-	-	-	✔ ‖	-	-
Ocrevus (ocrelizumab)	-	✔	-	✔	-	-	-

Drug	Improve walking in MS	Relapsing forms of MS, to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease in adults	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	Moderately to severely active ulcerative colitis in adults	Moderately to severely active Crohn's disease in adults
Plegridy (peginterferon β-1a)	-	✔	-	-	-	-	-
Ponvory (ponesimod)	-	✔	-	-	-	-	-
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 2021, Aubagio 2021, Avonex 2020, Bafiertam 2021, Betaseron 2021, Copaxone 2020, Extavia 2020, Gilenya 2019, Glatopa 2020, Kesimpta 2020, Lemtrada 2021, Mavenclad 2019, Mayzent 2021, mitoxantrone 2018, Ocrevus 2021, Plegridy 2021, Ponvory 2021, Rebif 2020, Tecfidera 2021, Tysabri 2020, Vumerity 2021, Zeposia 2021)

- 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

Multiple Sclerosis

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

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, 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 controlled trials (RCTs) 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 SC 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 IM + 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 IM, and 0.11 for glatiramer acetate. Glatiramer acetate performed significantly better than IFNβ-1a IM, reducing the risk of exacerbation by 31% (p = 0.027), and IFNβ-1a IM + glatiramer acetate performed significantly better than IFNβ-1a IM, 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, placebo-controlled, RCT. 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 2014[b])*. Neutralizing antibodies to IFN β-1a were identified in < 1% of all groups after 1 year (peginterferon β-1a SC every 2 weeks, 4 patients; peginterferon β-1a SC every 4 weeks, 2 patients; placebo, 2 patients) *(Calabresi et al 2014[b])*. 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 SC 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 SC every 4 week group (ARR 0.291). The peginterferon β-1a SC 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 SC 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 SC every 2 weeks group compared to the placebo-switch group *(Calabresi et al 2014[b], 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 SC. 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 were 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).
- Bioequivalency was demonstrated for Plegridy administered by IM and SC injection in an unpublished, open-label, crossover, single-dose, Phase 1 study of 136 healthy volunteers; this study was the basis for the FDA-approval of the IM route of administration for Plegridy (*Zhao et al 2020*). Injection site reactions were reported less frequently after IM dosing (14.4%) than after SC dosing (32.1%).

ORAL AGENTS

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) at 12 weeks 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, double-blind, RCT. 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 at 12 weeks *(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)*.

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 enrollment 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.
  - ARRs at 96 weeks, the primary outcome, 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 group had a lower risk of 3-month CDP vs placebo (hazard ratio [HR], 0.67; 95% CI, 0.48 to 0.93; p = 0.02). Lesions on MRI were significantly lower in the cladribine 3.5 mg/kg group vs placebo (p < 0.001 for all comparisons).

Oral Sphingosine-1-phosphate (S1P) receptor modulators

Gilenya (fingolimod)
- Gilenya (fingolimod) has been evaluated in 2 large, 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 2014[a])*. 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).

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

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. 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 on MRI 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 IM. Significant reductions in ARR were observed compared to IFNβ-1a IM 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 IM. 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 IM.
  - Clinically significant evidence of bradycardia, second-, or third-degree heart block was not noted after administration of the first dose in either trial.

Ponvory (ponesimod)

- Ponvory (ponesimod) was evaluated in the Phase 3, double-blind, parallel group study (OPTIMUM) in 1133 patients with relapsing forms of MS *(Kappos et al 2021)*. Patients were randomized to receive 20 mg ponesimod (titrated from 2 mg) (n = 567) or 14 mg teriflunomide (n = 566) once daily for 108 weeks. The primary endpoint of ARR was reduced with ponesimod compared to teriflunomide (rate ratio, 0.695; 99% CI, 0.536 to 0.902; p<0.001). In addition, the number of Gd-enhancing T1 lesions and the number of new or enlarging T2 lesions on MRI were also reduced with ponesimod. Confirmed disability progression outcomes at 12 weeks and 24 weeks were not significantly different between ponesimod and teriflunomide.

Oral Fumarates

Tecfidera (dimethyl fumarate)

- Tecfidera (dimethyl fumarate) was evaluated in two Phase 3 studies: DEFINE and CONFIRM *(Fox et al 2012, Gold 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 at 12 weeks *(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 confirmed disability progression at 12 weeks. 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)*.

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 2021*).
- 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%) 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.

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 2021*).

High Efficacy Infusibles and Injectables

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). The most frequently reported adverse effects with alemtuzumab were infusion-associated reactions, infections, and autoimmune events.

Kesimpta (ofatumumab)

- The two Phase 3, double-blind, double-dummy, active-controlled, multicenter, RCTs, the ASCLEPIOS I and II trials, included 1882 patients with relapsing MS who were treated with ofatumumab 20 mg SC every 4 weeks or teriflunomide 14 mg daily for up to 30 months. Approximately 40% of the patients in each group had no prior exposure to DMTs. Ofatumumab significantly reduced the ARR, the primary endpoint, compared with teriflunomide.
  - ASCLEPIOS I: ARR: 0.11 vs 0.22; difference, -0.11; 95% CI, -0.16 to -0.06; $p < 0.001$; RR, 0.49; 95% CI, 0.37 to 0.65; $p < 0.001$.
  - ASCLEPIOS II: ARR: 0.10 vs 0.25; difference, -0.15; 95% CI, -0.20 to -0.09; $p < 0.001$; RR, 0.42; 95% CI, 0.31 to 0.56; $p < 0.001$.
  - Pooled data demonstrated that the percentage of patients with confirmed disability worsening at 3 months was 10.9% vs 15.0% for ofatumumab vs teriflunomide, respectively (HR, 0.66; 95% CI, 0.50 to 0.86; $p = 0.002$). For the confirmed disability worsening at 6 months, the percentage was also lower in the ofatumumab group (8.1% vs 12.0%;

HR, 0.68; 95% CI, 0.50 to 0.92; p = 0.01). There was no significant difference between the groups for disability improvement.
  - For the MRI endpoints, the ofatumumab group had significantly fewer mean number of Gd-enhancing lesions and mean number of new or enlarging lesions per year on T2-weighted MRI (all p < 0.001). Brain volume loss did not differ significantly between groups in either trial *(Hauser et al 2020[a])*.

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%).
    - 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%; 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.
  - 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.
      - As of February 2018, the overall crude incidence rate of malignancies among patients from OPERA I and II who received ocrelizumab in the double-blind period or open-label extension was 0.40 per 100 patient-years of exposure to ocrelizumab. The incidence rate as of the data cutoff of May 2015 after the completion of the DB period was 0.28 for the ocrelizumab group and 0.14 for the IFN β-1a SC group (*Hauser et al 2020[b]*).
      - As of January 2019, the age- and sex-standardized incidence rate of all malignancies in the ocrelizumab all-exposure (all Phase 2 and 3 studies, plus 4 other trials) (0.22 per 100 patient-years; 95% CI, 0.16 to 0.33), remained stable over time, with confidence intervals overlapping and within epidemiological references from the Surveillance, Epidemiology, and End Results [SEER] Program of the National Cancer Institute, which reports

data on cancer incidence in approximately 28% of the general U.S. population (0.31 per 100 patient-years) (*Genentech 2020[a]*)
- Since breast cancer occurred in 6 out of 781 females treated with ocrelizumab (vs in none of 668 females treated with IFN β-1a SC or placebo), the labeling of ocrelizumab recommends that patients follow standard breast cancer screening guidelines (*Genentech 2020[b]*). In an analysis of the all-exposure ocrelizumab population from the trials through January 2019, the incidence rate of female breast cancer using age at event onset methodology was 0.15 (95% CI, 0.08 to 0.27) per 100 patient-years compared to 0.14 per 100 patient-years (95% CI, 0.14 to 0.14) based on SEER (*Genentech 2020[a]*).

- 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; 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; p = 0.04).
  - Additional secondary endpoints included changes in the T25FW, the total volume of hyperintense brain lesions on T2-weighted MRI, and brain volume loss.
    - The proportion of patients with 20% worsening of the T25FW 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.

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 motor 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 double-blind, placebo-controlled, RCTs 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, RCT 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 AAN 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

- The best initial treatment strategy is uncertain, but 2 main concepts include safety focused (IFNs or glatiramer) and efficacy (ie, natalizumab, ocrelizumab, ofatumumab) approaches (*Olek & Mowry 2021*). Retrospective observational studies have supported the earlier initiation of high efficacy DMT to reduce the risk of disability progression; however, evidence from RCTs is needed to determine the appropriate stage of MS in which to use a high efficacy DMT (*He et al 2020*).
- A 2017 systematic review evaluated the effect of high efficacy immunotherapies (ie, fingolimod, natalizumab, alemtuzumab) at different stages of MS (*Merkel et al 2017*). 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 β-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.
- 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 12 mg (RR, 0.40, 95% CI, 0.27 to 0.60; very low quality evidence) was 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 12 mg (mean difference = -0.6; 95% CI, -1.02 to -0.24) was 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).
- A 2020 network meta-analysis of 34 RCTs compared ofatumumab with other DMTs for RRMS *(Samjoo et al 2020)*. For the outcome of ARR, rate ratios were significantly improved with ofatumumab compared with teriflunomide, IFN β-1a SC and IM, IFN β-1b, glatiramer acetate, dimethyl fumarate, and fingolimod; no differences were detected in comparisons with cladribine, ocrelizumab, natalizumab, or alemtuzumab. Values for SUCRA indicated alemtuzumab was most likely to be most effective (96%), followed by ofatumumab (91%), natalizumab (88%), and ocrelizumab (85%).

Ulcerative Colitis

Zeposia (ozanimod)

- The efficacy and safety of ozanimod were evaluated in 2 multicenter, double-blind, placebo controlled RCTs in adult patients with moderately to severely active ulcerative colitis (*Zeposia prescribing information 2021)*. Patients were randomized to oral ozanimod 0.92 mg daily or placebo. All patients received an initial dose escalation of ozanimod or placebo prior to receiving their assigned dose on day 8. Patients with moderately or severely active ulcerative colitis were included if they had an inadequate response or were intolerant to previous therapies, including oral aminosalicylates, corticosteroids, immunomodulators, or biologic agents. In UC Study 1, patients (n = 645) received induction treatment for 10 weeks. In UC Study 2, patients who achieved a clinical response in UC Study 1 or an open-label arm at week 10 (n = 457) were re-randomized to maintenance treatment with ozanimod or placebo for 42 additional weeks (52 weeks total). Use of corticosteroids or aminosalicylates was allowed in UC Study 1, while patients had to be tapered from corticosteroids for entry into UC Study 2. The primary endpoint was clinical remission at week 10 in UC Study 1 and at 52 weeks in UC Study 2. Clinical remission was defined as a 3-component Mayo score (without the physician global assessment) which included the rectal bleeding subscore, stool frequency subscore, and endoscopy subscore.
  - In the UC Study 1, clinical remission was achieved by 18% with ozanimod and 6% of patients with placebo at 10 weeks (treatment difference, 12%; 95% CI, 8 to 17; $p < 0.0001$). In addition, the following secondary endpoints were improved with ozanimod vs placebo, respectively: clinical response (48% vs 26%; $p < 0.0001$), endoscopic improvement (27% vs 12%; $p < 0.0001$), and endoscopic-histologic mucosal improvement (13% vs 4%; $p < 0.001$).
  - In the UC Study 2, clinical remission was achieved by 37% of patients with ozanimod and 19% of patients with placebo at 52 weeks (treatment difference, 19%; 95% CI, 11 to 26). In addition, the following secondary endpoints were improved with ozanimod vs placebo, respectively: clinical response (60% vs 41%; $p < 0.0001$), endoscopic

improvement (46% vs 26%; p < 0.0001), corticosteroid-free clinical remission (32% vs 17%; p < 0.001), and endoscopic-histologic mucosal improvement (30% vs 14%; p < 0.001).

CLINICAL GUIDELINES

Multiple Sclerosis

- 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)*. 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 Gd-enhanced lesion) (Level B). Clinicians may advise discontinuation of DMT in people with SPMS who do not have ongoing relapses (or Gd-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 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)
- 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.

Ulcerative Colitis
- For the treatment of ulcerative colitis, 2019 guidelines from the American College of Gastroenterology (ACG) recommend 5-ASA therapy for induction of remission in mildly active ulcerative colitis, and budesonide, systemic corticosteroids, tumor necrosis factor (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-ASA (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 ulcerative colitis, the AGA strongly recommends using infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or ustekinumab over no treatment (*Feuerstein et al 2020*).

SAFETY SUMMARY

Interferons and glatiramer acetate
- 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 products (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. Cases of hepatic injury have also 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.

Oral agents

- 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. 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.
- Siponimod is contraindicated in patients with a cytochrome P4502C9*3/*3 genotype, presence of Mobitz type II second-degree, third degree AV block or sick 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, cutaneous malignancies, 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 and ponesimod are 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. They are also contraindicated in patients with Mobitz type II second- or third-degree AV block, sick sinus syndrome, or sinoatrial attack unless the patient has a functioning pacemaker. Ozanimod is also contraindicated in patients with severe, untreated sleep apnea and those taking a monoamine oxidase inhibitor. Warnings and precautions for ozanimod and ponesimod include an increased infection risk, macular edema, increased blood pressure, bradyarrhythmia and AV conduction delays, decline in pulmonary function, liver injury and cutaneous malignancies (ponesimod only). Women of childbearing potential should use effective contraception during and for 3 months after stopping ozanimod and 1 week after stopping ponesimod due to fetal risk. The most common adverse events (incidence > 10%) with ozanimod and ponesimod are upper respiratory tract infections, hepatic transaminase elevations, and hypertension (ponesimod only). Zeposia (ozanimod) does not have a recommendation for first-dose cardiac observation like fingolimod, ponesimod, and siponimod.
- 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 the fumarates. 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.

- 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, drug reaction with eosinophilia and systemic symptoms, and elevated blood pressure. Although not approved in pediatric patients, use of teriflunomide was associated with pancreatitis in a pediatric clinical trial. 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).
- 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.

High Efficacy Infusibles and Injectables

- Natalizumab has a boxed warning regarding the risk of PML, which 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), thrombocytopenia, and hepatotoxicity.
- Alemtuzumab is contraindicated in patients with human immunodeficiency virus (HIV) or active infection. 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, decreased immunoglobulin levels, 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.
    - No cases of PML were reported in the controlled Phase 2 or 3 studies or in the OLE of these studies. Outside of clinical trials, as of January 31, 2020, there have been 9 confirmed cases of PML in patients treated with ocrelizumab for MS. Of the 9 cases, 8 patients had been switched from natalizumab (n = 7) or fingolimod (n = 1). In 1 additional case, the patient had no prior exposure to DMTs but had contributing factors for PML including advanced age (78 years) and preexisting grade 1 lymphopenia which progressed to grade 2 during treatment (*Genentech 2020[c], Hauser et al 2020[b], Ng et al 2020*).
  - 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.
- Ofatumumab is contraindicated in patients with active hepatitis B virus infection. The prescribing information contains warnings and precautions regarding the risk of infection, injection-related reactions, reduction in immunoglobulins, and fetal risk. The most common adverse events (incidence > 10%) include upper respiratory tract infection, headache, injection-related reactions, and local injection site reactions.
- 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.

Symptomatic therapy

- 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.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration*

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ampyra (dalfampridine)	Tablet	Oral	Twice daily	• May be taken with or without food. Tablets should only be taken whole; do not divide, crush, chew, or dissolve.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				• 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 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)	Tablet	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 until verification that the plasma teriflunomide concentration is less than 0.02 mg/L. • Transaminase and bilirubin levels should be obtained within 6 months before initiation; transaminase levels should be

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				monitored for at least 6 months after initiation.
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)	Capsule (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, serum aminotransferase, alkaline phosphatase, and total bilirubin levels before initiation of therapy.
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. • 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.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
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)	Capsule	Oral	Once daily Approved for adults and pediatric patients 10 years of age or older. For pediatric patients ≤ 40 kg, a lower dose is recommended. 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. 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 heart rate [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 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 so patients 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

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				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 months before planned conception.
Kesimpta (ofatumumab)	Injection	SC	20 mg at weeks 0, 1, and 2 followed by subsequent dosing of 20 mg once monthly starting at week 4	• Prior to initiation, perform hepatitis B virus screening and tests for quantitative serum immunoglobulins. For patients with low serum immunoglobulins, immunology experts should be consulted.
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.	• Pre-medicate with high-dose corticosteroids prior to Lemtrada infusion for the first 3 days of each treatment course. • 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. • 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 > 200 cells/microliter, whichever occurs later. • Patients should complete any necessary immunizations at least 6 weeks prior to treatment with alemtuzumab. Important monitoring: • Complete blood count with differential, serum creatinine, and urinalysis (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.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
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 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.	• The use of Mavenclad in patients weighing less than 40 kg has not been investigated. • Mavenclad is contraindicated in pregnant women and in 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)	Tablet	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 For MS-related indications: 12 mg/m^2 given as a short IV infusion over 5 to 15 minutes 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	• 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 < 1500 cells/mm^3. • 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.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			develop at any time during treatment with mitoxantrone. .	• Mitoxantrone may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant. • Complete blood counts, including platelets, should be monitored prior to each 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
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	• 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. • 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. • 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. • Hepatitis B virus screening is required before the first dose. • Prior to initiation, quantitative serum immunoglobulin levels should be performed. For patients with low serum immunoglobulins, immunology experts should be consulted.
Plegridy (peginterferon β-1a)	Injection; pen, prefilled syringe for SC use; prefilled syringe for IM use	SC, IM	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 sites for SC administration are the abdomen, back of the upper arm, and thigh; IM injections should be administered in the 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.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ponvory (ponesimod)	Tablet	Oral	Once daily Titration: Initiate 14-day titration, starting with 2 mg once daily and increase to 20 mg by day 15 (refer to prescribing information for titration regimen).	• May be taken with or without food; must be swallowed whole. • Ponvory can cause fetal harm when administered to pregnant women. • Before treatment initiation, obtain complete blood count, ECG, liver function tests, ophthalmic evaluation, and test for varicella zoster virus. • 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.
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)	Capsule (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, serum aminotransferase, alkaline phosphatase, and total bilirubin levels before initiation of therapy.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
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)	Capsule (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, serum aminotransferase, alkaline phosphatase, and total bilirubin levels before initiation of therapy.
Zeposia (ozanimod)	Capsule	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.	• Dosing recommendations for MS and ulcerative colitis are the same. • 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. • 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 disability 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 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.
- 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 2019, Scolding et al 2015, Montalban et al 2018, Rae-Grant 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, Rae-Grant et al 2018)*.
- There are now 9 available oral agents. 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. Cases of PML have been reported in patients taking fingolimod and dimethyl fumarate.
  - Gilenya (fingolimod) is a S1P 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 S1P 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), the third S1P receptor modulator, has to significantly decrease ARR compared to IFNβ-1a; however, unlike other drugs in this class, it does not require first dose cardiac monitoring (*Comi et al 2019, Cohen et al 2019*).
  - Ponvory (ponesimod), a fourth S1P receptor modulator, reduced ARR compared to teriflunomide *(Kappos et al 2021)*.
  - 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 *(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 an oral fumarate that 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 (*Bafiertam prescribing information 2021*).

- 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 liver enzymes, 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, Mavenclad 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 *(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.
- Kesimpta (ofatumumab) is the first self-administered CD20-directed cytolytic antibody indicated for relapsing forms of MS. Ofatumumab has demonstrated superiority to teriflunomide in patients with relapsing forms of MS for the outcome of ARR *(Hauser et al 2020[a])*. Ofatumumab is self-administered monthly by SC injection after an initial loading regimen. Key warnings include the risk for infections, including PML and HBV reactivation. Injection-related reactions, possible reduction in immunoglobulins, and fetal risk (B cell depletion in infants born to mothers treated with ofatumumab during pregnancy) are other warnings. The most common AEs (incidence > 10%) were upper respiratory tract infection, headache, injection-related reactions, and local injection site reactions.
- 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.
- 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*).
- 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 quality of life in MS patients, 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. 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*).

- Zeposia (ozanimod) is the first S1P receptor modulator that is approved for moderate to severe ulcerative colitis in adults, in addition to its approval for MS *(Zeposia prescribing information 2021)*. The role in therapy for S1P receptor modulators in ulcerative colitis is not well-defined.

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Therapeutic Class Overview
Topical Lidocaine

INTRODUCTION

- Topical lidocaine is available as single entity and combination products (ie, lidocaine/prilocaine, lidocaine/hydrocortisone, lidocaine/tetracaine). These products are indicated for a number of conditions and are available in multiple dosage forms for topical use (ie, ointment, lotion, gel, cream, jelly, patch, solution) and as an oral solution.
- Lidocaine, prilocaine (amide-type local anesthetics) and tetracaine (ester local anesthetic) produce their analgesic effects through a reversible nerve conduction blockade by diminishing nerve membrane permeability to sodium. This action decreases the rate of membrane depolarization and increases the threshold for electrical excitability. The blockage affects all nerve fibers in the following sequence: autonomic, sensory and motor, with effects diminishing in reverse order. Loss of nerve function clinically is as follows: pain, temperature, touch, proprioception, skeletal muscle tone. Direct nerve membrane penetration is necessary for effective anesthesia (*Clinical Pharmacology 2020*).
- Systemic absorption of local anesthetics can produce effects on the central nervous and cardiovascular systems; however, the rate and extent of absorption after topical administration is dependent on concentration, total dose, the site of application, and length of exposure. Following topical administration of ointment or jelly, peak effects typically occur within 3 to 5 minutes (*Clinical Pharmacology 2020)*.
- This review focuses on select topical lidocaine products that are available by prescription. Lidocaine products that are used parenterally are not included. Additionally, there are many topical lidocaine products that are available over the counter (OTC); however, the specific brands and availability of OTC products will not be included in this review. To note, many agents within this class have been used safely and effectively for many years; however, there are limited published data evaluating the efficacy of these products for their approved indications.
- Medispan class: Local Anesthetics – Topical and Topical Anesthetic Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single Entity Agents	
lidocaine topical jelly 2%	✔
lidocaine topical gel 2%, 3%, 4%	✔
lidocaine lotion 3%**, 3.5%**	✔
lidocaine topical ointment 5%	✔
lidocaine oral viscous solution 2%	✔
lidocaine HCl topical solution 4%	✔
lidocaine HCl sterile solution 4%	✔
lidocaine topical cream 3%**, 3.25%**, 3.88%**, 4%**, 4.12%**	✔
lidocaine rectal cream 5%**	✔
lidocaine patch 5%	✔
lidocaine topical system 1.8%*	-
Combination Products	
lidocaine-prilocaine cream 2.5-2.5%**	✔
lidocaine-prilocaine cream 2.5-2.5% kits**	✔
lidocaine-prilocaine cream 2.5-2.5% & lidocaine gel 4% kit	✔
lidocaine-prilocaine cream 2.5-2.5% & lidocaine cream 3.88% kit†	-
lidocaine-prilocaine cream 2.5-2.5% & lido patch 5% kit ‡	-
lidocaine-hydrocortisone cream kit 2-2%**,3-0.5%**, 3-1%**, 3-2.5%**	✔

Drug	Generic Availability
lidocaine-hydrocortisone 2.8-0.55% with aloe gel kit**	✔
lidocaine-tetracaine cream 7-7%	✔

*only available as brand ZTlido
†only available as brand Prizotral
‡only available as brand Prilo Patch Kit
** Disclaimer: This drug has not been found by FDA to be safe and effective, and its labeling has not been approved by the FDA.

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

Table 2. Indications for Single-Entity Products**

Single-Entity Products	Indication
lidocaine jelly	For prevention and control of pain in procedures involving the male and female urethra, for topical treatment of painful urethritis, and as an anesthetic lubricant for endotracheal intubation (oral and nasal)
lidocaine gel 2%	For the local management of skin wounds, including pressure ulcers, venous stasis ulcers, first and second degree burns, and superficial wounds and scrapes.
lidocaine gel 3%	For the relief of pain, soreness, abrasions, minor burns, insect bites and discomfort due to pruritus, pruritic eczemas, pruritus ani, pruritus vulvae, hemorrhoids, anal fissures, and similar conditions of the skin and mucous membranes.
lidocaine gel 4%	For associated pain, painful wounds and wound healing in either open and closed injuries or conditions. Conditions of pain include topical pain, postsurgical pain and pain associated with various types of closed or open wounds. Conditions of closed wounds include soft tissue and bony injuries caused by contusions, hematomas, crush injuries and sprains/strains due to torsion, traction, compression and/or blunt trauma.
lidocaine lotion 3%	Pruritus, pruritic eczemas, abrasions, minor burns, insect bites, pain, soreness and discomfort due to pruritus ani, pruritus vulvae, hemorrhoids, anal fissures, and similar conditions of the skin and mucous membranes.
lidocaine lotion 3.5%	For use on normal intact skin for temporary relief of pain and itching due to minor cuts, minor scrapes, minor skin irritations, minor burns and insect bites
lidocaine ointment 5%	• For production of anesthesia of accessible mucous membranes of the oropharynx, • Anesthetic lubricant for intubation • For the temporary relief of pain associated with minor burns, including sunburn, abrasions of the skin, and insect bites.
lidocaine topical cream 3%, 3.88%, 4%, 4.12%	For the temporary relief of pain and itching associated with minor burns, sunburn, minor cuts, scrapes, insect bites, and minor skin irritation.
lidocaine topical cream 3.25%	For the relief of pruritus, pruritic eczemas, abrasions, minor burns, insect bites, pain, soreness, and discomfort due to pruritus ani, pruritus vulvae, hemorrhoids, anal fissures, and similar conditions of the skin and mucous membranes.
lidocaine rectal cream 5%	Temporary relief of pain and itching due to anorectal disorders
lidocaine patch 5% lidocaine topical system 1.8%	For relief of pain associated with post-herpetic neuralgia (PHN).
lidocaine oral topical solution 2% viscous	For the production of topical anesthesia of irritated or inflamed mucous membranes of the mouth and pharynx; for reducing gagging during the taking of x-ray pictures and dental impressions
lidocaine HCl sterile solution 4%	For the production of topical anesthesia of the mucous membranes of the respiratory tract or the genito-urinary tract
lidocaine HCl topical solution 4%	For the production of topical anesthesia of accessible mucous membranes of the

	oral and nasal cavities and proximal portions of the digestive tract.

** Disclaimer: Some products in this table (see Table 1) are not FDA-approved and have not had labeling approved by the FDA, but are available by prescription.

(*Prescribing Information: 2% Xylocaine viscous 2014, 4% Xylocaine-MPF 2010, 7T Lido gel 2018, Astero 2016, DermacinRx 2019, Gen7T 2019, Lido-K 2018, lidocaine ointment 5%, lidocaine HCl topical solution 2019, Lidoderm 2018, Lidodose 2018, Lidopin 2014, Lido Rx 2019, LMX4 2019, LMX 5 2018, PharmaPureRx lidocaine HCl 4.12% Cream 2019, Recticare 2019, ZTlido 2018)*

Table 3. Indications for Combination Products**

Combination Products	Indication
lidocaine-prilocaine cream 2.5-2.5%	Used as a topical anesthetic for use on: • Normal intact skin for local analgesia. • Genital mucous membranes for superficial minor surgery and as pretreatment for infiltration anesthesia.
lidocaine-prilocaine cream 2.5-2.5% kits	
lidocaine-prilocaine cream 2.5-2.5% & lidocaine gel 4% kit	
lidocaine-prilocaine cream 2.5-2.5% & lidocaine cream 3.88% kit	
lidocaine-prilocaine cream 2.5-2.5% & lido patch 5% kit	
lidocaine-hydrocortisone cream kit	For the anti-inflammatory and anesthetic relief of itching, pain, soreness and discomfort due to hemorrhoids, anal fissures, pruritus ani and similar conditions of the anal area.
lidocaine-tetracaine cream 7-7%	For use on intact skin in adults to provide topical local analgesia for superficial dermatological procedures such as dermal filler injection, pulsed dye laser therapy, facial laser resurfacing, and laser-assisted tattoo removal.

** Disclaimer: Some products in this table (see Table 1) are not FDA-approved and have not had labeling approved by the FDA, but are available by prescription.

(Prescribing Information: Agoneaze 2018, Lido-BDK 2018, lidocaine HCl-hydrocortisone acetate cream 2018, lidocaine HCl-hydrocortisone acetate with aloe gel 2018, Nuvakaan 2019, Pliaglis 2019, Prilo Patch 2019, Prizotral 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

- Lidocaine/prilocaine has been studied as an anesthetic agent in several settings. Lidocaine products have not consistently shown improvements in pain scores compared to treatment with placebo (*Hopper et al 2014, Minassian et al 2002, Moppett et al 2004*).
  - Comparison of various lidocaine formulations to lidocaine/prilocaine creams has demonstrated that they have a similar anesthetic effect (*Herberger et al 2003*, *Koh et al 2004*).
  - In an open-label trial of 41 patients, lidocaine-prilocaine 2.5-2.5% cream was found to be significantly more effective than inhalation of a nitrous oxide-oxygen mixture in relieving pain associated with debridement of leg ulcers ($p < 0.001$) (*Claeys et al 2011*).
- Several clinical studies have evaluated the effectiveness of lidocaine-tetracaine cream as a topical anesthetic for many types of laser procedures including pulsed dye, leg vein, non-ablative, facial resurfacing, tattoo removal, and hair removal. Overall, similar results have been found, showing statistically better visual analog score (VAS) pain scores compared to placebo or head-to-head with other topical anesthetics (ie, lidocaine-prilocaine cream) (*Alster and Lupton 2002, Alster et al 2012, Bryan 2002, Chen et al 2003, Chen et al 2005, Doshi et al 2003, Jih et al 2004*).
- Lidocaine 5%

- A randomized, double-blind, placebo-controlled, 2-period crossover trial (N = 32) evaluated patients with PHN who were regular users of lidocaine 5% plaster from open-label extension studies. Patients were assigned to receive 14 days of lidocaine 5% plaster followed by 14 days of placebo or vice versa with no washout period. The primary endpoint was the “time to exit” where patients withdrew because their pain relief was 2 points lower than their normal response on a 6-point categorical verbal rating scale of pain relief (worse, no pain relief, slight relief, moderate relief, a lot of relief, and complete relief). The median time to exit was 14 days for lidocaine 5% plaster and 3.8 days for placebo ($p < 0.001$) (*Galer et al 1999*). In patients with PHN, treatment with lidocaine 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 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*).
- The effectiveness of lidocaine patch 5% for the treatment of pain associated with PHN was demonstrated in a multi-center, open-label, phase 3 trial of up to 4 years duration. Patients applied up to 3 lidocaine 5% medicated plasters on the painful skin area for up to 12 hours a day. After 6 weeks, a mean pain relief of 4.3 ± 0.9 on a 6-point verbal-rating scale (1 = worse pain to 6 = complete relief) was reported and was maintained for the entire 12-month study and extension phase. The investigators' report for the global clinical impression of change was "very much improved" or "much improved" in about 80% of patients at each visit during the 12-month study. In the extension phase, the patient global impression of change was "very much" or "much" improved in 71% (49/69) at 24 months and 93% (40/43) at 36 months. In the safety population (n = 102) over the combined study period (4 years), drug-related adverse events included mainly administration site reactions: hypersensitivity (3.9%), pruritus (2.9%), irritation (2.9%), rash (2%), and skin reaction (1%) (*Sabatowski et al 2012*).
- A Cochrane systematic review of 12 small studies (N = 508) assessed the analgesic efficacy of topical lidocaine (5% patch, 5% cream, 5% gel, and 8% spray) vs placebo or active control for chronic neuropathic pain in adults. The limited information from single studies, mainly in PHN, indicated that topical lidocaine may be effective in treating neuropathic pain in a small number of patients and is well tolerated, at least in the short-term. There was no clear evidence of an effect on the incidence of adverse effects or withdrawals. However, the reviewers noted that the studies included ‘very low quality evidence’ and all had a ‘high risk of bias’ due to small size and incomplete outcome data (*Derry et al 2014*).
- In clinical studies, efficacy of the 5% lidocaine patch has consistently been reported to be superior to placebo and comparable or superior to oral pregabalin in patients with PHN pain or diabetic neuropathy (*Baron et al 2009a, Baron et al 2009b, Binder et al 2009, Rehm et al 2010, Rowbotham et al 1996*).

- Lidocaine topical system 1.8%
  - The approval of ZTlido (lidocaine topical system 1.8%) was based on trials that demonstrated the efficacy of *Lidoderm* for treatment of pain associated with PHN; no new clinical trials were required for FDA-approval (*The medical letter 2019*). In a single-dose, crossover study in 53 healthy volunteers, Ztlido 1.8% demonstrated equivalent exposure (area under the curve) and peak concentration of lidocaine to Lidoderm (*ZTlido prescribing information 2018*).

CLINICAL GUIDELINES

- Consensus guidelines for the use of topical anesthetics are lacking, therefore, decision making regarding the use of these agents is based on patient-specific factors and available comparative efficacy data.
  - The FDA recommends against using topical OTC medications for teething pain as some products may cause harm (*FDA Drug Safety* Communication *2018*).
  - The American Academy of Pediatrics (AAP) recommends managing teething pain with a chilled (not frozen) teething ring or gently rubbing/massaging with the caregiver's finger. Use of topical anesthetics for teething is discouraged by the AAP and American Academy of Pediatric Dentistry (AAPD) (*AAPD 2012).*
  - The 2010 European Federation of Neurological Societies (EFNS) guidelines on the pharmacological treatment of neuropathic pain suggest topical lidocaine may be considered first-line if there are concerns of adverse events with other oral medications in elderly patients who have PHN (*Attal et al 2010*).

SAFETY SUMMARY

- **Contraindications**
  - Hypersensitivity to any component of the formulation; hypersensitivity to another local anesthetic of the amide type.
- **Warnings**
  - *All drugs in class*
    - Methemoglobinemia: Cases of methemoglobinemia have been reported in association with local anesthetic use.

- Overexposure: To avoid overexposure that could lead to adverse effects:
  - Do not use for longer duration or over larger surface areas than recommended.
  - Consider total amount of local anesthetics absorbed from all formulations.
  - Do not apply to mucous membranes or broken or inflamed skin.
  - Use with caution in patients who may be more sensitive to systemic effects, including acutely ill or debilitated patients, or those with severe hepatic disease or pseudocholinesterase deficiency.
- Risk of secondary exposure to children and pets: store and dispose out of reach of children and pets due to the risk of accidental exposure and resulting toxicity.
- Eye irritation: avoid contact with eyes

○ *Oral topical lidocaine viscous solution*

- Boxed warning: Life-threatening and fatal events in infants and young children. There have been postmarketing cases of seizures, cardiopulmonary arrest, and death in patients < 3 years of age with use of lidocaine 2% viscous solution when it was not administered in strict adherence to the dosing and administration recommendations. Lidocaine 2% viscous solution should generally not be used for teething pain. For other conditions, the use of lidocaine 2% viscous solution in patients < 3 years of age should be limited to those situations where safer alternatives are not available or have been tried but failed. To decrease the risk of serious adverse events, caregivers should be instructed to strictly adhere to the prescribed dose and frequency of administration, and store the prescription bottle safely out of reach of children.

○ *Lidocaine patch and topical system*

- The lidocaine patch is only recommended for use on intact skin.
- Placement of external heat sources, such as heating pads or electric blankets, over lidocaine patches is not recommended.

- **Key drug interactions**
  - Lidocaine and lidocaine-prilocaine cream should be used with caution in patients receiving Class I antiarrhythmic drugs (such as tocainide and mexiletine) since the toxic effects are additive and potentially synergistic.
- **Adverse events**
  - Lidocaine topical patch: application site reactions such as irritation, erythema, and pruritus.
  - Topical lidocaine and prilocaine: application site erythema (21% to 30%), application site pain, genital mucous membrane burning (17%).
  - Topical lidocaine and tetracaine: erythema (47%), skin discoloration (16%), and edema (14%).
  - Patients with severe hepatic impairment are at increased risk of developing lidocaine toxicity.

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
lidocaine	Jelly 2%	Topical	Adults: No more than 30 mL (600 mg) in any 12-hour period according to the prescribing information	
lidocaine	Gel 2%, 3%, 4%	Topical	Apply to affected area ≤ 4 times daily as needed	
lidocaine	Lotion 3%, 3.5%, 4%	Topical	Apply a thin film to affected area 2 or 3 times daily	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
lidocaine	Ointment 5%	Topical	Adults: A single application not exceeding 5 g of ointment; maximum: 20 g per day.	
lidocaine	Viscous solution 2%	Topical	Adults: 15 mL orally no more frequently than every 3 hours; 8 doses per 24 hours. Pediatrics: ≥ 3 years of age: recommendations vary by age and weight. < 3 years of age: ≤ 1.2 mL (maximum: 4 doses per 12-hour period; use only if the underlying condition requires treatment with product volume of ≤ 1.2 mL)	Not approved for relief of teething pain and discomfort in infants and children; serious adverse (toxic) effects have been reported. Max: 4.5 mg/kg/dose (or 300 mg/dose).
lidocaine	Solution 4%	Topical	Adults: 1 to 5 mL (40 to 200 mg) per dose when used as a spray, applied with cotton applicators or packs, as when instilled into a cavity; maximum dose: 4.5 mg/kg, not to exceed 300 mg per dose Pediatrics: Dose varies with age and weight (maximum dose: 4.5 mg/kg)	
lidocaine	Cream 2%, 3%, 3.25%, 3.88%, 4%, 4.12%	Topical	Apply a thin film to the affected area 2 to 4 times daily for skin irritation.	
lidocaine	Rectal cream 5%	topical	Apply to affected area up to 6 times daily	
lidocaine	Topical system 1.8% Patch 5%	Topical	Apply patch to most painful area. Up to 3 patches may be applied in a single application. Patch(es) may remain in place for up to 12 hours in any 24-hour period.	Patches may be cut into smaller sizes with scissors prior to removal of the release liner
lidocaine-prilocaine	2.5-2.5% cream, 2.5-2.5% kit, 2.5-2.5% & 3.88% kit	Topical	Adults: A thick layer of lidocaine and prilocaine cream is applied to intact skin and covered with an occlusive dressing.	Should not be used in neonates with a gestational age less than 37 weeks nor in infants under

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				the age of 12 months who are receiving treatment with methemoglobin-inducing agents.
lidocaine-prilocaine and lidocaine	lidocaine-prilocaine cream 2.5-2.5% & lido patch 5% kit	Topical	Cream: A thick layer of lidocaine and prilocaine cream is applied to intact skin and covered with an occlusive dressing. Patch: Apply patch to most painful area. Up to 3 patches may be applied in a single application. Patch(es) may remain in place for up to 12 hours in any 24-hour period.	Lidocaine and prilocaine cream should not be used in neonates with a gestational age less than 37 weeks nor in infants under the age of 12 months who are receiving treatment with methemoglobin-inducing agents
Lidocaine-hydro-cortisone	2-2%, 3-0.5%, 3-1%, 3-2.5%, 2.8-0.55% kits	Topical	Twice daily or as directed.	
Lidocaine-tetracaine	Cream 7-7%	Topical	Apply 20 to 30 minutes before procedure.	See full prescribing information for amount according to treatment site.

(*Drug Facts & Comparison 2020, Lexicomp Online 2020*)

See the current prescribing information for full details.

CONCLUSION

- Many of the topical lidocaine and lidocaine/prilocaine products are available generically and are available in different formulations including cream, ointment, jelly, gel, and as a topical patch.
- Lidocaine produces its analgesics effects through a reversible nerve conduction blockade by diminishing nerve membrane permeability to sodium.
- In general, adverse reactions associated with topical lidocaine are dose-related and may result from high plasma levels due to excessive dosage or rapid absorption, hypersensitivity, idiosyncrasy, or diminished tolerance. Common adverse reactions include localized skin reactions.
- Clinical evidence supporting the use of the lidocaine 5% patch in the treatment of PHN is limited due to the lack of comparative data to show clinical effectiveness.
  - A Cochrane review found no evidence from good quality randomized controlled studies to support the use of topical lidocaine to treat neuropathic pain, although individual studies indicated that it is effective for relief of pain (*Derry et al 2014*).
- The evidence to support the use of lidocaine 5% patch for other types of pain is uncertain due to the lack of available evidence as the clinical trials that were conducted had small sample sizes and a short follow-up period, leading to a high risk of bias. However, EFNS guidelines suggest lidocaine patches can be considered first line for elderly patients with PHN at high risk for severe adverse effects with oral medications.

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Publication Date: April 1, 2020

Therapeutic Class Overview
Pancreatic Enzymes

INTRODUCTION

- Exocrine pancreatic insufficiency occurs in patients with diseases affecting the pancreas including chronic pancreatitis, cystic fibrosis, and carcinomas following resection. As a result of pancreatic enzyme deficiency, patients often develop malnutrition, including low levels of micronutrients, fat-soluble vitamins, and essential fatty acids, as well as weight loss and steatorrhea (*Nakajima et al 2012*).
- In addition to lifestyle modifications, pancreatic enzyme replacement therapy (PERT) with pancrelipase improves clinical symptoms (stool frequency and consistency) and malnutrition (*Nakajima et al 2012*).
- The pancrelipase products catalyze the hydrolysis of fats to monoglyceride, glycerol, and free fatty acids, proteins into peptides and amino acids, and starches into dextrins and short chain sugars such as maltose and maltriose.
- Pancrelipase products were available before the 1938 Food, Drug and Cosmetic Act required all new drugs to be subject to new drug applications (NDA). As a result, safety and efficacy studies were never performed with these products. In April 2004, the Food and Drug Administration (FDA) declared that all orally administered pancreatic enzyme products are considered new drugs and would require the submission and approval of an NDA if manufacturers wished to continue marketing their products. As of April 2010, manufacturers of unapproved pancrelipase products were required to discontinue the manufacturing and distribution of their products, or apply for FDA approval. The most recent version of postmarketing guidance for the use pancreatic enzyme products was updated in October 2016. The FDA does stipulate that these products are not interchangeable (*FDA postmarketing guidance 2016*).
- There are currently 5 available FDA-approved pancrelipase products for the treatment of exocrine pancreatic insufficiency (EPI). The specific FDA-approved indications of the available products are outlined in Table 2.
  - These products primarily differ in their available strengths.
  - All of the pancrelipase products are of porcine origin and contain a mixture of the digestive enzymes lipase, protease, and amylase.
- Due to the potential for enzymatic breakdown in the stomach, most of these products are formulated as enteric-coated, delayed-release capsules to delay drug release until entering the lower digestive tract. One exception is Viokace, which is formulated as a tablet and must be taken in combination with a proton pump inhibitor (PPI).
- The manufacturer dosing recommendations are generally the same across products, as the dosing is in accordance with the Cystic Fibrosis Foundation guidelines. Minor differences may exist for infant dosing based on the smallest strength available for a particular product.
- Consensus clinical guidelines support the use of PERT in the management of chronic pancreatitis and cystic fibrosis (*Borowitz et al 1995, Borowitz et al 2009, Lahiri et al 2016, Stallings et al 2008, Yankaskas et al 2004*). The Cystic Fibrosis Foundation recommends the use of pancreatic enzymes in infants, children, and adults with evidence of pancreatic insufficiency. Pancrelipase is generally dosed based on the lipase units of the formulation and may be calculated as weight-based dosing or on the basis of the fat content of a meal or snack (*Borowitz et al 2009).*
- Medispan Class: Gastrointestinal Agents, Digestive Aids - Digestive Enzymes, Pancrelipase (Lipase-Protease-Amylase)

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Creon (pancrelipase)	-
Pancreaze (pancrelipase)	-
Pertzye (pancrelipase)	-
Viokace (pancrelipase)	-
Zenpep (pancrelipase)	-

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Creon	Pancreaze	Pertzye	Viokase	Zenpep
Treatment of EPI due to cystic fibrosis, chronic pancreatitis, pancreatectomy or other conditions	✔				
Treatment of EPI due to cystic fibrosis or other conditions		✔	✔		✔
Treatment of adults with EPI due to chronic pancreatitis or pancreatectomy in combination with a PPI				✔	

(Prescribing information: Creon 2020, Pancreaze 2020, Pertzye 2020, Viokace 2020, Zenpep 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

- Despite relatively recent FDA approval of several pancreatic enzyme products, there are limited clinical studies available (*Colombo et al 2009, Graff et al 2010[a], Graff et al 2010[b], Gubergrits et al 2011, Toskes et al 2011, Trapnell et al 2009, Trapnell et al 2011, Whitcomb et al 2010, Van de Vijver et al 2011*). To date, only 1 active-comparator study has compared agents head-to-head (*Taylor et al 2016*).
- Colombo et al evaluated Creon in patients < 24 months of age with cystic fibrosis and EPI (n = 12). Two weeks treatment with Creon resulted in a significant increase in the mean coefficient of fat absorption (CFA) (the primary endpoint) from 58% at baseline to 84.7% (p = 0.0013). Statistically significant improvements in stool fat content were also reported in the Creon group (p = 0.001) (*Colombo et al 2009*).
- *Trapnell et al* reported a statistically significant improvement in the CFA during a double-blind (DB), short-term, 2-period crossover study of cystic fibrosis patients ≥ 12 years of age (n = 32) with EPI who received Creon treatment compared to patients receiving placebo (88.6% vs 49.6%; p < 0.001) (*Trapnell et al 2009*).
- Creon was studied in 17 pediatric patients 7 to 11 years of age with cystic fibrosis and EPI. In a crossover study design, treatment with Creon was associated with a statistically significant increase in the CFA compared to treatment with placebo (least squares mean [LSM], 82.8% vs 47.4% [standard error {SE}, 2.7% for each]; p < 0.001). Furthermore, Creon was more effective compared to placebo when patients were stratified by their baseline CFA ≤ 50% (p < 0.001) and > 50% (p = 0.008) (*Graff et al 2010[a]*).
- In a 7-day, DB, randomized, placebo-controlled (PC), parallel-group trial of patients ≥ 18 years of age with chronic pancreatitis or total or partial pancreatectomy, those treated with Creon experienced a significantly greater mean ± standard deviation change from baseline in CFA compared to patients treated with placebo (32.1 ± 18.5 vs 8.8 ± 12.5%; p < 0.0001). In addition, statistically significant improvements in coefficient of nitrogen absorption (CNA), stool fat, stool frequency, and stool nitrogen content occurred with Creon treatment (p < 0.005 for all) (*Whitcomb et al 2010*).
- In a 6-month, open-label (OL) extension of the Whitcomb et al trial, patients achieved a significantly reduced daily stool frequency compared to baseline (-1 ± 1.3; p < 0.001). Moreover, a greater percentage of patients reported no abdominal pain (66% vs 37.3%), an improvement in abdominal pain (44.7% vs 10.6%) and greater stool consistency compared to baseline (68.1% vs 21.6%; p values not reported) (*Gubergrits et al 2011*).
- Pancreaze was evaluated in a 7-day study of 49 patients with cystic fibrosis and EPI. All patients received Pancreaze during the OL phase and were subsequently randomized to continue on Pancreaze or placebo. Pancreaze treatment significantly improved fat absorption as demonstrated by a significantly lower mean change in CFA between the OL and DB phases for Pancreaze compared to placebo (-1.5% vs -34.1%; p < 0.001) (*Trapnell et al 2011*).
- Pertzye, an enteric-coated, bicarbonate-buffered pancreatic enzyme, was evaluated in a DB, PC, cross-over trial of 24 children and adults with cystic fibrosis and EPI. There was statistically significant improvement in the CFA in active treatment vs placebo (82.5% vs 46.3%, p < 0.001). Stool frequency and stool weight were reduced by 40% and 50%,

respectively, in the active treatment groups as well (p < 0.001 for both). The addition of bicarbonate to the product may increase the release and activation of the enzymes, although no product comparison studies have been done (*Konstan et al 2013*).

- Viokace, the only non-enteric-coated agent in class, was evaluated in a randomized, DB, trial of 50 adults with EPI due to chronic pancreatitis (n = 32) or pancreatectomy (n = 18). Patients were randomized to pancrelipase (22 tablets/day [20,880 lipase units/tablet]) or placebo, in combination with a PPI, and maintained on a controlled high fat diet of 100 grams of fat/day. After a 72-hour stool collection, the mean CFA was 48% for Viokace -treated patients and 57% for placebo-treated patients after the wash-out period; and at the end of the DB period 86% and 58%, respectively (mean difference, 28%; 95% CI, 21 to 37%; p ≤ 0.0001) favoring treatment with Viokace (*Micromedex 2020, Viokace prescribing information 2020*).
- *Toskes et al* evaluated 2 doses of Zenpep in 72 patients with chronic pancreatitis and EPI. The mean CFA was significantly higher with low-dose and high-dose Zenpep compared to the placebo run-in period (88.8% vs 89.9% vs 82%; p < 0.001); however, there was no statistically significant difference between the 2 doses of Zenpep (p = 0.228) (*Toskes et al 2011*).
- One randomized, DB, active-comparator, cross-over, noninferiority trial compared Zenpep and Creon in cystic fibrosis patients aged ≥ 12 years living in Europe. Patients had EPI secondary to cystic fibrosis and were stabilized on diet and treatment. A total of 96 patients (89.6% completed study) were randomized to Zenpep or Creon with 25,000 lipase units for 28 days and then each group crossed over to the other treatment with no washout. Zenpep and Creon were considered non-inferior to each other in terms of fat absorption (LSM CFA over 72 hours, 84.1% vs 85.3% [SE, 1.1 for each], respectively; p = 0.297). No significant difference in body weight, signs and symptoms of EPI, and patient-reported overall health, perceived well-being, and cystic fibrosis symptoms. The number of patients reporting treatment emergent adverse events were numerically lower for Zenpep (19.6%) vs Creon (25.6%). Overall, the efficacy and safety of Zenpep and Creon were similar (*Taylor et al 2016*).
- A systematic review of 14 trials evaluated the efficacy and safety of PERT in children and adults with CF, compared different formulations of PERT, and their appropriateness in different age groups. Data did not support one PERT formulation was superior to another for outcomes related to weight, height, or body mass index (BMI). In 2 trials (n = 41), delayed-release microsphere formulations had less fat in the stool and fewer incidences of abdominal pain. There was no difference between any PERT formulations for any other bowel symptoms (eg, abdominal pain, flatulence, constipation), quality of life, adverse events or for any measure of lung disease. None of the trials reported the number of days in hospital or the incidence of vitamin deficiency (*Somaraju et al 2020*).

CLINICAL GUIDELINES

- Clinical guidelines for cystic fibrosis and chronic pancreatitis support the use of the PERT products in accordance with the recommended dosing. Doses of PERT should be commenced at the lowest recommended dose and titrated based on presence of malabsorption to the lowest effective dose (*Borowitz et al 1995, Borowitz et al 2009, Lahiri et al 2016, Stallings et al 2008, Yankaskas et al 2004*).
- The Cystic Fibrosis Foundation guidelines recommend the following growth and weight-status recommendations for children and adolescents (*Stallings et al 2008)*:
  - For patients aged > 2 years, energy intakes of 110 to 200% of requirements for healthy patients of similar age, sex, and size results in improved weight gain.
  - Maintenance of a normal weight- and stature-for-age in children, and a normal weight-for-height in adults, was associated with better forced expiratory volume (FEV_1) and survival.
  - Children and adolescents aged 2 to 20 years should maintain a BMI ≥ 50th percentile. Children aged < 2 years should reach a weight-for-length ≥ 50th percentile by 2 years. For adults, women should maintain a BMI ≥ 22 while men should maintain a BMI ≥ 23. These recommendations were based on results showing that maintenance of these growth parameters was associated with higher FEV_1 measurements.
  - For children and adults, PERT dosing should be 500 to 2500 units lipase per kg body weight per meal; or < 10,000 units lipase per kg body weight per day; or < 4000 units lipase per gram dietary fat.

SAFETY SUMMARY

- Pancreatic enzyme products have no known contraindications.
- The warnings and precautions associated with pancrelipase products include allergic reactions, fibrosing colonopathy, hyperuricemia, oral mucosal irritation, and viral exposure.
- There is a theoretical risk of viral transmission with all pancreatic enzyme products.
- The most common adverse effects with pancrelipase are diarrhea, dyspepsia, neck pain, and nasal congestion. Serious adverse effects associated with pancrelipase include fibrosing colonopathy, hyperuricemia, and lymphadenopathy.
- No significant drug interactions have been identified with pancrelipase.
- Viokace tablets contain lactose monohydrate and may not be tolerated by patients who have lactose intolerance.
- Irritation of the oral mucosa may occur if pancreatic enzyme products are retained in the mouth. After administration, the mouth should be inspected and rinsed with water, milk, or formula if necessary to remove product remaining on the oral mucosa (*Katkin et al 2020*).
- A pediatric postmarketing pharmacovigilance review of the 5 pediatric enzyme products was conducted by the FDA for any adverse events with serious outcomes during the period of June 2013 to May 2018. There was no evidence from these data to suggest that there any pediatric safety concerns with the pediatric pancreatic enzymes; routine monitoring is recommended with these agents *(FDA postmarketing pharmacovigilance review 2018).*

DOSING AND ADMINISTRATION

- The FDA has updated questions and answers for healthcare professions regarding the approved use of pancreatic enzyme products. In terms of switching a patient from 1 pancreatic enzyme product to another, the guidance suggests considering initiating therapy with a similar amount of lipase, and then adjusting based on patient response. Adjustments to a new dose may take 1 to 2 weeks depending upon the patient. Individual responses should be monitored (*FDA postmarketing guidance 2016).*

Table 3. Dosing and Administration

Drug	Dosage Form: Strength*	Usual Recommended Dose	Administration Considerations
Creon (pancrelipase)	Delayed-release capsule: 3000/9500/15,000 units 6000/19,000/30,000 units 12,000/38,000/60,000 units 24,000/76,000/120,000 units 36,000/114,000/180,000 units	Treatment of EPI due to cystic fibrosis, chronic pancreatitis, pancreatectomy or other conditions (adults and children ≥ 4 years old): Initial: 500 lipase units/kg per meal; maximum, 2500 lipase units/kg per meal (or ≤ 10,000 lipase units/kg daily) or < 4000 lipase units/g fat ingested per day Treatment of EPI due to cystic fibrosis, chronic pancreatitis, pancreatectomy or other conditions (children > 12 months and < 4 years old): Initial: 1000 lipase units/kg per meal; maximum, 2500 lipase units/kg per meal (or ≤ 10,000 lipase units/kg daily) or < 4000 lipase units/g fat ingested per day Treatment of EPI due to cystic fibrosis, chronic pancreatitis, pancreatectomy or other conditions (infants ≤ 12 months old): 3000 lipase units (1 capsule) per 120 mL of formula or breast-feeding	For infants < 12 months old, capsule contents may be administered directly to the mouth followed by breast milk or formula; do not mix capsule contents directly into formula or breast milk prior to administration Take with meals and snacks with sufficient fluid. Swallow capsule whole. For patients unable to swallow the whole capsule, the contents can be sprinkled on soft acidic food, such as applesauce.

Drug	Dosage Form: Strength*	Usual Recommended Dose	Administration Considerations
		Dosage should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet.	
Pancreaze† (pancrelipase)	Delayed-release capsule: 2600/6200/10,850 units 4200/14,200/24,600 units 10,500/35,500/61,500 units 16,800/56,800/98,400 units 21,000/54,700/83,900 units	Treatment of EPI due to cystic fibrosis or other conditions (adults and children ≥ 4 years old): Initial: 500 lipase units/kg per meal; maximum, 2500 lipase units/kg per meal (or ≤ 10,000 lipase units/kg daily) or < 4000 lipase units/g fat ingested per day Treatment of EPI due to cystic fibrosis or other conditions (children > 12 months and < 4 years old): Initial: 1000 lipase units/kg per meal; maximum: 2500 lipase units/kg per meal (or ≤ 10,000 lipase units/kg daily) or < 4000 lipase units/g fat ingested per day Treatment of EPI due to cystic fibrosis or other conditions (infants ≤ 12 months old): 2600 lipase units (1 capsule) per 120 mL of formula or per breast-feeding Dosage should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet.	For infants < 12 months old, capsule contents may be administered directly to the mouth followed by breast milk or formula; do not mix capsule contents directly into formula or breast milk prior to administration Take with meals and snacks with sufficient fluid. Swallow capsule whole. For patients unable to swallow the whole capsule, the contents can be sprinkled on soft acidic food with a pH of 4.5 or less, such as applesauce.
Pertzye (pancrelipase)	Delayed-release capsule: 4000/14,375/15,125 units 8000/28,750/30,250 units 16,000/57,500/60,500 units 24,000/86,250/90,750 units	Treatment of EPI due to cystic fibrosis or other conditions (adults and children ≥ 4 years old and weight ≥ 16 kg): Initial: 500 lipase units/kg per meal; maximum: 2500 lipase units/kg per meal (or ≤ 10,000 lipase units/kg daily) or < 4000 lipase units/g fat ingested per day Treatment of EPI due to cystic fibrosis or other conditions (children > 12 months but < 4 years old and weight ≥ 8 kg): Initial: 1000 lipase units/kg per meal; maximum: 2500 lipase units/kg per meal (or ≤ 10,000 lipase units/kg daily) or < 4000 lipase units/g fat ingested per day Treatment of EPI due to cystic fibrosis or other conditions (infants up to 12 months): 4000 lipase units (1 capsule) per 120 mL of formula or per breast feeding	For infants < 12 months old, capsule contents may be administered directly to the mouth prior to each feeding; do not mix capsule contents directly into formula or breast milk prior to administration. Take with meals and snacks with sufficient fluid. Swallow capsule whole. For patients unable to swallow the whole capsule, the contents can be sprinkled on soft acidic food with a pH of 4.5

Drug	Dosage Form: Strength*	Usual Recommended Dose	Administration Considerations
		Dosage should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet.	or less, such as applesauce. Consume the entire capsule contents immediately. Careful not to crush the microsphere contents.
Viokace (pancrelipase)	Tablet: 10,440/39,150/39,150 units 20,880/78,300/78,300 units	Treatment of adults with EPI due to chronic pancreatitis or pancreatectomy in combination with a PPI: Initial: 500 lipase units/kg per meal; maximum: 2500 lipase units/kg per meal (or ≤ 10,000 lipase units/kg daily) or < 4000 lipase units/g fat ingested per day Dosage should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet.	Take with meals and snacks with sufficient fluid. Swallow tablet whole. Tablets are not enteric coated and should be taken in combination with a PPI.
Zenpep (pancrelipase)	Delayed-release capsule: 3000/10,000/14,000 units 5000/17,000/24,000 units 10,000/32,000/42,000 units 15,000/47,000/63,000 units 20,000/63,000/84,000 units 25,000/79,000/105,000 units 40,000/126,000/168,000 units	Treatment of EPI due to cystic fibrosis or other conditions (adults and children ≥ 4 years old): Initial: 500 lipase units/kg per meal; maximum: 2500 lipase units/kg per meal (or ≤ 10,000 lipase units/kg daily) or < 4000 lipase units/g fat ingested per day Treatment of EPI due to cystic fibrosis or other conditions (children > 12 months but < 4 years old): Initial: 1000 lipase units/kg per meal; maximum: 2500 lipase units/kg per meal (or ≤ 10,000 lipase units/kg daily) or < 4000 lipase units/g fat ingested per day Treatment of EPI due to cystic fibrosis or other conditions (infants ≤ 12 months old): 3000 lipase units (1 capsule) per 120 mL of formula or breast-feeding Dosage should be individualized based on clinical symptoms, the degree of steatorrhea present, and the fat content of the diet.	For infants < 12 months old, capsule contents may be administered directly to the mouth followed by breast milk or formula; do not mix capsule contents directly into formula or breast milk prior to administration Take with meals and snacks with sufficient fluid. Swallow capsule whole. For patients unable to swallow the whole capsule, the contents can be sprinkled on soft acidic food, with a pH of 4.5 or less such as applesauce.

See the current prescribing information for full details

*Dosage expressed as lipase/protease/amylase

†Dosage recommendations for pancreatic enzyme replacement therapy were published following the Cystic Fibrosis Foundation Consensus Conferences. Pancreaze should be administered per recommendations with 1 exception. The Conferences recommend doses of 2000 to 4000 lipase units in infants up to 12 months. Pancreaze is available in a 2600 lipase unit capsule. The recommended dose of Pancreaze is contained correctly within the table.

CONCLUSION

- There are currently 5 available pancrelipase products indicated as PERTs for the treatment of EPI due to cystic fibrosis, chronic pancreatitis, and other conditions. These agents include Creon, Pancreaze, Pertzye, Viokace, and Zenpep. Of these, Creon and Viokace are also approved for EPI resulting from pancreatectomy. Creon, Pancreaze, Pertzye, and Zenpep are approved for use in infants less than 12 months of age. The safety and efficacy of Viokace in children have not been established.
- All of these products with the exception of Viokace are formulated as enteric-coated, delayed-release capsules to prevent their breakdown in the stomach and enhance drug release in the duodenum. Viokace is formulated as a tablet and must be taken in combination with a PPI. Viokace may not be tolerated in patients with lactose intolerance.
- The approval of these products resulted from the FDA's decision to require all manufacturers of pancrelipase products to submit a NDA and receive approval for continued marketing and manufacturing. Historically, the generic pancrelipase products were available before the Food, Drug and Cosmetic Act required the safety and efficacy of a drug to be established before marketing.
- Limited available clinical studies have demonstrated that pancrelipase is associated with statistically significant improvements in the CFA, CNA, and stool frequency and consistency compared to placebo. Studies were generally of short duration, enrolled only a small number of patients, and have not demonstrated clinically meaningful differences between treatments *(Colombo et al 2009, Graff et al 2010[a], Graff et al 2010[b], Gubergrits et al 2011, Taylor et al 2016, Toskes et al 2011, Trapnell et al 2009, Trapnell et al 2011, Whitcomb et al 2010, Van de Vijver et al 2011*).
- Clinical guidelines for cystic fibrosis and chronic pancreatitis support the use of the PERT products in accordance with each product's recommended dosing (*Borowitz et al 1995, Borowitz et al 2009, Lahiri et al 2016, Stallings et al 2008, Yankaskas et al 2004*).

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Publication Date: March 27, 2021

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 2021*).
- 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 2021*).
- 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 2021*). Bydureon pen is being phased out and replaced with Bydureon BCise, an autoinjector device that allows for more convenient administration (*AstraZeneca 2021).*
- 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) and semaglutide (Wegovy) are also indicated as adjunctive therapy for chronic weight management; however, the use of liraglutide and semaglutide 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 BCise (exenatide ER)*	-
Byetta (exenatide)	
Ozempic (semaglutide)	-
Rybelsus (semaglutide)	-
Symlin (pramlintide)	-
Trulicity (dulaglutide)	-
Victoza (liraglutide)	-

*Bydureon pen has been discontinued by the manufacturer and has been replaced by the BCise autoinjector device.

(*DRUGS@FDA 2021*, *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 2. FDA Approved Indications

Indication	Adlyxin (lixisenatide)	Byetta (exenatide)	Bydureon BCise (exenatide ER)	Ozempic (semaglutide)	Rybelsus (semaglutide)	Symlin (pramlintide)	Trulicity (dulaglutide)	Victoza (liraglutide)
Indications								
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 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.	✔							
Not indicated in treatment of patients with T1DM.		✔	✔	✔	✔		✔	✔
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.	✔							
Should not be used with other products containing the active ingredient.		✔	✔					✔

(Prescribing information: *Adlyxin 2019*, *Bydureon BCise 2020, Byetta 2021, Ozempic 2021, Rybelsus 2021, Symlin 2019, Trulicity 2021, Victoza 2020*)

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 hemoglobin A1c (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 open-label (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, gastrointestinal (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 2019*).

- 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 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% confidence interval [CI], -0.62% to -0.02%) (*Bydureon BCise Prescribing Information 2020, 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 [MD], -1.06%; 95% CI, -1.65 to -0.46; $p < 0.001$), which was maintained over an additional 26-week OL extension (MD, -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 2019, 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 2019, Rosenstock et al 2014*).
  - GetGoal-P was a 24-week, DB study which found that lixisenatide 20 mcg once daily in combination with pioglitazone with 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 2019, 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 MD of lixisenatide vs insulin glulisine 3 times daily was 0.23 ($p = 0.0002$) (*Adlyxin Prescribing Information 2019, 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 MD vs exenatide was 0.17% ($p = 0.0175$) (*Adlyxin Prescribing Information 2019, 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 2021*).
  - 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 2021*).
  - 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 2021*).
  - 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, multicenter (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-1 receptor agonists *(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-1 receptor agonists class and higher than those observed with empagliflozin and sitagliptin *(Buse et al 2019).*
  - PIONEER 2 (N = 822) was a 52-week, Phase 3a, OL, MC RCT that compared Rybelsus 14 mg (n = 412) to the SGLT2 inhibitor 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-1 receptor agonist 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 SGLT2 inhibitor *(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 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% 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 (HF) 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 HF 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 HF were non-significantly 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 macro albuminuria, 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 major adverse cardiovascular event (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 (HR, 0.79; 95% 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 2021)*.

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 (*Avgerinos et al 2020*, *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)*.
- A systematic review and meta-analysis of 16 observational cohort studies in patients with T2DM (N = 285,436) found that overall, the results favored GLP-1 receptor agonists for all-cause mortality (HR, 0.63; 95% CI, 0.44 to 0.89) and CV events (HR, 0.84; 95% CI, 0.75 to 0.94) vs other antidiabetic treatment regimens (including OADs and insulin); results for hospitalization for HF were neutral (HR, 0.94; 95% CI, 0.78 to 1.14) (*Herrera Comoglio et al 2020*).
- A systematic review and network meta-analysis comparing treatments for T2DM found that patients at increased CV risk receiving background metformin (N = 145,694) had a reduced risk of all-cause mortality and CV death with the addition of oral semaglutide (odds ratio [OR], 0.50; 95% CI, 0.31 to 0.83 and OR, 0.51; 95% CI, 0.28 to 0.94, respectively) or liraglutide (OR, 0.84; 95% CI, 0.73 to 0.97 and OR, 0.78; 95% CI, 0.65 to 0.93) vs placebo. The addition of exenatide ER only reduced all-cause mortality vs placebo (OR, 0.86; 95% CI, 0.76 to 0.98). The odds of stroke were lowered with both dulaglutide (OR, 0.76; 95% CI, 0.62 to 0.94) and subcutaneous semaglutide (OR, 0.61; 95% CI, 0.37 to 0.99) (*Tsapas et al 2020*).
- A meta-analysis of the 10 PIONEER trials demonstrated that when compared to an active comparator, oral semaglutide significantly reduced HbA1c by 0.33% ($p < 0.00001$) and body weight by 1.52 kg ($p < 0.00001$), and significantly increased the number of patients who achieved an HbA1c < 7.0% by 47% ($p = 0.0006$).The clinical significance of the changes in HbA1c and body weight with oral semaglutide vs other antidiabetic agents is unclear (*Li et al 2021*).
- A network meta-analysis was performed to compare the effect of newer antidiabetic agents (SGLT2 inhibitors, GLP-1 receptor agonists, and DPP-4 inhibitors) on a composite kidney outcome (kidney death and clinical end-stage kidney disease). A total of 7 RCTs were included (N = 58,346) with patients being randomized to either placebo or canagliflozin (n = 14,543), dapagliflozin (n = 17,160), empagliflozin (n = 7018), linagliptin (n = 6979), liraglutide (n = 9340), and semaglutide (n = 3297). Dapagliflozin showed the highest reduction in the risk of the composite kidney outcome (HR, 0.53; 95% CI, 0.43 to 0.66), followed by empagliflozin (HR, 0.61; 95% CI, 0.53 to 0.70), canagliflozin (HR, 0.63; 95% CI, 0.54 to 0.74), semaglutide (HR, 0.64; 95% CI, 0.46 to 0.88), and liraglutide (HR, 0.78; 95% CI, 0.67 to 0.91) *(Cha et al 2021)*.

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 58 trials evaluated the efficacy and safety of glucose-lowering drugs used as an adjunct to insulin therapy in adults with type 1 diabetes (*Avgerinos et al 2021*). Relevant results from the network meta-analysis for pramlintide are as follows: pramlintide was superior to placebo for reduction in bolus insulin dose (MD, -4.36 units; 95% CI, -8.37 to -0.35); pramlintide was superior to rosiglitazone and placebo for change in body weight (MD, -2.78 kg [95% CI, -4.85 to -0.71] and MD, -1.73 kg [95% CI, -2.41 to -1.06], respectively); and pramlintide increased the risk of treatment discontinuation and nausea vs placebo (OR, 2.53 [95% CI, 1.61 to 3.97] and OR, 4.07 [95% CI, 2.57 to 6.42], respectively)

- 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 (MD, -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 2021, Buse et al 2020, Das et al 2020, 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 ASCVD, HF, or CKD, independent of HbA1c. Metformin is considered the drug of choice for children with T2DM *(ADA 2021, Buse et al 2020, Copeland et al 2013, Das et al 2020, Garber et al 2020, KDIGO 2020, Rangaswami et al 2020)*.

- **ADA: Standards of Medical Care in Diabetes: Pharmacological therapy for T2DM** *(ADA 2021)*
  - 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).
  - choice of add-on therapy should be determined based on 1) whether the patient has indicators of high risk or established ASCVD, CKD, or HF; and 2) in patients without these conditions, whether there is a compelling need to minimize hypoglycemia or to minimize weight gain or promote weight loss.
    - If ASCVD predominates, recommendations are:
      - Preferably a GLP-1 receptor agonist with proven cardiovascular disease (CVD) benefit; or
      - An SGLT2 inhibitor with proven CVD benefit (if estimated glomerular filtration rate [eGFR] is adequate)
    - If HF predominates, recommendations are:
      - Preferably an SGLT2 inhibitor with proven benefit in this population (ie, dapagliflozin and empagliflozin)
    - If CKD predominates, recommendations are:
      - Preferably an SGLT2 inhibitor with evidence of reducing CKD progression in cardiovascular outcome trials if eGFR is adequate (ie, canagliflozin and dapagliflozin); or
      - If the SGLT2 inhibitor is not tolerated or is contraindicated, or if the eGFR is less than adequate, a GLP-1 receptor agonist with proven CVD benefit

- In patients with T2DM and CKD and thus at increased risk of cardiovascular events, either an SGLT2 inhibitor with proven CVD benefit or GLP-1 receptor agonist with proven CVD benefit.

▪ In patients without established ASCVD, CKD, or HF, recommendations are:
- If there is a compelling need to minimize hypoglycemia: a DPP-4 inhibitor, a GLP-1 receptor agonist, an SGLT2 inhibitor, or a TZD; or
- If there is a compelling need to minimize weight gain or promote weight loss: a GLP-1 receptor agonist with good efficacy for weight loss or an SGLT2 inhibitor.

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 CV disease benefits.
- GLP-1 receptor agonists based on exendin-4 have been proven to be safe in CV disease, but they have not been shown to confer CV 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. 2020 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

Drug Class	Hypoglycemia	Weight	Renal/GU	GI	Cardiac	Bone	Ketoacidosis
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 CV 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-1 receptor agonists increase insulin and glucagon production in the liver, increase glucose uptake in muscle and adipose tissue, and decrease hepatic glucose production. Three GLP-1 receptor agonists have been found to significantly reduce the risk of ASCVD in adults with T2DM who are at high ASCVD risk.

- **American College of Cardiology: Expert Consensus Decision Pathway on Novel Therapies for Cardiovascular Risk Reduction in Patients with Type 2 Diabetes** *(Das et al 2020)*

- Based on the CV benefits with GLP-1 receptor antagonists and SGLT2 inhibitors, a discussion of benefits should be initiated with patients who are at high risk for ASCVD, HF, or diabetic kidney disease (DKD).
  - A GLP-1 receptor antagonist with CV benefit is recommended in patients with established or very high risk for ASCVD. Albiglutide [discontinued in the US], dulaglutide, liraglutide, and injectable semaglutide have proven benefit in reducing CV events. Exenatide once weekly and oral semaglutide have demonstrated numerically favorable but not statistically significant reductions in CV events. Lixisenatide is not associated with a reduction in ASCVD event risk.
  - The ACC pathway considers dulaglutide, liraglutide, and injectable semaglutide as the preferred GLP-1 receptor agonists for patients with T2DM and ASCVD or at high risk for ASCVD.
  - Concomitant use of SGLT2 inhibitors or GLP-1 receptor antagonists with sulfonylurea, glinides, or insulin increases the risk of hypoglycemia.
    - When starting an SGLT2 inhibitor or GLP-1 receptor antagonist for CV benefit in patients with well-controlled baseline HbA1c, SFUs should be weaned or stopped, and insulin doses should be decreased by approximately 20%. Treatment with DPP-4 inhibitors should be discontinued prior to initiating a GLP-1 receptor antagonist.
    - Patients should monitor for hypoglycemia for the first 4 weeks of therapy. Consider discontinuing sulfonylurea agents and glinides or decreasing insulin based on glucose monitoring.

- **American Heart Association: Scientific Statement on Cardiorenal Protection with the Newer Antidiabetic Agents in Patients with Diabetes and Chronic Kidney Disease** *(Rangaswami et al 2020)*
  - Initiation of an SGLT2 inhibitor or GLP-1 receptor agonist is recommended in patients with T2DM and CKD, given their renoprotective benefits and reduction of CV AEs.
    - Given that the benefit appears to be a class wide effect, selection of a specific SGLT2 inhibitor or GLP-1 receptor antagonist should be based on affordability.
    - Phenotype of CVD may influence selection of SGLT2 inhibitor versus GLP-1 receptor agonists, as SGLT2 inhibitors display dominant benefits for HF and GLP-1 receptor agonists for ASCVD.
    - Severity of CKD may also be considered when selecting an agent, since GLP-1 receptor antagonists are better studied in severe CKD.

- **Kidney Disease Improving Global Outcomes (KDIGO): Clinical Practice Guideline for Management in Chronic Kidney Disease** *(KDIGO 2020)*
  - First line therapy for patients with T2DM and CKD with an eGFR ≥30 ml/min/1.73 m^2 includes metformin and an SGLT2 inhibitor, with additional therapy as needed to achieve glycemic control.
    - Preference should be given to SGLT2 inhibitors with CV and kidney benefits.
    - If HbA1c goals are not achieved with metformin and SGLT2 inhibitors, or a patient is unable to use either medication, a long-acting GLP-1 receptor agonist with cardiovascular benefits is recommended.
    - Insulin and SFU doses may need to be decreased or stopped in the setting of hypoglycemia when used with GLP-1 receptor agonists and SGLT2 inhibitors.
    - Medications within the following classes should be utilized if glycemic control is not achieved with first line or preferred second line agents: DPP-4 inhibitors, insulin, SFUs, TZDs, and alpha-glucosidase inhibitors.

SAFETY SUMMARY

- GLP-1 receptor agonists are contraindicated in patients with hypersensitivity to any component of the products. With the exception of exenatide twice daily injection 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). Exenatide and exenatide ER are also contraindicated in patients with a history of drug-induced immune-mediated thrombocytopenia from exenatide products.
- All GLP-1 receptor agonists, except exenatide twice daily injection 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. Dulaglutide, exenatide, and exenatide ER are not recommended for patients with severe gastrointestinal disease, including gastroparesis; lixisenatide is also not recommended for patients with gastroparesis. 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. Dulaglutide also carries a warning for diabetic retinopathy complications based data from a CV outcomes trial. 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.
- The pregnancy risks for dulaglutide, exenatide, exenatide ER, liraglutide, pramlinitide, 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 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.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
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 MACE in patients with established CV disease, and dulaglutide is also approved to reduce the risk of MACE in patients with multiple CV risk factors. 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. Bydureon pen is being phased out and replaced by Bydureon BCise, an autoinjector device that allows for more convenient administration (*AstraZeneca 2021).* 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 PIONEER 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 twice daily injection, all of the agents (including exenatide ER) have a boxed warning regarding the risk of thyroid C-cell tumors. Exenatide and exenatide ER are contraindicated in patients with a history of drug-induced immune-mediated thrombocytopenia from exenatide products. 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. Dulaglutide, exenatide and exenatide ER are not recommended for patients with severe gastrointestinal disease, including gastroparesis; lixisenatide is also not recommended for patients with gastroparesis. Liraglutide and exenatide ER also have a warning for acute gallbladder disease, while dulaglutide and semaglutide have a warning for diabetic retinopathy complications.
- According to current clinical guidelines for the management of T2DM, metformin is recommended first-line for the initial pharmacologic treatment of T2DM, and GLP-1 receptor agonists are among the second-line options. GLP-1 receptor agonists or SGLT2 inhibitors should be considered for patients with established ASCVD, high ASCVD risk, HF, or CKD, independent of HbA1c *(ADA 2021, Das et al 2020, Garber et al 2020, KDIGO 2020, Rangaswami et al 2020).* A 2020 AHA scientific statement and 2020 KDIGO guideline both note that GLP-1 receptor agonists are preferred over SGLT2 inhibitors for patients with severe CKD (*Rangaswami et al 2020, KDIGO 2020)*. A 2020 ACC expert consensus decision pathway for patients with T2DM and ASCVD or high risk for ASCVD recognizes dulaglutide, liraglutide, and injectable semaglutide as the preferred GLP-1 receptor agonists (*Das 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 2021, Garber et al 2020*).

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Publication Date: July 26, 2021

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] 2021[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 2021[b])*.
- In 2018, an estimated 34.2 million people, or 10.5%, of the United States (US) population had diabetes mellitus, with 7.3 million estimated to be undiagnosed *(Centers for Disease Control and Prevention [CDC] 2020)*.
- 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 2021)*. 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)*. A novel formulation of insulin lispro, Lyumjev (insulin lispro-aabc) was also approved in June 2020 (*Drugs@FDA 2021*). Lyumjev is a new formulation of Humalog with a quicker onset; appearance in the blood occurs approximately 1 minute after injection of Lyumjev (*Eli Lilly press release 2020, Lyumjev prescribing information 2020*).
  - 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 and Semglee (insulin glargine) were FDA approved via new drug applications (NDAs) under the 505(b)(2) pathway. As of March 2020, the NDA for Semglee was automatically

deemed to be a biologic licensing application (BLA) via section 351(a) via the Biologics Price Competition and Innovation Act *(Fierce Biotech FDA press release 2015, Drugs@FDA 2021, Hagen 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.
- 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)	✔ *
Lyumjev (insulin lispro-aabc)	-
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)	-
Semglee (insulin glargine)	-
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)	-

Drug	Generic Availability
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 2021, Purple Book: Database of Licensed Biological Products 2021)

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 (insulin lispro)			✔ *#
Afrezza (insulin human)		✔ §	
Apidra (insulin glulisine)			✔ #
Fiasp (insulin aspart)			✔
Humalog (insulin lispro)			✔
Lyumjev (insulin lispro-aabc)		✔ #	
Novolog (insulin aspart)			✔
Short-Acting Insulins			
Humulin R (insulin, regular, human recombinant)			✔ ¥
Novolin R (insulin, regular, human recombinant)			✔
Intermediate-Acting Insulins			
Humulin N (insulin, NPH human recombinant isophane)			✔
Novolin N (insulin, NPH human recombinant isophane)			✔
Long-Acting Insulins			
Basaglar (insulin glargine)			✔ ‡
Lantus (insulin glargine)			✔ ‡
Levemir (insulin detemir)			✔ †
Semglee (insulin glargine)			✔ †‡¶
Toujeo (insulin glargine U-300)			✔ †¶
Tresiba (insulin degludec)			✔ ‖
Combination Insulins, Rapid-Acting and Intermediate-Acting			
Humalog Mix 50/50 Humalog Mix 75/25 (insulin lispro protamine/insulin lispro)	✔		
Novolog Mix 70/30 (insulin aspart protamine/insulin aspart)		✔	
Combination Insulins, Short-Acting and Intermediate-Acting			

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
Humulin 70/30 (NPH, human insulin isophane/regular human insulin)		✔	
Novolin 70/30 (NPH, human insulin isophane/regular human insulin)			✔

*Indicated for patients ≥ 3 years of age for T1DM and adults with T2DM.
† 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.
#Should generally be used in regimens with an intermediate or long-acting insulin.
¥ Humulin R U-500 is useful for the treatment of insulin-resistant patients with diabetes requiring daily doses of more than 200 units.

(Prescribing information: Admelog 2020, Afrezza 2018, Apidra 2020, 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 2020, Lyumjev 2020, Novolin 70/30 2019, Novolin N 2019, Novolin R 2019, Novolog 2019, Novolog Mix 70/30 2019, Semglee 2020, Toujeo 2020, 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 2020, 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 number of comparative effectiveness reviews revealed that both insulin aspart and insulin lispro produced comparable lowering of glycosylated hemoglobin (HbA1c) in patients with T2DM compared to regular insulin *(Fullerton et al 2018, 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, Garg et al 2005, Melo et al 2019, Nørgaard et al 2018, Rayman et al 2007, Seufert et al 2021).*
- 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, Nørgaard et al 2018, 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, Fullerton et al 2016, Fullerton et al 2018, 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 (MA) 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), and severe hypoglycemia (RR, 0.68; 95% CI, 0.60 to 0.77), and lower post-prandial glucose (PPG) (mean difference [MD], -19.44 mg/dL; 95% CI, -21.49 to -17.39) and 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]).* Afrezza was also compared to insulin lispro in a 16-week randomized-controlled trial (RCT) including 138 patients with T1DM. Afrezza met the prespecified non-inferiority margin of 0.4% reduction of HbA1c from baseline. PPG 90 minutes after a meal was significantly lower with Afrezza vs insulin lispro but the between-group difference diminished thereafter (*McGill et al 2021*). A 24-week RCT that included adults with T2DM receiving basal insulin compared prandial Afrezza to insulin aspart. Both Afrezza and insulin aspart groups experienced reductions in mean HbA1c to 7.9% and 7.7%, respectively, from a baseline mean of 8.9% to 9% across groups; the predefined equivalency margin of 0.4% for the mean treatment difference was not met (*Hoogwerf et al 2021*).
- Fiasp was evaluated in the Onset clinical trial program. Onset 1 was a 26-week, Phase 3, AC, RCT that compared Fiasp (mealtime and post meal) to Novolog in patients with T1DM. Both mealtime and post meal 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) *(Russell-Jones et al 2017).* Onset 2 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%; $p < 0.0001$) *(Bowering et al 2017).* Onset 3 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 *(Rodbard et al 2017[b]).* Onset 9 was a 16-week RCT in adults with T2DM inadequately controlled on a basal-bolus insulin regimen. Patients were randomized to receive mealtime Fiasp + insulin degludec with or without metformin (n = 546) or Novolog + insulin degludec with or without metformin (n = 545).

Change in HbA1c in Fiasp-treated patients was found to be non-inferior to Novolog-treated patients (ETD, -0.04%; 95% CI, -0.11 to 0.03). Fiasp demonstrated superior reduction in 1-hour PPG increment vs Novolog (p = 0.001), but differences at 2, 3, and 4 hours were not significant between groups. Treatment-emergent severe hypoglycemia or blood glucose confirmed hypoglycemia was significantly lower with Fiasp vs Novolog (estimated treatment ratio, 0.81; 95% CI, 0.68 to 0.97) (*Lane et al 2020*).

- 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 non-inferiority 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, parallel group, 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.
- The safety and efficacy of Lyumjev were evaluated in two 26-week, Phase 3, DB/OL, PG, RCTs in both T1DM (N = 1222) (PRONTO-T1D) and T2DM (N = 673) patients (PRONTO-T2D). Patients were randomized to receive Lyumjev or Humalog. The change in HbA1c for Lyumjev-treated patients was found to be noninferior in both trials (PRONTO-T1D: mealtime Lyumjev: ETD, -0.08%; 95% CI, -0.16 to 0.00; p = 0.06 for noninferiority; post meal Lyumjev: ETD, +0.13%; 95% CI,0.04 to 0.22; p = 0.003 for noninferiority; PRONTO-T2D: mealtime Lyumjev: ETD, 0.06%; 95% CI, -0.05 to 0.16; noninferiority). Lyumjev significantly lowered PPG 1- and 2-hours post dose compared to Humalog. Rates of hypoglycemia were similar between the treatment arms in both trials *(Blevins et al 2020, Klaff et al 2020)*.
- 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 MAs *(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, 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, Semlitsch et al 2020, 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 (FPG) 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 MA 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 HbA1c 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 MA 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 MA 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 FPG 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 MA of 15 trials with 16,694 patients that compared Tresiba to Lantus found that Tresiba was associated with improved mean reduction in FPG (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 MA 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 2019).*
- 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, 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. The use of an 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*).

- The safety and efficacy of Semglee and reference insulin glargine were compared in 2 OL RCTs enrolling 558 (INSTRIDE 1; *Blevins et al 2018*) and 127 (INSTRIDE 3) patients with T1DM. In both trials, patients also received mealtime insulin lispro. INSTRIDE 1 demonstrated non-inferiority of Semglee to reference insulin glargine for LSMD in change in HbA1c from baseline to week 24 (0.03%; standard error [SE], 0.046; 95% CI, −0.066 to 0.117), as did INSTRIDE 3 from baseline to week 36 (LSMD, 0.01%; 95% CI, -0.08 to 0.101). The safety profile of products did not significantly differ in either trial. Semglee was also compared to reference insulin glargine in 560 patients with T2DM in an OL RCT (INSTRIDE 2). This trial included patients who were insulin-naïve and insulin-non-naïve receiving OADs. Semglee was non-inferior to the reference insulin glargine for LSMD in change in HbA1c from baseline to week 24 (0.06%; 95% CI, -0.10 to 0.22). The safety profile was also similar between products in this trial; (*Blevins et al 2019, Blevins et al 2020[a]*).
- 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 MA 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 2019).*
  - To further inform the differences between basal insulin agents, a network meta-analysis (NMA) (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 (SR) 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)*. Similar conclusions were made in a 2020 SR (*Ampudia-Blasco 2020).*
- 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, Rosenstock et al 2020).*
- 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 SR and MA evaluated the efficacy and safety of insulin degludec/liraglutide vs insulin glargine/lixisenatide treatment in T2DM (*Cai et al 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).*
    - A 2020 MA including 8 RCTs (N = 3828) compared insulin glargine/lixisenatide to other treatment intensification strategies in people whose T2DM was inadequately controlled (*Home et al 2020*). The estimated difference in HbA1c reduction with insulin glargine/lixisenatide vs premixed insulin, three times daily mealtime insulin + basal insulin, and once daily mealtime insulin + basal insulin was -0.50 %-units (95% CI, -0.93 to -0.06), -0.35 %-units (- 95% CI, -0.89 to 0.13) and -0.68 %-units (95% CI, -1.18 to -0.17), respectively. Safety was similar or improved with insulin glargine/lixisenatide vs other insulin regimens.
  - 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 ETD 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)*.

- A MA of 26 studies (n = 24,348) demonstrated that insulin did not significantly increase the risk of all-cause and CV mortality, acute MI, or stroke in patients with T2DM. Insulin did significantly increase the risk of severe hypoglycemia vs other antidiabetic regimens (RR, 2.98; 95% CI, 2.47 to 3.61) (*Rados et al 2021*).

CLINICAL GUIDELINES

T1DM Overview

- 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 2021[b], Chiang et al 2018, Garber et al 2020)*.

T2DM 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 2021[b], Copeland et al 2013, Buse et al 2020, 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 chronic kidney disease (CKD), independent of HbA1c. Metformin is considered the drug of choice for children with T2DM *(ADA 2021[b], Buse et al 2020, Copeland et al 2013, Das et al 2020, Garber et al 2020, KDIGO 2020, Rangaswami et al 2020)*.
- 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 *(ADA 2021[b], Buse et al 2020, Garber et al 2020)*. Insulin therapy is usually started once patients are not achieving glycemic goals with noninsulin therapies. 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

Guidelines relevant to clinical decision making for insulin products in patients with diabetes are summarized below.

- **ADA: Standards of Medical Care in Diabetes – 2021** *(ADA 2021[b])*
  - 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).

- 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 ≥ 1.5% to 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.
  - 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. 2021 ADA Factors to Consider for Antihyperglycemic Therapies in T2DM

Class*	Efficacy	Hypoglycemia	Weight	ASCVD	HF	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: dulaglutide†, liraglutide†, semaglutide† Neutral: exenatide once weekly, lixisenatide	Neutral	SQ, oral	Benefit (driven by albuminuria outcomes): liraglutide, semaglutide, dulaglutide
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; DKD = diabetic kidney disease; DPP-4i = dipeptidyl peptidase 4 inhibitor; GLP-1ra = glucagon-like peptide-1 receptor agonist; HF = heart failure; 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.
    - 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. Basal (long-acting) insulin is recommended 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.
    - 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.

- **2019 Update to: Management of Hyperglycemia in Type 2 Diabetes, 2018: A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)** (*Buse et al, 2020*)
  - 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. Additional recommendations from the ADA-EASD report with regard to insulin therapy are as follows:
    - For patients with established ASCVD or 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).

- **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.

- 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.
- Glycemic treatment regimens should be kept as simple as possible.

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.

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
Afrezza (insulin human)	Single-use cartridges: 4, 8, 12 units Available in cartons with a single dosage and in titration packs with multiple dosages	Inhalation	Generally given 3 times daily at the beginning of a meal.	Safety and efficacy in pediatric patients or in renal or hepatic dysfunction have not been established.
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.
Lyumjev (insulin lispro-aabc)	100 U/mL: cartridge, KwikPen, Junior KwikPen, Tempo Pen, vial 200 U/mL: KwikPen	SC, IV (U-100 only)	Administer at the start of the meal or within 20 minutes after starting the meal. Use in a regimen with intermediate- or long-acting insulin when administered by SC injection.	Safety and efficacy in children have not been established. Use prefilled pens 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.	Safety and efficacy in children < 2 years with T1DM and in children with T2DM have not been established.

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
			Use in a regimen with intermediate- or long-acting insulin when administered by SC injection.	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: 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.	U-500: well-controlled studies in children not available. Dosing in pediatric patients must be individualized. Dose conversion should not be performed when using the U-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.

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
				Use with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Lantus (insulin glargine)	100 U/mL: SoloStar pen, vial	SC	Daily May be administered at any time of day, but at same time every day.	Safety and efficacy in children < 6 years with T1DM and in children with T2DM have not been established. Use SoloStar pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Semglee (insulin glargine)	100 U/mL; prefilled 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 Semglee prefilled pen with caution in patients with visual 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	SC	Daily	Safety and efficacy in children < 1 year have not been

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
	200 U/mL: FlexTouch pen		May be administered at any time of day (should be same time of day in pediatric patients).	established (use in children ≥ 1 year with T2DM is supported by evidence from adult T2DM studies). The recommended number of days between dose increases is 3 to 4 days. Pediatric patients requiring < 5 units daily should use the U-100 vial. Use FlexTouch pen with caution in patients with visual impairment who rely on audible clicks to dial their dose.
Combination Insulins, Rapid-Acting and Intermediate-Acting				
Humalog Mix 50/50 Humalog Mix 75/25 (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).

Drug	Available Formulations	Route	Usual Recommended Frequency*	Comments
				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.
See the current prescribing information for full details

(Clinical Pharmacology 2021)

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 may fall into 1 of 4 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 or products that contain the same insulin (*Lilly 2019[a], Lilly 2019[b], Novo Nordisk 2019*).
- Safety profiles of the injectable rapid-acting insulins are comparable, with the exception of Afrezza, 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. Afrezza has a boxed warning for bronchospasm and is contraindicated in patients with chronic lung disease. 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 2021[b], Chiang 2018).*
- 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 2021[b], Buse et al 2020, Garber et al 2020).*

- 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 2021[b], Buse et al 2020, Garber et al 2020).*
- 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 2021[b], Buse et al 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 ETDs 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, Home et al 2020, 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.
- Guidelines from the ADA and EASD 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 the patient is above the target HbA1c by ≥ 1.5 to 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 2021[b], Buse et al 2020).*

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Publication Date: March 8, 2021

Therapeutic Class Review
Anti-gout agents

MEDICATION*	MARKETER	AVAILABILITY
Colchicine/probenecid	Various	**Generic**: 0.5 mg/500 mg tablet
Colcrys (colchicine)†	Takeda	**Brand:** 0.6 mg tablet
Gloperba (colchicine) §	Romeg Therapeutics	**Brand:** 0.6 mg/5 mL oral solution
Krystexxa (pegloticase)	Horizon Pharma	**Brand:** 8 mg injection
Mitigare (colchicine)†	Hikma Americas	**Brand**: 0.6 mg capsule
Probenecid	Various	**Generic:** 500 mg tablet
Uloric (febuxostat)	Takeda	**Brand:** 40 mg, 80 mg tablets
Zyloprim (allopurinol)	Casper	**Brand/Generic:** 100 mg, 300 mg tablets
Purpose of Review: To evaluate the safety and efficacy of the anti-gout agents for formulary consideration.		

*Brand names are indicated by bolded text; generic-only products are indicated by non-bolded text
†Colcrys and Mitigare are also available as co-licensed products under the brand name of colchicine
§Not yet available commercially

Note: Information on indications, pharmacology, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

SUMMARY

Background

- 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 risk of cardiovascular (CV) events, including death, is significantly greater in patients with gout than in those without gout *(Choi et al 2007, Krishnan et al 2008).*
- Colchicine has been used for centuries to treat and prevent gout in adults. It was used before 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 Colcrys was officially FDA-approved for gout treatment and prophylaxis, as well as treatment of Familial Mediterranean fever. In 2014, the FDA approved Mitigare, a brand of colchicine, with an approved generic colchicine that followed a few months later. An oral liquid colchicine formulation, Gloperba, was FDA-approved in January 2019 for the prophylaxis of gout flares. Its approval was based on published colchicine studies.
- Zurampic (lesinurad) and Duzallo (lesinurad/allopurinol), FDA-approved for hyperuricemia associated with gout in 2015 and 2017, respectively, were discontinued by the manufacturer on February 1, 2019. Per the manufacturer, discontinuation was due to low utilization, rather than safety or efficacy reasons *(Ironwood Pharmaceuticals 2019).*
- During Uloric's (febuxostat) phase 3 clinical trials, there was a safety signal noted for CV events; however, the results were not found to be statistically significant. Upon approval of febuxostat in 2009, a warning for CV risk was added to the package insert, and the FDA mandated a post-marketing CV safety trial for febuxostat vs allopurinol (*FDA 2019*).
  - The results of this safety clinical trial (discussed in the Clinical Efficacy section below) led to the addition of a boxed warning for CV death and a change to the indication for febuxostat as a second-line therapy after allopurinol (see Indication section below).
  - Additional CV safety trials (in Japan and Europe) are underway to provide additional data regarding the CV risk of febuxostat vs allopurinol *(Katsiki and Borghi 2018).*

Indication

Table 1. FDA-approved indications for anti-gout agents

Indications	Allopurinol	Colchicine
Management of patients with signs and symptoms of primary or secondary gout	✓	
Prophylaxis and treatment of acute gout flares		✓
Chronic management of hyperuricemia in adult patients with gout who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable		
Treatment of hyperuricemia associated with gout and gouty arthritis		
Treatment of chronic gouty arthritis when complicated by frequent, recurrent acute attacks of gout		
Treatment of chronic gout in adult patients refractory to conventional therapy		

- Various anti-gout agents listed in the table above have additional indications that are unrelated to gout, and will therefore not be a part of this therapeutic class review.

Pharmacology

- Both allopurinol and febuxostat are xanthine oxidase inhibitors (XOIs) that lower serum uric acid (sUA); however, the mechanism by which they inhibit xanthine oxidase (XO) differs.
  - Allopurinol inhibits XO, the enzyme responsible for the conversion of hypoxanthine to xanthine and then xanthine to uric acid; this leads to a decrease in sUA.
  - Febuxostat lowers sUA levels by occupying a channel in the XO dimer and impairing access to purine base substrates at the active site of XO catalysis.
- The exact mechanism by which colchicine exerts its sUA lower effects is not fully understood. However, it is thought to reduce lactic acid production by leukocytes, which results in a decrease in uric acid deposition. It is also thought to reduce phagocytosis, with abatement of the inflammatory response.
- Pegloticase is a uric acid specific enzyme, which is a recombinant uricase, and achieves its therapeutic effects by catalyzing the oxidation of uric acid to allantoin, thereby lowering sUA.
- Probenecid is a uricosuric and renal tubular blocking agent. It inhibits the tubular reabsorption of urate, thus increasing the urinary excretion of uric acid and decreasing sUA levels.

Clinical Efficacy

- CARES is a double-blind (DB), multicenter (MC), randomized, noninferiority trial that compared febuxostat 40 to 80 mg orally daily (n = 3098) to allopurinol 200 to 600 mg orally daily (dose adjusted based on renal function; n = 3092) for a median follow-up period of 32 months. Patients in this study were diagnosed with gout and had a history of CV disease (eg, myocardial infarction [MI], hospitalization for unstable angina or transient ischemic attacks [TIA], stroke, peripheral vascular disease [PVD], or diabetes mellitus [DM] with evidence of micro- or macrovascular disease) *(White et al 2018)*.
  - There was a large discontinuation rate of 56.6% during the study, as well as 45.0% of patients lost during the follow-up period.
  - A determination of noninferiority of febuxostat to allopurinol required that the upper bound of the one-sided confidence interval (CI) of the hazard ratio (HR) for the end points be < 1.3.
  - The results of the modified intent-to-treat analysis are listed in Table 2 below.

Table 2. Results for primary and secondary endpoints in CARES trial

	Endpoint	Febuxostat	Allopurinol	HR	p-value
		n (%)	HR (95% CI)		
Primary endpoint	Composite of CV death, nonfatal MI, nonfatal stroke, or urgent revascularization due to unstable angina	335 (10.8)	321 (10.4)	1.03 (0.87 to 1.23)	0.66
Secondary endpoints	CV death	134 (4.3)	100 (3.2)	1.34 (1.03 to 1.73)	0.03
	Nonfatal MI	111 (3.6)	118 (3.8)	0.93 (0.72 to 1.21)	0.61
	Nonfatal stroke	71 (2.3)	70 (2.3)	1.01 (0.73 to 1.41)	0.94
	Urgent revascularization due to unstable angina	49 (1.6)	56 (1.8)	0.86 (0.59 to1.26)	0.44

	Composite of CV death, nonfatal MI, or nonfatal stroke	296 (9.6)	271 (8.8)	1.09 (0.92 to 1.28)	0.33
	Death from any cause	243 (7.8)	199 (6.4)	1.22 (1.01 to 1.47)	0.04

Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction

- While no statistically significant difference was found between the treatment groups with respect to the primary end point, there were differences noted between the treatment groups for 2 of the 6 secondary endpoints above.
  - As noted in the table above, the febuxostat group showed statistically significantly higher rates of all-cause mortality (HR 1.22; 95% CI, 1.01 to 1.47) and CV mortality (HR 1.34; 95% CI, 1.03 to 1.73) compared with the allopurinol group.
- 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.
- Several meta-analyses have been published to support the use of colchicine, febuxostat, and pegloticase in the treatment of gout *(Seth et al 2014, Sundy et al 2011, Tayar et al 2012, Van Echteld et al 2014).*

Place in Therapy

- The American College of Rheumatology (ACR) is in the process of updating its guidelines for the management of gout (anticipated completion in the early part of 2020). Their 2012 guidelines (Part 1 and 2) for the treatment and prophylaxis of gout, however, make the following key recommendations (*Khanna et al 2012*):
  - An acute gouty arthritis attack should be treated with pharmacologic therapy, initiated within 24 hours of onset.
  - Established urate-lowering therapy (ULT) should be continued, without interruption, during an acute gout attack.
  - Monotherapy with non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or colchicine is recommended as first-line agents for an acute gout attack (combination therapy is appropriate in patients experiencing severe pain).
  - XOI therapy with either allopurinol or febuxostat is recommended as the first-line pharmacologic ULT in gout.
    - Probenecid is recommended as an alternative first-line pharmacologic ULT 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 ULT 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.
  - Pegloticase is appropriate for patients with severe gout disease burden and refractoriness to, or intolerance of, appropriately dosed oral urate-lowering options.
- Agency for Healthcare Research and Quality (AHRQ): Diagnosis and Management of gout: Current state of evidence *(AHRQ 2017)*
  - Effective treatments for gout attacks include NSAIDs, colchicine, and corticosteroids.
  - ULT, including allopurinol and febuxostat, reduce sUA.
    - Based on the data from systematic reviews, ULT did not reduce the frequency of gout attacks during the initial 6 months of therapy. The increased risk of gout attacks with initiation of ULT was ameliorated with the concomitant use of prophylactic agents (eg, colchicine, NSAIDs).
    - After 12 months of ULT, the frequency of gout attacks was reduced.
- Management of acute and recurrent gout: A clinical practice guideline from the American College of Physicians (ACP) *(Qaseem et al 2016)*
  - The ACP recommends corticosteroids, NSAIDs, or colchicine to treat patients with acute gout.
  - Low-dose colchicine is recommended for treating acute gout.
  - The ACP recommends against initiating long-term ULT in most patients after the first gout attack or in patients with infrequent attacks.
  - Febuxostat and allopurinol are equally effective at decreasing sUA levels.
  - Prophylactic therapy with low-dose colchicine or low-dose NSAIDs helps to reduce the risk for acute gout attacks in patients initiating ULT.

Safety

- Key warnings/precautions for allopurinol include skin rash, bone marrow suppression, and requirement for adequate fluid intake (to prevent formation of xanthine calculi and to prevent renal precipitation or urates in patients receiving concomitant uricosuric agents). Key adverse effects with allopurinol include skin rash, gout flares, diarrhea, and nausea.
- Contraindications for colchicine include concomitant use with drugs that inhibit cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) in patients with renal or hepatic impairment. Colchicine use should be avoided in patients with renal or hepatic impairment. The most common adverse effects with colchicine are gastrointestinal (GI) in nature.
- Febuxostat carries a recently added boxed warning for CV death. Febuxostat is contraindicated in patients who are

concurrently on azathioprine or mercaptopurine therapy. Key adverse effects include liver function abnormalities, nausea, arthralgia, and rash.
- Pegloticase has a boxed warning for anaphylaxis and infusion reactions, as well as Glucose-6-phosphate dehydrogenase (G6PD) deficiency-associated hemolysis and methemoglobinemia. Pegloticase use is contraindicated in patients with G6PD deficiency. The most common adverse effects include gout flare, infusion reactions, and nausea.
- Probenecid is contraindicated in patients < 2 years of age and known blood dyscrasias or kidney stones. The most common adverse effects include central nervous system (CNS), genitourinary, and hematologic adverse effects.

Dosing
- Allopurinol
  - Allopurinol is dosed once or twice daily and is titrated at weekly intervals until the target sUA < 6 mg/dL is achieved.
  - The dose of allopurinol should be adjusted according to the patient's renal function.
- Colchicine
  - The dose for colchicine for gout prophylaxis is 0.6 mg orally (with or without food) once or twice daily, with a maximum daily dose of 1.2 mg.
  - For the treatment of gout flares, 1.2 mg should be administered at the first sign of flare, followed by 0.6 mg 1 hour later.
- Febuxostat
  - The recommended dose of febuxostat is 40 or 80 mg orally once daily.
  - No dose adjustments are recommended in patients with mild or moderate renal or hepatic impairment. However, 40 mg orally daily is recommended for patients with severe renal impairment.
- Pegloticase
  - The recommended dose is 8 mg intravenously (IV), administered over ≥ 120 minutes, every 2 weeks.
  - Pre-infusion medications (eg, antihistamines, corticosteroids) are recommended, and the patient should be monitored for anaphylaxis for approximately 1 hour post-infusion. If an infusion reaction occurs, the infusion may be slowed or stopped and restarted at a slower rate, at the discretion of the physician.
- Probenecid
  - The recommended dose of probenecid is 250 mg orally twice daily for 1 week, then 500 mg twice daily.
  - Probenecid should not be started until an acute gouty attack has subsided.
- Probenecid/colchicine
  - The initial dose is 1 tablet orally once daily for 1 week, followed by a maintenance dose of 1 tablet orally twice daily.

Conclusion
- Agents such as allopurinol, colchicine, and probenecid have been available for many years; however, the armamentarium of anti-gout agents is not as robust as required to treat this painful form of inflammatory arthritis. Newer agents such as febuxostat, lesinurad, and pegloticase have been approved in the last 2 decades; however, lesinurad was recently removed from the market due to low utilization.
- The CARES CV safety study determined that there were no statistically significant differences between febuxostat and allopurinol for the majority of study endpoints; however, statistically significantly higher rates of all-cause mortality and CV death were demonstrated with febuxostat.
  - Based on the FDA's evaluation of the results of this study, a boxed warning was added to the febuxostat label, which indicates an increased risk of CV death with febuxostat use. Additionally, the FDA required a change to the indication such that febuxostat is limited to use in patients who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable.
  - It is important to note that the CARES trial had a large discontinuation rate during the study and the post-treatment follow-up period. It is possible that the large discontinuation rate may have biased the results toward the null hypothesis. Additionally, the patients in this trial had significant comorbidities; the study population may not be representative of the general gout population. Further CV safety studies are underway and may provide additional data to determine the true CV risk of febuxostat vs allopurinol.

BACKGROUND

- Gout may progress to a chronic and persistent condition, with development of tophi (solid deposits of monosodium urate [MSU] crystals in joints, cartilage, tendons, bursae, bone, and soft tissue), a condition called chronic tophaceous gout *(Newberry 2016).*
- The prevalence of gout among U.S. adults in 2007 to 2008 was 3.9% (8.3 million people) *(Zhu et al 2011).*
  - Both the incidence and prevalence of the disease appear to be increasing since at least the late 1970s in the U.S. (*Becker and Gaffo 2019).*
- Gout tends to occur earlier in life in men than women and is rare in childhood (*Becker and Gaffo 2019*).
- Clinical manifestations include excruciatingly painful acute attacks of gouty arthritis, the formation of tophaceous MSU

crystal deposits in joints and other body tissues, chronic joint damage, renal stone formation, and potential renal insufficiency *(Roddy and Choi 2014).*

- Key risk factors for gout include (*Becker and Gaffo 2019):*
  - Increased longevity and age-associated CV, metabolic, and renal diseases in the population.
  - Use of medications that alter urate balance as an unintended consequence of treatment for these chronic disorders (and to prevent organ rejection among transplant recipients).
  - Increased dietary intake of foods and food additives (such as high-fructose corn syrup) that contribute to the development of obesity and DM.
- A definitive diagnosis should be sought when a gout flare is suspected, both to exclude alternative explanations for the acute event and to ensure that long-term therapy is not prescribed unnecessarily. The diagnosis is most secure when supported by visualization of urate crystals by experienced examiners in a sample of fluid aspirated from an affected joint (or bursa). Ultrasonography of joints and adjacent soft tissues is useful for guiding fluid aspiration and can identify specific abnormalities that are highly sensitive and specific for urate crystal deposition (*Becker and Gaffo 2019).*
- Management for the prevention of recurrent gout flares and damage to joints and other tissues from urate crystal deposition includes pharmacologic therapy, as well as lifestyle modification and other strategies for risk reduction *(Becker and Perez-Ruiz 2019).*
- Long-term success in maintaining subsaturating sUA is accompanied by clinical benefits that include cessation of gout flares, resolution of tophi, and improvement in patient physical function and health-related quality of life *(Becker and Perez-Ruiz 2019).*
- Treatments to prevent recurrent gout flares are strongly indicated in patients with multiple recurrent gout flares annually or with clinical or imaging findings that indicate joint injury (gouty arthropathy) or the development of tophi, as well as in selected patients with renal disease, urolithiasis, or marked hyperuricosuria *(Becker and Perez-Ruiz 2019).*
  - Preventing recurrent gout flares, progressive gouty arthritis, and tophi often requires the long-term use of drugs that reduce sUA either by enhancing renal excretion of uric acid (uricosuric agents) or by decreasing urate synthesis (XOIs) or both.
  - Precise definitions of frequent or disabling flares are not strictly established. Two or more flares annually is often quoted as an indication for ULT. However, a lower threshold for treatment may be considered after discussion with the patient if even infrequent flares are especially prolonged, interfere with vocational or avocational activities, and/or continue to recur over several years.
- The risk of CV events, including death, is significantly greater in patients with gout than in those without gout *(Choi et al 2007, Krishnan et al 2008).*
- Colchicine has been used for centuries to treat and prevent gout in adults. It was used before the creation of the FDA, and therefore was “grandfathered” without receiving FDA approval. In 2006, however, colchicine was formally studied and Colcrys was officially FDA-approved for gout treatment and prophylaxis, as well as treatment of Familial Mediterranean fever. In 2014, the FDA approved Mitigare, a brand of colchicine, with an approved generic colchicine that followed a few months later. An oral liquid colchicine formulation, Gloperba, was FDA-approved in January 2019 for the prophylaxis of gout flares. Its approval was based on published colchicine studies.
- Zurampic (lesinurad) and Duzallo (lesinurad/allopurinol), FDA-approved for hyperuricemia associated with gout in 2015 and 2017, respectively, were discontinued by the manufacturer on February 1, 2019. Per the manufacturer, discontinuation was due to business reasons, rather than safety or efficacy reasons *(Ironwood Pharmaceuticals 2019).*
- During Uloric’s (febuxostat) phase 3 clinical trials, there was a safety signal noted for CV events; however, the results were not found to be statistically significant. Upon approval of febuxostat in 2009, a warning for CV risk was added to the package insert, and the FDA mandated a post-marketing CV safety trial for febuxostat (*FDA 2019*).
  - The results of this safety clinical trial lead to the addition of a boxed warning for CV death and a change to the indication for febuxostat as a second-line therapy after allopurinol.
  - Additional CV safety trials (in Japan and Europe) are underway to provide additional data regarding the CV risk of febuxostat vs allopurinol *(Katsiki and Borghi 2018).*

INDICATIONS

Table 3. FDA-approved indications for anti-gout agents

Indication	Allopurinol	Colchicine	Febuxostat	Pegloticase	Probenecid	Probenecid/ colchicine
Management of patients with signs and symptoms of primary or secondary gout*	✓					
Prophylaxis and treatment of acute gout flares†		✓				
Chronic management of hyperuricemia in adult patients with			✓§			

gout who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable						
Treatment of the hyperuricemia associated with gout and gouty arthritis					✓	
Treatment of chronic gouty arthritis when complicated by frequent, recurrent acute attacks of gout						✓
Treatment of chronic gout in adult patients refractory to conventional therapy				✓§		
Management of patients with leukemia, lymphoma, and malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels†	✓					
The management of patients with recurrent calcium oxalate calculi whose daily uric acid excretion exceeds 800 mg/day in male patients and 750 mg/day in female patients‡	✓					
As adjuvant therapy with penicillin or with ampicillin, methicillin, oxacillin, cloxacillin, or nafcillin, for elevation or prolongation of plasma levels by whatever route the antibiotic is given†					✓	
Treatment of familial Mediterranean disease†		✓				

*Signs and symptoms include acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy
†This indication will not be reviewed as part of this therapeutic class review
‡Therapy in such patients should be carefully assessed initially and reassessed periodically to determine in each case that treatment is beneficial and that the benefits outweigh the risks
§Limitation of use: not recommended for the treatment of asymptomatic hyperuricemia

PHARMACOLOGY

- Both allopurinol and febuxostat are XOIs that lower sUA; however, the way that they inhibit XO differs.
  - Allopurinol is a structural analogue of the natural purine base, hypoxanthine. By inhibiting XO, the enzyme responsible for the conversion of hypoxanthine to xanthine and of xanthine to uric acid, there is a decrease in production of sUA. Allopurinol is metabolized to the corresponding xanthine analogue, oxipurinol (alloxanthine), which also is an inhibitor of XO catabolism, without disrupting the biosynthesis of purines.
  - Febuxostat lowers sUA levels by occupying a channel in the XO dimer and impairing access to purine base substrates at the active site of XO catalysis.
- The exact mechanism by which colchicine exerts its sUA lower effects is not fully understood. However, it is thought to involve the following:
  - A reduction in lactic acid production by leukocytes, which results in a decrease in uric acid deposition.
  - A reduction in phagocytosis, with abatement of the inflammatory response.
    - Colchicine is not an analgesic, though it relieves pain in acute attacks of gout.
- Pegloticase is a uric acid specific enzyme, which is a recombinant uricase, and achieves its therapeutic effects by catalyzing the oxidation of uric acid to allantoin, thereby lowering sUA.
- Probenecid is a uricosuric and renal tubular blocking agent. It inhibits the tubular reabsorption of urate, thus increasing the urinary excretion of uric acid and decreasing sUA levels.

CLINICAL EFFICACY

STUDY DESIGN ABBREVIATIONS: AC = active control; CI = confidence interval, DB = double-blind; HR = hazard ratio; MC = multi-center; OL = open-label; OR = odds ratio; PC = placebo-controlled; PG = parallel-group; RCT = randomized controlled trial; RR = relative risk; SB = single-blind; SC = single-center; XO = crossover

***Search Strategy**: Studies supporting the FDA-approved indications were identified using search terms "allopurinol, colchicine, febuxostat, pegloticase, or probenecid" and "gout" through April 15, 2019. Manufacturer submitted data were also reviewed when available. A comprehensive PubMed literature search was performed for human studies published in English. Assessment of each study's design (eg, randomization, blinding methodology, appropriateness of treatment outcomes, etc.), validity and importance was completed. Review of patient data in groups to which they were randomized (intention to treat analysis), accounting for patient withdrawals, and baseline characteristics was completed.*

Study 1. White WB et al, *N Engl J Med.* 2018;378:1200-1210

Study Objective: To determine whether febuxostat was noninferior to allopurinol with regard to major CV events in patients with gout and CV disease.	
Study Design, Follow-up	**Treatment Groups***
• DB, MC, randomized, noninferiority trial (N = 6190)	• Febuxostat 40 mg to 80 mg per day (n = 3098) • Allopurinol 200 mg to 600 mg per day* (n = 3092) *For allopurinol, the dose was adjusted based on renal function and for febuxostat, the dose was adjusted based on sUA • Colchicine, an NSAID (with lansoprazole), or prednisone prophylaxis were administered for acute gout attacks
Inclusion Criteria	**Exclusion Criteria**
• Male or female patients (≥ 50 or ≥ 55 years of age, respectively) with diagnosis of gout based on ACR criteria • sUA ≥ 7.0 mg/dL or ≥ 6.0 mg/dL with inadequately controlled gout) • History of CV disease (MI, hospitalization for unstable angina or TIA, stroke, PVD, or DM with evidence of micro- or macrovascular disease)	• Secondary hyperuricemia • History of xanthinuria • Active peptic ulcer disease • ULT or other exclusionary medication < 7 days prior to randomization • History of cancer (other than basal cell carcinoma of the skin) within 5 years prior to the first dose of study medication • MI or stroke within 60 days of screening • Liver transaminases > 2 times upper limit of normal • CLcr < 30 mL/min
Primary Endpoint	**Secondary Endpoints**
• Primary composite end point: first occurrence of CV death, nonfatal MI, nonfatal stroke, or urgent revascularization for unstable angina	• Composite of CV death, nonfatal MI, or nonfatal stroke as well as the individual components of the primary endpoint • Death from any cause, urgent cerebrovascular revascularization, transient ischemic attack, hospitalization for heart failure, arrhythmias not associated with ischemia, and venous thromboembolic events

- **Results:**
  - Baseline characteristics were balanced between both treatment groups.
  - Patients were followed for up to 85 months, with a median follow-up period of 32 months.
  - Of note, treatment was discontinued in 56.6% of patients, and 45.0% were lost during the follow-up period. The discontinuation rates were similar between both treatment groups (57.3% in the febuxostat group and 55.9% in the allopurinol group), as well as the percentage of patients lost during the follow-up period (45.0% in the febuxostat group and 44.9% in the allopurinol group).
  - A determination of noninferiority of febuxostat to allopurinol required that the upper bound of the one-sided CI of the HR for the end points be < 1.3.
  - The results of the modified intent-to-treat analysis are listed in Table 4 below.

Table 4. Results for primary and secondary endpoints in CARES trial

	Endpoint	Febuxostat	Allopurinol	HR	p-value
		n (%)		HR (95% CI)	
Primary endpoint	Composite of CV death, nonfatal MI, nonfatal stroke, or urgent revascularization due to unstable angina	335 (10.8)	321 (10.4)	1.03 (0.87 to 1.23)	0.66

Secondary endpoints	CV death	134 (4.3)	100 (3.2)	1.34 (1.03 to 1.73)	0.03
	Nonfatal MI	111 (3.6)	118 (3.8)	0.93 (0.72 to 1.21)	0.61
	Nonfatal stroke	71 (2.3)	70 (2.3)	1.01 (0.73 to 1.41)	0.94
	Urgent revascularization due to unstable angina	49 (1.6)	56 (1.8)	0.86 (0.59 to 1.26)	0.44
	Composite of CV death, nonfatal MI, or nonfatal stroke	296 (9.6)	271 (8.8)	1.09 (0.92 to 1.28)	0.33
	Death from any cause	243 (7.8)	199 (6.4)	1.22 (1.01 to 1.47)	0.04

Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction

- While no statistically significant difference was found between the treatment groups with respect to the primary end point, there were statistically significant differences noted between the treatment groups for 2 of the 6 secondary endpoints above.
  - As noted in the table above, febuxostat group showed significantly higher rates of all-cause mortality (HR 1.22; 95% CI, 1.01 to 1.47) and CV mortality (HR 1.34; 95% CI, 1.03 to 1.73) compared with the allopurinol group.
  - Additionally, the rate of CV death was statistically significantly greater in febuxostat-treated patients vs allopurinol-treated patients (HR 1.34; 95% CI, 1.03 to 1.73).
- **Authors' conclusion:**
  - In patients with gout and major CV coexisting conditions, febuxostat was noninferior to allopurinol with respect to rates of adverse CV events. All-cause mortality and CV mortality were higher with febuxostat than with allopurinol.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Takeda Pharmaceuticals
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - This was a reasonably-designed clinical trial with independent reviewers conducting the analyses.
    - The treatment groups were fairly well-balanced.
  - **Study limitations:**
    - This population was fairly ill with multiple comorbidities; this trial population may not be representative of the general population.
    - There was a large discontinuation rate during the trial and during the follow-up period; this may have biased the data toward the null hypothesis.
    - A portion of patients in the febuxostat group were not maximized on their aspirin doses.

Study 2. Seth et al, *Cochrane Database Syst Rev.* 2014;10:CD006077.

Study Objective: To assess the efficacy and safety of allopurinol compared with placebo and other ULT for treating chronic gout.	
Study Design	**Treatment Groups**
• Cochrane review, meta-analysis of 11 RCTs (n = 4531)	• Allopurinol • Febuxostat • Colchicine or probenecid • Benzbromarone* • Placebo *Not available in the US
Inclusion Criteria	**Exclusion Criteria**
• RCTs and quasi clinical controlled trials involving patients with gout • Adults with a diagnosis of chronic gout • Diagnosis of gout based on ACR criteria or based on the diagnosis by the trial author or treating physician	• Populations that included a mix of people with chronic gout and asymptomatic hyperuricemia, unless results for the chronic gout population could be separated out for analysis
Primary Endpoints	**Secondary Endpoints**
• Frequency of acute gout attacks and the number of participants with an acute gout attack	• Health-related quality of life (HRQoL) • Participant global assessment of treatment success

• Serum urate normalization as measured by percent change in sUA from baseline, absolute change in sUA from baseline (mmol/L or mg/dL) or proportion of participants achieving a target sUA (eg, < 6 mg/dL) • Pain, as measured by visual analogue scale (VAS), numerical rating scale (NRS), Likert scales or qualitative scales • Function (activity limitation), as measured by the Health Assessment Questionnaire for Rheumatoid Arthritis (HAQ-DI), 36-item Short Form (SF-36) Physical Health component or other validated gout specific function measures. • Tophus regression, using physical measurement techniques or ultrasound-guided measurements • Proportion of participant withdrawals due to adverse effects • Proportion of participants with serious adverse effects	• Proportion of participants with adverse effects

- **Results:**
  - Moderate-quality evidence from 1 trial (57 participants) indicated allopurinol 300 mg daily probably does not reduce the rate of gout attacks (2/26 with allopurinol vs 3/25 with placebo; risk ratio (relative risk) 0.64; 95% CI, 0.12 to 3.52 but increases the proportion of participants achieving a target sUA over 30 days (25/26 with allopurinol vs 0/25 with placebo, RR 49.11, 95% CI, 3.15 to 765.58; number needed to treat for an additional beneficial outcome [NNTB] = 1).
  - In 2 studies (453 participants), there was no significant increase in withdrawals due to adverse effects (6% with allopurinol vs 4% with placebo, RR 1.36; 95% CI, 0.61 to 3.08) or serious adverse effects (2% with allopurinol vs 1% with placebo, RR 1.93; 95% CI, 0.48 to 7.80).
  - One trial reported no difference in pain reduction or tophus regression, but did not report outcome data or measures of variance sufficiently and the differences between groups could not be calculated. Neither trial reported function.
  - Low-quality evidence from 3 trials (1136 participants) 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, RR 0.89; 95%CI, 0.71 to 1.1); however more participants may achieve target sUA levels (4 trials; 2618 participants) 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, NNTB with febuxostat = 4).
  - Two trials reported no difference in tophus regression between allopurinol and febuxostat over a 28- to 52-week period; but as the investigators did not provide variance, mean difference between groups could not be calculated.
  - The trials did not report pain reduction or function.
  - Moderate-quality evidence from pooled data from 3 trials (2555 participants) comparing allopurinol up to 300 mg daily vs febuxostat 80 mg daily indicated no difference in the number of withdrawals due to adverse effects (7% with allopurinol vs 8% with febuxostat, RR 0.89; 95% CI, 0.62 to 1.26) or serious adverse effects (4% with allopurinol vs 4% with febuxostat, RR 1.13; 95% CI, 0.71 to 1.82) over a 24- to 52-week period.
- **Author's conclusion:**
  - This review found low- to moderate-quality evidence indicating similar effects on withdrawals due to adverse effects and serious adverse effects and incidence of acute gout attacks when allopurinol (100 to 600 mg daily) was compared with placebo, benzbromarone (100 to 200 mg daily) or febuxostat (80 mg daily). There was moderate-quality evidence of little or no difference in the proportion of participants achieving target sUA when allopurinol was compared with benzbromarone. However, allopurinol seemed more successful than placebo and may be less successful than febuxostat (80 mg daily) in achieving a target sUA level (≤ 6 mg/dL; ≤ 0.36 mmol/L) based on moderate- to low-quality evidence. Single studies reported no difference in pain reduction when allopurinol (300 mg daily) was compared with placebo over 10 days, and no difference in tophus regression when allopurinol (200 to 300 mg daily) was compared with febuxostat (80 mg daily). None of the trials reported on function, HRQoL, or participant global assessment of treatment success, where further research would be useful.
- **Study Appraisal**
  - **Study sponsorship:**
    - Internal: (1) University Hospital Southampton NHS Foundation Trust, UK (2) School of Public Health and Preventative Medicine, Monash University, Australia (3) Division of Rheumatology, University of British Columbia, Vancouver, Canada (4) Institute for Work & Health, Toronto, Canada.
    - External: No sources of support supplied
  - **Study rating:**
    - N/A (MA)
  - **Study limitations:**
    - There were only 2 trials that compared allopurinol to placebo, and these trials were so different that the efficacy

data couldn't be pooled for analysis.
- Some trials had a variable duration of follow up.
- Some trials had small sample sizes.
- Three studies used low-dose allopurinol 100 to 300 mg daily (depending on renal function) compared with a reasonable dose of febuxostat 80 mg daily.
- One study was at high risk of performance and detection bias, while a few other studies had an unclear risk of performance and detection bias.

Study 3. Van Echteld et al, *Cochrane Database Syst Rev.* 2014;8:CD006190.

Study Objective: To evaluate the benefits and harms of colchicine for the treatment of acute gout.	
Study Design	**Treatment Groups**
• Cochrane review, meta-analysis of 2 RCTs (n = 124)	• Low dose colchicine (1.8 mg) per day • High dose colchicine (0.5 mg every 2 hours until relief in 1 study and 4.8 mg total in another study) • Placebo
• Inclusion Criteria	• Exclusion Criteria
• RCTs and quasi clinical controlled trials investigating the benefits and harms of colchicine in acute gout • Adults with a diagnosis of acute gout (author defined or presence of monosodium crystals in joint aspirate, or patients fulfilling the ACR, Rome, or New York criteria for gout)	• Populations that included a mix of people with acute gout and other musculoskeletal pain, unless results for the acute gout population could be separated out for analysis
Primary Endpoints	
• Benefits: Defined as ≥ 50% decrease in pain • Harms: Defined as study participation withdrawal due to adverse effects • Reduction of inflammation (joint swelling/erythema/tenderness) • Function of target joint (movement) • Patient global assessment of treatment success • HRQoL • Total number and types of adverse effects and serious adverse effects	

- **Results:**
  - Based upon pooled data from 2 trials (124 participants), there was low-quality evidence that a greater proportion of people receiving high-dose colchicine experienced a ≥ 50% decrease in pain from baseline up to 32 to 36 hours compared with placebo (35/74 in the high-dose colchicine group vs 12/50 in the placebo group (RR 2.16; 95% CI, 1.28 to 3.65), with an NNTB of 4 (95% CI, 3 to 12). However, the total number of adverse effects (diarrhea, vomiting, or nausea) was greater in those who received high-dose colchicine vs placebo (62/74 in the high-dose colchicine group vs 11/50 in the placebo group [RR 3.81; 95% CI, 2.28 to 6.38]), with a number needed to treat to harm (NNTH) of 2 (95% CI, 2 to 5).
  - 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 one joint of 12. They reported the proportion of people who achieved a 50% reduction in this composite score. Based upon 1 trial (n = 43), there was low-quality evidence that more people in the high-dose colchicine group had a 50% or greater decrease in composite score from baseline up to 32 to 36 hours compared to the placebo group (11/22 in the high-dose colchicine group vs 1/21 in the placebo group [RR 10.50; 95% CI, 1.48 to 74.38] and 45% absolute difference). Based upon data from 1 trial (n = 103), there was low-quality evidence that low-dose colchicine was more efficacious than placebo with respect to the proportion of people who achieved a 50% or greater decrease in pain from baseline up to 32 to 36 hours (low-dose colchicine 31/74 vs placebo 5/29 [RR 2.43; 95% CI, 1.05 to 5.64]), with an NNTB of 5 (95% CI, 2 to 20).
  - There were no additional harms in terms of adverse effects (diarrhea, nausea or vomiting) with low-dose colchicine compared to placebo (19/74 and 6/29 respectively [RR 1.24; 95% CI, 0.55 to 2.79]). Based upon data from 1 trial (126 participants), there was low-quality evidence that there are no additional benefits in terms of the proportion of people achieving 50% or greater decrease in pain from baseline up to 32 to 36 hours with high-dose colchicine compared to low-dose (19/52 and 31/74 respectively [RR 0.87, 95% CI, 0.56 to 1.36]). However, there were statistically significantly more adverse effects in those who received high-dose colchicine (40/52 vs 19/74 in the low-dose group [RR 3.00; 95% CI, 1.98 to 4.54]), with an NNTH of 2 (95% CI, 2 to 3).
  - No trials reported function of the target joint, patient-reported global assessment of treatment success, HRQoL, or withdrawals due to adverse effects. No studies were identified comparing colchicine to NSAIDs or other active treatments such as glucocorticoids (by any route).
- **Author's conclusion**:

- Based upon only 2 published trials, there is low-quality evidence that low-dose colchicine is likely to be an effective treatment for acute gout. The evidence was downgraded because of a possible risk of selection and reporting biases and imprecision. Both high- and low-dose colchicine improve pain when compared to placebo. While there is some uncertainty around the effect estimates, compared with placebo, high-dose but not low-dose colchicine appears to result in a statistically significantly greater number of adverse effects. Therefore low-dose colchicine may be the preferred treatment option. There are no trials about the effect of colchicine in populations with comorbidities or in comparison with other commonly used treatments, such as NSAIDs and glucocorticoids.

- **Study Appraisal**
  - **Study sponsorship:**
    - Internal: Cochrane Musculoskeletal Group, Australian Editorial Base, Australia
    - External: No sources of support supplied
  - **Study rating:**
    - N/A (MA)
  - **Study limitations:**
    - Potential for selection bias in 1 trial
    - Risk of selective reporting in another trial
    - Both trials had small sample sizes
    - Data were only available for pain, inflammation, and adverse effects

Study 4. Tayar et al, *Cochrane Database Syst Rev.* 2012;11:CD008653.

Study Objective: To evaluate the benefits and harms of febuxostat for chronic gout	
Study Design	**Treatment Groups**
• Cochrane review, meta-analysis of 4 RCTs and 2 OLTs (n = 3978)	• Febuxostat 40 mg, 80 mg, 120 mg, 240 mg • Allopurinol (varying doses) • Placebo
Inclusion Criteria	**Exclusion Criteria**
• RCTs and quasi controlled trials in patients with gout • Adults with a diagnosis of chronic gout • Patients 16 years of age meeting the preliminary ACR criteria for acute arthritis of primary gout or given a diagnosis of gout as described by the authors	• Populations that included a mix of people with chronic gout and asymptomatic hyperuricemia, unless results for the chronic gout population could be separated out for analysis
Primary Endpoints	**Secondary Endpoints**
• Frequency of gout flares • Change in sUA and percent change in sUA from baseline at final visit • Harms: As assessed by the incidence of patients with adverse effects (total and serious adverse effects, liver function test abnormalities, skin reactions, CV events, hypertension, and diarrhea) and withdrawal rates (and specific reasons for withdrawals)	• Tophus burden as measured by size measurement of individual tophus (regression of tophi), including disappearance of tophi and velocity of tophus regression • HRQoL, assessed by SF-36 • Pain (assessed via VAS, NRS, or qualitative scale) • Musculoskeletal function • Patient global and physician global assessment • Joint imaging

- **Results:**
  - Patients taking febuxostat 120 mg and 240 mg reported more frequent gout flares than in the placebo group 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 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; with an absolute treatment benefit of 75% and 87% (95% CI, 68 to 80% and 81 to 91%), respectively.
  - Total discontinuation rates were significantly higher in the febuxostat 80 mg group compared to placebo (RR 1.4; 95% CI, 1.0 to 2.0, absolute risk increase 11%; 95% CI, 3 to 19%). No other differences were observed. 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 harms. 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 (95% CI, 1.6 to 2.2, 95% CI, 1.9 to 2.5) with an absolute treatment benefit of 29% and 44% (95% CI, 25% to 33%, 95% CI, 38% to 50%), respectively, at 24 to 52 weeks. Total discontinuation rates were higher for febuxostat 80 mg and 120 mg compared to allopurinol (RR 1.5; 95% CI, 1.2 to 1.8, absolute risk increase 11%; 95% CI, 6% to 16%; and RR 2.6; 95% CI, 2.0 to 3.3, absolute risk

increase 20%; 95% CI, 3% to 14%, respectively).
  - Discontinuations due to adverse effects were similar across groups. Total adverse effects were lower for febuxostat 80 mg and 120 mg compared with allopurinol (RR 0.93; 95% CI, 0.87 to 0.99, absolute risk increase 6%; 95% CI, 0.7% to 11%; and RR 0.90; 95% CI, 0.84 to 0.96, absolute risk increase 8%; 95% CI, 3% to 13%, respectively). No other relevant differences were noted. After 3 years of follow-up there were no statistically significant differences regarding effectiveness and harms between febuxostat 80 mg or 120 mg and allopurinol groups (adverse effect rate per 100 patient-years 227, 216, and 246, respectively).
- **Author's conclusion:**
  - Although the incidence of gout flares requiring treatment may be increased in patients taking febuxostat compared to placebo or allopurinol during early treatment, no such increase in gout flares was observed in the long-term follow-up study when compared to allopurinol. Febuxostat at any dose was shown to be beneficial in achieving sUA levels < 6.0 mg/dL and reducing sUA levels in the period from baseline to final visit when compared to placebo and to allopurinol. However, the grade of evidence ranged from low to high, which indicates that further research is needed.
- **Study Appraisal**
  - **Study sponsorship:**
    - Internal: The University of Texas M.D. Anderson Cancer Center, not specified.
    - External: No sources of support supplied
  - **Study rating:**
    - N/A (MA)
  - **Study limitations:**
    - All febuxostat studies were funded by the manufacturer, TAP Pharmaceuticals, owned by Takeda Global Growth & Development Center.
    - Selective reporting: Some trials failed to report pre-specified secondary outcomes.

Study 5. Sundy et al. *JAMA*. 2011;306:711.

Study Objective: To assess the efficacy and tolerability of pegloticase in managing refractory chronic gout.	
Study Design, Follow-up	**Treatment Groups**
• Two 6-month, replicate, DB, PC, RCTs	• Pegloticase 8 mg IV every 2 weeks (biweekly treatment group) (Trial C0405 n = 43, Trial C0406 n = 42) • Pegloticase 8 mg IV alternating with placebo (monthly treatment group) (Trial C0405 n = 41, Trial C0406 n = 43) • Placebo (Trial C0405 n = 20, Trial C0406 n = 23)
Inclusion Criteria	**Exclusion Criteria**
• Refractory gout: ○ Baseline sUA of 8.0 mg/dL or greater and at least 1 of the following: 3 or more self-reported gout flares during the previous 18 months; 1 or more tophi; and gouty arthropathy, defined clinically or radiographically as joint damage due to gout • Contraindication to treatment with allopurinol or history of failure to normalize UA despite 3 or more months of treatment with the maximum medically appropriate allopurinol dose	• G6PD deficiency • Prior treatment with a uricase-containing agent • Pregnancy • Unstable angina • Uncontrolled hypertension (> 150/95 mm Hg) or cardiac arrhythmia • Uncompensated congestive heart failure, renal dialysis, or solid organ transplant
Primary Endpoint	**Secondary Endpoints**
• Proportion of sUA responders (sUA < 6.0 mg/dL) in each pegloticase treatment group vs the placebo group	• Tophus resolution • Reductions in the proportion of patients with gout flare and in the number of flares per patient during months 1 to 3 and 4 to 6 of the trial • Reductions in tender joint count (TJC) and swollen joint count (SJC) • Patient-reported changes in pain, physical function, and quality of life (QOL), measured, respectively, by the Health Assessment Questionnaire (HAQ) pain scale

- **Results:**
  - 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 UA < 6.0 mg/dL throughout the trial. The proportion of sUA responders (defined as an sUA < 6.0 mg/dL for ≥ 80% of the time during months 3 and 6) in both pegloticase treatment groups was significantly greater than for the placebo group in the pooled analysis (p < 0.001 for both) and

in the individual trials.
  - When analyzed separately by dose, patients treated with biweekly pegloticase experienced response rates of 47% (20/43; 95% CI, 31% to 62%) and 38% (16/42; 95% CI, 24% to 54%) in the 2 trials. Patients treated with monthly pegloticase reported response rates of 20% (8/41; 95% CI, 9% to 35%) and 49% (21/43; 95% CI, 33% to 65%) in the 2 trials. Response rates were 0% in both placebo groups (95% CI, 0% to 17% and 0% to 15% in the 2 trials).
  - Forty percent of patients in the biweekly pegloticase group and 21% in the monthly group had a complete response (CR) for 1 or more tophi by the final visit compared with 7% of patients receiving placebo (p = 0.002 and p = 0.20, respectively). During months 1 to 3, both the incidence of gout flares (proportion of patients suffering at least 1 flare) and the number of flares per patient were higher for pegloticase-treated patients compared with the placebo group. However, with continued treatment during months 4 to 6, significant reductions were seen in the proportion of patients with gout flare in the biweekly treatment group vs the placebo group. Flares per patient were also numerically fewer during this period with biweekly pegloticase treatment compared with placebo treatment, but the difference was not significant.
  - There were also reductions in TJC and SJC in patients treated with pegloticase compared with the respective values in placebo recipients, but only differences in TJC were statistically significant.
  - Both pegloticase dosing groups reported significant improvements in physical function and QOL compared with placebo. VAS were significantly reduced with biweekly pegloticase vs placebo. Treatment with biweekly pegloticase was also associated with significant changes from baseline in HAQ-DI scores and SF-36 Physical Component Summary scores that met or exceeded the minimum clinically important differences established for the respective instrument in inflammatory arthritides.
- **Authors' Conclusion:**
  - Among patients with chronic gout, elevated sUA level, and allopurinol intolerance or refractoriness, the use of pegloticase 8 mg either every 2 weeks or every 4 weeks for 6 months resulted in lower sUA levels compared with placebo.
- **Study Appraisal**
  - **Study sponsorship:**
    - Internal: Savient Pharmaceuticals
    - External: None reported
  - **Study rating:**
    - N/A (MA)
  - **Study limitations:**
    - Study sponsorship by manufacturer

CLINICAL GUIDELINES

- **Agency for Healthcare Research and Quality (AHRQ): Diagnosis and Management of gout: Current state of evidence** *(AHRQ 2017)*
  - See Appendix B for an explanation regarding the levels of evidence.
  - Effective treatments for gout attacks include NSAIDs, colchicine, and corticosteroids (high strength of evidence).
  - ULT, including allopurinol and febuxostat, reduce sUA (high strength of evidence).
    - Based on the data from systematic reviews, ULT did not reduce the frequency of gout attacks during the initial 6 months of therapy (high strength of evidence). The increased risk of gout attacks with initiation of ULT was ameliorated with the concomitant use of prophylactic agents (eg, colchicine, NSAIDs) (high strength of evidence).
    - After 12 months of ULT, the frequency of gout attacks was reduced (moderate strength of evidence).
- **Management of acute and recurrent gout: A clinical practice guideline from the American College of Physicians (ACP)***(Qaseem et al 2016)*
  - See Appendix A for an explanation regarding the levels of evidence.
  - The ACP recommends corticosteroids, NSAIDs, or colchicine to treat patients with acute gout (strength: strong recommendation, high-quality evidence).
    - Corticosteroids should be considered first-line in patients without contraindications, as they are generally safer and a low-cost treatment option.
    - Moderate-quality evidence shows no difference between the different NSAIDs.
  - Low-dose colchicine is recommended for treating acute gout (strength: strong recommendation, moderate-quality evidence).
    - Moderate-quality evidence suggests that lower doses of colchicine (1.2 mg followed by 0.6 mg 1 hour later) are as effective as higher doses at reducing pain and associated with fewer GI adverse effects.
  - The ACP recommends against initiating long-term ULT in most patients after the first gout attack or in patients with infrequent attacks (strength: recommendation, moderate-quality evidence).
    - In cases of recurrent gout (≥ 2 episodes per year) or problematic gout (eg, gout associated with tophi, chronic renal disease, or urolithiasis), shared decision making with the patient is warranted to review possible harms and benefits of ULT.

- It is recommended that physicians discuss benefits, harms, costs, and individual preferences with patients before initiating ULT, including concomitant prophylaxis, in patients with recurrent gout attacks (strength: recommendation, moderate-quality evidence).
  - Upon resolution of acute gout, some patients have no or a few attacks over many years, whereas others have more frequent or recurrent attacks.
  - Febuxostat and allopurinol are equally effective at decreasing sUA levels.
  - Prophylactic therapy with low-dose colchicine or low-dose NSAIDs helps to reduce the risk for acute gout attacks in patients initiating ULT.

- **American College of Rheumatology: Guidelines for the management of gout. Part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia** (*Khanna et al 2012*)
  - Per the ACR Web site, the 2012 gout guidelines are being revised and are anticipated to be completed in early 2020.
  - See Appendix C for an explanation regarding the levels of evidence.
  - Indications for pharmacologic ULT include:
    - Any patient with established diagnosis of gouty arthritis and:
      - Tophus/tophi by clinical exam or imaging study
      - Frequent attacks of acute gouty arthritis (≥ 2 attacks/year)
      - Chronic kidney disease stage 2 or worse
      - Past urolithiasis
  - Recommendations for treating sUA target:
    - The minimum sUA target is < 6 mg/dL
    - sUA lowering < 5 mg/dL may be needed to improve gout signs and symptoms
    - If sUA target is achieved, the following is recommended for the long-term management of gout:
      - Continue gout attack prophylaxis if there are ongoing gout symptoms and/or signs (≥ 1 tophus on physical exam).
      - After palpable tophi and all acute and chronic gouty arthritis gout symptoms have been resolved, continue all measures (including ULT) needed to maintain sUA < 6 mg/dL indefinitely.
    - If sUA target is not achieved, the following is recommended:
      - Increase intensity of ULT and reevaluate sUA.
      - When sUA target is achieved, recommendations for long-term management of gout should be followed.
  - XOI therapy with either allopurinol or febuxostat is recommended as the first-line pharmacologic ULT in gout.
    - Allopurinol
      - Starting dosage should be no greater than 100 mg/day for any patient. Patients with stage 4 or worse chronic kidney disease should be started on 50 mg/day.
      - The maintenance dose should be gradually titrated upward every 2 to 5 weeks to appropriate maximum dose in order to treat chosen sUA target.
      - Dose can be increased to > 300 mg/day, even in patients with renal impairment, provided adequate patient education and monitoring for drug toxicity is present.
      - Prior to initiation, consider HLA-B*5801 screening in selected patients.
  - Probenecid is recommended as an alternative first-line ULT option in the setting of contraindication or intolerance to ≥ 1 XOI agent.
  - sUA should be lowered sufficiently to durably improve signs and symptoms of gout, with a target < 6 mg/dL at a minimum, and often < 5 mg/dL.
  - Combination oral ULT with 1 XOI and 1 uricosuric agent is appropriate when the sUA target has not been met by appropriate dosing of a XOI.
  - Pegloticase is appropriate for patients with severe gout disease burden and refractoriness to, or intolerance of, appropriately dosed oral ULT options.
  - For refractory gout, the recommendations are as follows:
    - An attempt should be made to maximize the XOI dose.
    - Febuxostat can be substituted for allopurinol or vice versa in the event of drug intolerance and adverse events, and such a substitution should be considered after initial failure of upward dose titration of 1 XOI.
    - Effective therapeutic options include addition of a uricosuric agent (eg, probenecid) to an XOI drug or vice versa.
    - Pegloticase is appropriate for patients with severe gout disease burden and refractoriness to, or intolerance of, conventional and appropriately-dosed ULT. It is not recommended as a first-line ULT agent for any case scenarios.
    - There is a lack of consensus on the appropriate duration of pegloticase therapy relative to intended and achieved decrease in symptoms and signs of gout, including decrease in tophus size.

- **American College of Rheumatology: Guidelines for the Management of Gout. Part 2: Therapy and Anti-inflammatory Prophylaxis of Acute Gouty Arthritis** (*Khanna et al 2012*)
  - Per the ACR Web site, the 2012 gout guidelines are being revised and are anticipated to be completed in early 2020.
  - See Appendix C for an explanation regarding the levels of evidence.
  - An acute gouty arthritis attack should be treated with pharmacologic therapy, initiated within 24 hours of onset.
  - Established ULT should be continued, without interruption, during an acute attack of gout.

- Monotherapy with an NSAID (with proton pump inhibitor where indicated), corticosteroids, or colchicine is recommended as first-line agents for an acute gout attack.
  - Low-dose colchicine or low-dose NSAIDs are recommended first-line.
  - If colchicine or NSAIDs are not tolerated, contraindicated, or ineffective, then second-line options, such as low dose prednisone or prednisolone (≤ 10 mg/day), can be utilized.
  - If the patient is experiencing severe pain, particularly for a polyarticular attack or an attack affecting multiple large joints, initial combination therapy is an appropriate option.
- If there is an inadequate outcome, switching to an alternate monotherapy or add-on combination therapy is appropriate.
- If there is a successful outcome, consider indications for ULT or adjustment of ongoing ULT (see Part 1 of guidelines).

SAFETY

- **Contraindications**
  - Allopurinol
    - Patients who have developed a severe reaction to allopurinol should not be restarted on allopurinol
  - Colchicine
    - Concomitant colchicine and drugs that inhibit CYP3A4 and P-gp should be avoided in patients with renal or hepatic impairment
    - Colchicine should be avoided in patients with both renal and hepatic impairment
  - Febuxostat
    - Concomitant azathioprine or mercaptopurine therapy
  - Pegloticase
    - G6PD deficiency
  - Probenecid
    - Children < 2 years of age
    - Known blood dyscrasias or uric acid kidney stones
    - Should not be started until an acute gouty attack has subsided
- **Key warnings/precautions**
  - Allopurinol
    - Allopurinol should be discontinued at the first appearance of skin rash or other signs which may indicate an allergic reaction.
    - There may be an increased risk of hypersensitivity reactions to allopurinol in patients with decreased renal function receiving concomitant thiazides. Caution should be exercised if administering this combination.
    - Dose adjustments may be required when administering allopurinol with mercaptopurine or azathioprine.
    - A few cases of reversible clinical hepatotoxicity, and in some patients, asymptomatic rises in serum alkaline phosphatase or serum transaminase have been observed.
    - Caution should be exercised when partaking in activities that require alertness, as allopurinol may cause drowsiness.
    - A fluid intake sufficient to yield a daily urinary output of ≥ 2 liters and the maintenance of a neutral or slightly alkalinized urine are recommended to prevent the possible formation of xanthine calculi and to prevent renal precipitation or urates in patients receiving concomitant uricosuric agents.
    - Bone marrow suppression has been reported 6 weeks to 6 years after allopurinol initiation.
  - Colchicine
    - Fatal overdoses have been reported with colchicine in adults and children.
    - Blood dyscrasias have been reported at therapeutic colchicine doses.
    - Life threatening and fatal drug interactions have been reported with concomitant use of colchicine and P-gp or strong CYP3A4 inhibitors.
    - Neuromuscular toxicity: Myotoxicity including rhabdomyolysis may occur; especially in combination with other drugs known to cause this effect (eg, statins, fibrates).
  - Febuxostat
    - **Boxed warning**: CV death
      - Gout patients with established CV disease treated with febuxostat had a higher rate of CV death compared to those treated with allopurinol in a CV outcome study.
      - The risks and benefits of febuxostat should be considered when deciding to prescribe or continue patients on this medication. Febuxostat should only be used in patients who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable.
    - Gout flare: An increase in gout flares is frequently observed during initiation of anti-hyperuricemic agents including febuxostat. If a gout flare occurs during treatment, febuxostat need not be discontinued. Gout flare prophylaxis may be beneficial for up to 6 months.
    - Hepatic effects: Post-marketing reports of hepatic failure, sometimes fatal, have occurred. Causality cannot be excluded. Febuxostat should not be restarted if liver injury is confirmed and no alternate etiology can be found.

- Serious skin reactions: Postmarketing reports of serious skin and hypersensitivity reactions, including Stevens-Johnson Syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TENS) have been reported in patients taking febuxostat. Febuxostat should be discontinued if serious skin reactions are suspected.

- Pegloticase
  - **Boxed warning:** Anaphylaxis and infusion reactions; G6PD deficiency-associated hemolysis and methemoglobinemia
    - Anaphylaxis reactions have been reported during and after pegloticase administration. Anaphylaxis may occur with any infusion and generally manifests within 2 hours of the infusion; however, delayed-type hypersensitivity reactions have been reported.
    - Pegloticase should be administered in a healthcare setting by a healthcare provider(s) prepared to manage anaphylaxis and infusion reactions. Patients should be closely monitored for an appropriate period of time post infusion.
    - sUA levels should be monitored prior to infusions; treatment may be discontinued if sUA levels increase above 6 mg/dL particularly when 2 consecutive levels > 6 mg/dL are observed.
    - Patients should be screened for G6PD deficiency prior to pegloticase initiation. Hemolysis and methimoglobinemia have been reported with pegloticase in this patient population. Pegloticase should not be administered to patients with G6PD deficiency.
  - Infusion reactions
  - Gout flares: Gout flare prophylaxis is recommended for at least the first 6 months of therapy.
  - Congestive heart failure (CHF): CHF exacerbation may occur; patients should be monitored closely post infusion.
- Probenecid
  - Maintenance doses of colchicine or NSAIDs generally should be given prophylactically when probenecid is begun, due to increased risk of gout flares.
  - Increase in plasma concentration of methotrexate is possible when used concurrently with probenecid; concomitant use should be avoided if possible and if not, then methotrexate dose should be reduced.
  - Severe allergic reactions and anaphylactic reactions are possible.
  - Use with caution in patients with peptic ulcer disease.

- **Key adverse effects**
  - Allopurinol
    - Skin rash (may be severe and fatal), incidence = 1% to 3%
    - Acute gout attacks following initiation of allopurinol
    - Diarrhea
    - Nausea
    - Increase in alkaline phosphatase
  - Colchicine
    - The most common adverse effects reported are diarrhea, nausea, vomiting, and abdominal pain.
  - Febuxostat
    - Adverse effects that occurred in ≥ 1% of patients treated with febuxostat and at least 0.5% greater than noted in patients receiving placebo include:

Table 5. Adverse reactions for febuxostat compared to placebo and allopurinol*

Adverse reactions	Placebo	Febuxostat		Allopurinol*
	n = 134	40 mg n = 757	80 mg n = 1279	n = 1277
Liver function abnormality	0.7%	6.6%	4.6%	4.2%
Nausea	0.7%	1.1%	1.3%	0.8%
Arthralgia	0%	1.1%	0.7%	0.7%
Rash	0.7%	0.5%	1.6%	1.6%

*Of the patients who received allopurinol, 10 received 100 mg, 145 received 200 mg, and 1122 received 300 mg, based on level of renal impairment.

    - The most common adverse effect leading to discontinuation form therapy was liver function abnormalities in 1.8% of patients on febuxostat 40 mg, 1.2% on febuxostat 80 mg, and 0.9% on allopurinol.
  - Pegloticase
    - Adverse effects that occurred in ≥ 5% of patients in clinical trials include:
      - Gout flare (77% with pegloticase vs 81% with placebo)
      - Infusion reaction (26% with pegloticase vs 5% with placebo)
      - Nausea (12% with pegloticase vs 2% with placebo)
      - Contusion or ecchymosis (11% with pegloticase vs 5% with placebo)
      - Chest pain (6% with pegloticase vs 2% with placebo)

- Anaphylaxis (5% with pegloticase vs 0 with placebo)
  - Probenecid
    - CNS: Headache, dizziness
    - Acute symptoms of gout
    - GI: hepatic necrosis, vomiting, anorexia
    - Genitourinary: Nephrotic syndrome, uric acid stones, renal colic, costovertebral pain, urinary frequency
    - Hematologic: Aplastic anemia, leukopenia, hemolytic anemia, anemia
    - Integumentary: Dermatitis, alopecia, flushing

- **Drug Interactions**

Table 6. Key drug interactions for anti-gout agents

Precipitant Drug	Object Drug		Description
Allopurinol	Ampicillin, amoxicillin	↔	Risk of skin rash with allopurinol coadminstration as compared with either drug alone
Allopurinol	Azathioprine, mercaptopurine	↑	Increase in levels of azathioprine and mercaptopurine, as these drugs are metabolized by XO. A Reduction of azathioprine and mercaptopurine dose of one-third to one-fourth of usual dose is required.
Colchicine	Cyclosporine	↑	Significant increase in colchicine plasma levels. Fatal colchicine toxicity has been reported with cyclosporine.
Colchicine	Macrolides and related antibiotics	↑	Significant increase in colchicine plasma levels. Fatal colchicine toxicity has been reported with clarithromycin, a strong CYP3A4 inhibitor.
Colchicine	Nefazodone	↑	Significant increase in colchicine plasma levels
Colchicine	Protease inhibitors	↑	Significant increase in colchicine plasma levels
Colchicine	Verapamil, diltiazem	↑	Significant increase in colchicine plasma levels; neuromuscular toxicity seen with verapamil and diltiazem interactions
Febuxostat	Azathioprine, mercaptopurine	↑	Increase in levels of azathioprine and mercaptopurine, as these drugs are metabolized by XO; use with azathioprine and mercaptopurine is contraindicated.
Probenecid	Methotrexate	↑	Increase in methotrexate levels
Probenecid	NSAIDs	↑	Increase toxicity of NSAID possible

DOSAGE AND ADMINISTRATION

- Allopurinol
  - The dose should be is based on signs/symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy)
  - The initial dose recommended is 100 mg/day orally as a single or divided dose with increases at weekly intervals by 100 mg until sUA < 6 mg/dL
  - Maintenance dosing
    - Mild gout: 200 to 300 mg/day as a single or divided dose
    - Moderate-severe gout: 400 mg to 600 mg/day as a single or divided dose
    - Maximum dose = 800 mg/day
- Colchicine
  - For gout prophylaxis, the recommended dose is 0.6 mg orally (with or without food) once or twice daily. The maximum daily dose 1.2 mg.
  - For the treatment of gout flares, 1.2 mg should be administered at the first sign of flare, followed by 0.6 mg 1 hour later.
- Febuxostat
  - The recommended dose is 40 or 80 mg orally once daily. More specifically, the recommended starting dose is 40 mg once daily; for patients who do not achieve a sUA of < 6 mg/dL after 2 weeks, the dose should be increased to 80 mg once daily.
  - No dose adjustments are recommended in patients with mild or moderate renal or hepatic impairment. However, 40 mg orally daily is recommended for patients with severe renal impairment.
  - Febuxostat can be taken with or without food or antacid use.
- Pegloticase
  - The recommended dose is 8 mg IV, administered over ≥ 120 minutes, every 2 weeks.
  - Pre-infusion medications (eg, antihistamines, corticosteroids) are recommended.
    - If an infusion reaction occurs, the infusion may be slowed or stopped and restarted at a slower rate, at the

discretion of the physician.
    - Patients should be monitored for anaphylaxis for approximately 1 hour post-infusion.
- Probenecid
    - The recommended dose is 250 mg orally twice daily for 1 week, then 500 mg twice daily.
    - Probenecid should not be started until an acute gouty attack has subsided.
- Probenecid/colchicine
    - The initial dose is 1 tablet orally once daily for 1 week, followed by a maintenance dose of 1 tablet orally twice daily.
    - Probenecid/colchicine should not be started until an acute gouty attack has subsided.

SPECIFIC POPULATIONS

- **Geriatrics**
    - Allopurinol, probenecid
        - Safety and effectiveness have not been established in this patient population.
    - Colchicine
        - Due to the increased incidence of renal impairment in elderly patients (and other comorbidities), a lower dose should be considered.
    - Febuxostat, pegloticase
        - No dosage adjustments are necessary in elderly patients.
- **Pediatrics**
    - Allopurinol, colchicine, febuxostat, pegloticase, probenecid
        - Safety and effectiveness have not been established in this patient population.
- **Renal dysfunction**
    - Allopurinol
        - Patients with decreased renal function should receive lower doses of allopurinol.
    - Colchicine
        - Dose reduction or alternatives should be considered for the prophylaxis of gout flares in patients with renal impairment.
        - Colchicine is not effectively removed by hemodialysis. Patients on hemodialysis should be monitored carefully for colchicine toxicity.
    - Febuxostat
        - No dosage adjustments are necessary for mild to moderate renal impairment; however, for patients with severe renal impairment (CLcr 15 to 29 mL/min), a lower dose is recommended.
    - Pegloticase
        - No dosage adjustments are required for patients with renal impairment.
    - Probenecid
        - Probenecid may not be beneficial in patients with chronic renal insufficiency, particularly in patients with a CLcr ≤ 30 mL/minute.
- **Hepatic dysfunction**
    - Allopurinol, pegloticase
        - The safety and effectiveness have not been established in this patient population.
    - Colchicine
        - Dose reduction or alternatives should be considered for the prophylaxis of gout flares in patients with hepatic impairment.
    - Febuxostat
        - No dosage adjustments are necessary for mild to moderate hepatic impairment (Child-Pugh Class A or B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C).
- **Pregnancy and nursing**
    - Allopurinol, febuxostat, pegloticase
        - The safety and effectiveness have not been established in this patient population.
    - Colchicine, probenecid
        - Both colchicine and probenecid cross the placental barrier. As with other drugs, its use requires that the anticipated benefit would outweigh the potential hazards.

IMPORTANT PRODUCT AVAILABILITY AND STORAGE REQUIREMENTS

- Pegloticase must be stored in its original carton and maintained under refrigeration between 36° to 46°F at all times. The vial should not be shaken or frozen, and it should be protected from light.

APPENDICES

Appendix A. ACP guideline grading system *(Qaseem et al 2016)*
Table 7. ACP grading system

Quality of evidence	Strength of recommendation	
	Benefits clearly outweigh risks and burdens or risks and burden clearly outweigh benefits	**Benefits finely balanced with risks and burdens**
High	Strong	Weak
Moderate	Strong	Weak
Low	Strong	Weak

Appendix B. AHRQ Strength of evidence scale (*AHRQ 2017)*
Table 8. Strength of evidence scale

Quality of evidence	Description
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit a conclusion.

Appendix C. ACR grading system *(Khanna et al 2012*)
Table 9. ACR Evidence grades for recommendations

Levels	Description
Level A	Supported by multiple randomized clinical trials or meta-analyses
Level B	Derived from a single randomized trial or nonrandomized studies
Level C	Consensus opinion of experts, case studies, or standard of care

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Publication date: 5/6/2019

Therapeutic Class Overview
Carbidopa/Levodopa Agents

INTRODUCTION

- Parkinson's disease (PD) is a neurodegenerative disorder caused by progressive dopamine depletion in the nigrostriatal pathway of the brain and characterized by the cardinal manifestations of tremor, bradykinesia, and rigidity. Although traditionally recognized as a motor disorder, PD is a complex multifactorial condition that also includes neuropsychiatric and other non-motor manifestations. It is estimated that nearly 1 million people in the United States have PD *(Chou 2020, National Institute of Environmental Health Sciences [NIEHS] 2020)*.
- Current treatment options for PD include levodopa, dopamine agonists (DAs) (eg, bromocriptine, pramipexole, ropinirole), monoamine oxidase (MAO)-B inhibitors, anticholinergic agents, amantadine, and catechol-O-methyl transferase (COMT) inhibitors *(Spindler et al 2021)*.
- The dopamine precursor levodopa is the most effective drug for the symptomatic treatment of PD and is the first choice if symptoms, especially bradykinesia, become troublesome. Levodopa is combined with the peripheral decarboxylase inhibitor carbidopa to block its conversion to dopamine in the systemic circulation and liver prior to crossing the blood-brain barrier. This prevents nausea, vomiting, and orthostatic hypotension *(Spindler et al 2021)*.
- Levodopa-induced complications develop within several years of starting levodopa in a substantial number of patients; complications include motor fluctuations ("wearing off" phenomenon), dyskinesia, and dystonia. It is estimated that these motor complications occur in 30% to 40% of patients during the first 5 years and 60% or more after 10 years. The risk of motor complications increases with higher levodopa doses and younger age of PD onset *(Spindler et al 2021, Liang et al 2021)*.
- Treatment strategies for managing levodopa-induced dyskinesia include adjusting the levodopa doses and dosing schedule or adding an additional antiparkinson medication. For patients who fail oral and transdermal medical therapies, other options include deep brain stimulation, continuous carbidopa-levodopa intestinal gel infusion, and continuous subcutaneous apomorphine infusion *(Liang et al 2021)*.
- Levodopa combination products are available in several formulations. Immediate-release (IR) tablets, orally disintegrating tablets (ODT), and extended-release (ER) tablets are available in multiple strengths. Rytary, an extended-release (ER) capsule, contains microbeads of carbidopa and levodopa that, after dissolving, are absorbed at different rates. Stalevo tablets include entacapone, a COMT inhibitor, to prolong and potentiate the levodopa effect; this may be useful for patients experiencing end-of-dose "wearing off" periods. Duopa, an enteral suspension, is given as a continuous infusion for patients with motor fluctuations in advanced PD *(Chou et al 2021)*. The newest levodopa product, Inbrija, is an inhalation powder intended to be used as an adjunct to oral carbidopa/levodopa therapy for the intermittent treatment of OFF episodes.
- Medispan class: Antiparkinson Dopaminergics; Levodopa Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
carbidopa/levodopa ODT	✔
Duopa (carbidopa/levodopa) enteral suspension	-
Inbrija (levodopa) inhalation powder	-
Lodosyn (carbidopa) tablets	✔
Rytary (carbidopa/levodopa) ER capsules	-
Sinemet (carbidopa/levodopa) tablets	✔
carbidopa/levodopa ER tablets	✔
Stalevo (carbidopa/levodopa/entacapone) tablets	✔

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	carbidopa/levodopa ODT	Duopa (carbidopa/levodopa)	Inbrija (levodopa)	Lodosyn (carbidopa)	Rytary (carbidopa/levodopa)	Sinemet (carbidopa/levodopa), carbidopa/levodopa ER tablets	Stalevo (carbidopa/levodopa/ entacapone)
Treatment of PD, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication	✔				✔	✔	
Treatment of motor fluctuations in patients with advanced PD		✔					
Intermittent treatment of OFF episodes in patients with PD treated with carbidopa/levodopa			✔				
Treatment of PD • Stalevo can be used: ○ To substitute (with equivalent strengths of each of the 3 components) carbidopa/levodopa and entacapone previously administered as individual products ○ To replace carbidopa/levodopa therapy (without entacapone) when patients experience the signs and symptoms of end-of-dose "wearing-off" and when they have been taking a total daily dose of levodopa ≤ 600 mg and have not been experiencing dyskinesias							✔
For use with carbidopa/levodopa or with levodopa in the treatment of PD, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication • Lodosyn can be used: ○ With carbidopa/levodopa in patients for whom the dosage of carbidopa/levodopa provides less than adequate daily dosage of carbidopa ○ With levodopa in the occasional patient whose dosage requirement of carbidopa and levodopa necessitates separate titration of each medication ○ With carbidopa/levodopa or with levodopa to permit administration of lower doses of levodopa with reduced nausea/vomiting, more rapid dose titration, and with a somewhat smoother response				✔			

(*Prescribing information: carbidopa/levodopa ODT 2016, carbidopa/levodopa ER 2020, Duopa 2020, Inbrija 2020, Lodosyn 2020, Rytary 2019, Sinemet 2020, Stalevo 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

Carbidopa/levodopa

- Although the efficacy of levodopa in PD has been widely established in clinical practice, there have been few placebo-controlled (PC) studies evaluating its effects. A systematic review of the available evidence concluded that levodopa is clinically efficacious as monotherapy for symptomatic PD *(Fox et al 2018)*. A Cochrane Review of trials comparing DAs (with or without levodopa) vs placebo and/or levodopa in patients with early PD demonstrated that while patients on a DA were less likely to develop dyskinesia, dystonia, or motor fluctuations, symptomatic control of PD was better with levodopa. Adverse effects (AEs) such as edema, somnolence, constipation, dizziness, and hallucinations were also increased in DA-treated patients vs levodopa-treated patients *(Stowe et al 2008)*.
- ELLDOPA, a multicenter (MC), double-blind (DB), PC, dose-ranging, randomized controlled trial (RCT), evaluated the effect of levodopa on the rate of progression of PD in 361 patients with early PD for 42 weeks. Patients were randomized to either carbidopa/levodopa (3 different doses) or placebo therapy. The primary outcomes were the change in Unified Parkinson Disease Rating Scale (UPDRS) scores and the percent change in the ratio of the specific striatal [^{123}I]β-CIT uptake to the nondisplaceable striatal [^{123}I]β-CIT uptake between the two images (prior to baseline and at week 40). The mean difference between the total score on the UPDRS was 7.8 units in the placebo group, 1.9 units in the groups receiving levodopa at a dose of 150 mg/day and 300 mg/day, and -1.4 units in those receiving 600 mg/day ($p < 0.001$). The mean percent decline in the [^{123}I]β-CIT uptake was significantly greater with levodopa than placebo (-6%, -4%, and -7.2% among those receiving levodopa at 150 mg/day, 300 mg/day, and 600 mg/day, respectively vs -1.4% among those receiving placebo) ($p = 0.036$). The patients receiving the highest dose of levodopa had significantly more dyskinesia, hypertonia, infection, headache, and nausea than those receiving placebo. The authors concluded that from a clinical perspective, the ELLDOPA study did not find that levodopa hastens the progression of PD. Small doses were found to be effective, although less so than higher doses *(The Parkinson Study Group 2004)*.
- A 5-year, MC, DB, parallel-group, RCT compared the long-term clinical and safety effects of IR and controlled release (CR) carbidopa/levodopa in 618 levodopa-naïve PD patients. The mean dose of IR medication after 5 years was 426 ± 205 mg/day and 510 ± 224 mg/day for the bioavailable dose of CR medication ($p = 0.02$). After 5 years, 20.6% of the IR group and 21.8% of the CR group had motor fluctuations or dyskinesia (not statistically significant). The prevalence of AEs did not differ between the treatment arms. The authors concluded that despite the progressive nature of PD, both the IR and CR formulations of carbidopa/levodopa maintained similar control in PD after 5 years. The low incidence of motor fluctuations or dyskinesia was not significantly different between treatment groups and may be partly attributed to the relatively low doses of levodopa used throughout the trial *(Koller et al 1999)*.

Carbidopa/levodopa + entacapone

- The efficacy and safety of adjuvant COMT inhibitor therapy (entacapone or tolcapone) to carbidopa/levodopa therapy were examined in a Cochrane Review of 14 RCTS of PD patients with motor fluctuations (N = 2566). Eight trials examined entacapone 200 mg added to each levodopa dose vs placebo in 1560 patients. Compared with placebo, entacapone significantly reduced levodopa dose (weighted mean difference: 55 mg/day; $p < 0.00001$), reduced OFF-time (difference: 41 minutes; $p = 0.004$), and improved UPDRS activities of daily living and motor scores ($p < 0.05$ for both). Entacapone also significantly increased the risk of dyskinesia, nausea, vomiting, diarrhea, constipation, and dizziness ($p \leq 0.01$ for all). Tolcapone was shown to provide similar benefits in relieving levodopa-induced complications, but also raised liver enzyme levels in some patients *(Deane et al 2004)*.
  - Due to risk of liver toxicity, tolcapone should only be used in PD patients who are not responding satisfactorily to or are not appropriate candidates for other adjunctive therapies *(Tolcapone prescribing information 2018)*.

Duopa

- The efficacy and safety of Duopa were evaluated in 3 clinical trials of patients with advanced PD who had persistent motor fluctuations despite optimized treatment with oral carbidopa/levodopa. The primary efficacy measure was mean change in OFF-time from baseline to the end of the study. ON-times with and without dyskinesias were also measured.
  - In a 12-week, DB, PC, RCT, patients (N = 71) were randomized to receive Duopa or placebo per percutaneous endoscopic gastrostomy with jejunal tube (PEG-J). Those who were in the Duopa group received placebo IR carbidopa/levodopa and those in the placebo intestinal gel infusion group received active IR carbidopa/levodopa. Duopa demonstrated a statistically significant reduction in OFF-time compared with IR carbidopa/levodopa (-4.04 hours vs -2.14 hours, respectively; treatment difference: -1.91 hours; $p = 0.0015$). Duopa was associated with a statistically significantly greater improvement than IR carbidopa/levodopa in ON-time without troublesome dyskinesia (4.11 hours vs 2.24 hours, respectively; treatment difference: 1.86 hours; $p = 0.0059$) and in ON-time without

dyskinesia (3.37 hours vs 1.09 hours, respectively; treatment difference: 2.28 hours; p = 0.0142). Significant improvements in the UPDRS II (ability to engage in activities of daily living) score and health-related quality of life (HRQoL), as measured by the Parkinson's Disease Questionnaire (PDQ-39), were also reported in patients receiving Duopa vs IR carbidopa/levodopa *(Olanow et al 2014)*.

- In a 52-week, open-label extension study, all patients received Duopa (N = 62). Those continuing Duopa maintained their improved OFF-time; however, this value was not statistically significant compared to the mean OFF-time at the start of the extension study (mean change in hours/day: -0.42; p = 0.377). Duopa-naïve patients showed a statistically significant improvement in OFF-time from the start of the extension study (mean change in hours/day: −2.34; p < 0.001). Statistically significant improvements in ON-time without troublesome dyskinesia from the start of the extension study were demonstrated in both Duopa-naïve (mean change in hours/day: 2.19; p = 0.005) and Duopa-continuing patients (mean change in hours/day: 1.00; p = 0.036, respectively). In regard to HRQoL, both the Duopa-continuing and Duopa-naïve groups demonstrated statistically significant improvements in the overall UPDRS Part IV score, a measure of motor complications associated with PD *(Slevin et al 2015)*.
- In a 54-week open-label study, all patients received Duopa (N = 354). OFF-time was significantly decreased from baseline to last visit by 4.4 hours/day (p < 0.001). This improvement was sustained throughout all visits from weeks 4 to 54. Similarly, ON-time without troublesome dyskinesia increased by 4.8 hours/day (p < 0.001), and ON-time with troublesome dyskinesia decreased by 0.4 hours/day (p = 0.023). These improvements were sustained at all visits. Statistically significant improvements in UPDRS Parts II and III (activities of daily living and motor examination), UPDRS Part IV dyskinesia items, and HRQoL were observed at the study end compared with baseline *(Fernandez et al 2015)*.

Inbrija

- The efficacy and safety of Inbrija for the treatment of OFF episodes in patients with PD treated with oral carbidopa/levodopa were evaluated in a 12-week, DB, PC, RCT. Patients with at least 2 hours of OFF time per day were randomized to receive Inbrija inhalation powder 60 mg (n = 113), 84 mg (n = 114), or placebo (n = 112) as needed for OFF episodes. The average use of Inbrija or placebo was approximately 2 doses per day. Change in UPDRS Part III (motor) score from pre-dose (OFF state) to 30 minutes post-dose was significantly greater in the Inbrija 84 mg group vs placebo at week 12 (least squares mean change in Inbrija group: -9.83 vs -5.91 in placebo; between-group difference: -3.92; 95% CI, -6.84 to -1.00; p = 0.0088). The proportion of patients who returned to an ON state and sustained the ON state through 60 minutes post-dose was 58% for Inbrija 84 mg and 36% for placebo (p = 0.003) *(LeWitt et al 2019)*.
- The effect of Inbrija on pulmonary function was evaluated in PD patients treated with oral carbidopa/levodopa in a 12-month, open-label, RCT. Patients were randomized to receive Inbrija 84 mg (n = 278) or to an observational cohort receiving oral standard of care therapy (n = 130). There was no significant difference in pulmonary function as assessed by spirometry parameters between the Inbrija and observational cohort groups at 52 weeks. Exploratory endpoints in the Inbrija group included improvements in UPDRS Part III scores, as well as patient-reported measures such as daily OFF time *(Grosset et al 2018a [poster], Grosset et al 2018b [poster], Inbrija prescribing information 2020)*.

Rytary

- The efficacy and safety of Rytary were evaluated in 3 DB, RCTs; 2 trials were conducted in advanced PD patients vs carbidopa/levodopa IR and carbidopa/levodopa + entacapone, and 1 trial was conducted in early PD patients vs placebo.
  - In comparison to IR carbidopa/levodopa (n = 192), Rytary (n = 201) demonstrated a statistically significant improvement in the percentage of OFF-time in advanced PD patients, from a baseline of 36.9% to 23.8% for the Rytary group and from a baseline of 36.0% to 29.8% for the IR carbidopa/levodopa group (p < 0.0001). This translated to the Rytary group experiencing an additional reduction of 1 hour in OFF-time compared to the IR carbidopa/levodopa group (p < 0.0001) *(Hauser et al 2013)*.
  - In a crossover study of advanced PD patients, all patients received either Rytary or carbidopa/levodopa + entacapone (n = 91). Rytary demonstrated a statistically significant improvement in the percentage of OFF-time, from a baseline of 36.3% (both Rytary and carbidopa/levodopa + entacapone patients) to 24.0% vs 32.5% in the carbidopa/levodopa + entacapone group (p < 0.0001). Hence, compared with carbidopa/levodopa + entacapone treatment, Rytary reduced OFF-time by 1.4 hours *(Stocchi et al 2014)*.
  - The PC study randomized 381 levodopa-naïve patients to 3 strengths of Rytary (145 mg, 245 mg, or 390 mg) given 3 times daily or placebo. All dosages demonstrated a statistically significant improvement in UPDRS measures vs placebo throughout the study and at 30 weeks (p < 0.0001). Rytary was well tolerated, with the most commonly reported AEs being nausea, dizziness, and headache; the authors concluded that Rytary 145 mg 3 times daily appeared to provide the best overall balance between efficacy and safety *(Pahwa et al 2014)*.

CLINICAL GUIDELINES

- The American Academy of Neurology (AAN) practice parameter on initiation of treatment for PD *(Miyasaki et al 2002)* recommends that in patients who require the initiation of dopaminergic treatment, levodopa or a DA may be used; the choice depends on the relative impact of improving motor disability (better with levodopa) compared with the lessening of motor complications (better with DAs).
  - Treatment of PD patients with cabergoline, ropinirole, and pramipexole results in fewer motor complications (wearing off, dyskinesias, "on/off" motor fluctuations) than levodopa, but is also associated with more frequent adverse events, including hallucinations, somnolence, and edema.
  - Amantadine is noted to have a modest effect on all features of PD with a mild adverse effect profile.

- European Federation of Neurological Societies (EFNS) and Movement Disorders Society (MDS) - European Section (ES) *(Oertel et al 2011)*
  - This joint guideline outlines recommendations for treatment of late (complicated) PD, including treatment of motor complications and the nonmotor symptoms of PD. A summary of the treatment of motor complications is provided.
  - Motor fluctuations: Wearing -" off" (end of dose akinesia, predictable "on"-" off")
    - In the early phase, when motor fluctuations are just becoming apparent, adjustments in frequency of levodopa dosing during the day (4 to 6 daily doses) may attenuate wearing-" off".
    - COMT inhibitors or MAO-B inhibitors may be added: No recommendations can be made on which treatment should be chosen first. On average, all reduce "off" time by about 1 to 1.5 hours per day.
      - No difference has been demonstrated between entacapone and rasagiline. Tolcapone, although more effective than entacapone, is potentially hepatotoxic, and is only recommended in patients who have failed all other available medications.
      - Rasagiline should not be added to selegiline due to cardiovascular (CV) safety issues.
    - DAs may be added: efficacious in reducing "off" time in patients experiencing wearing-"off". Currently, no DA has proven better than another; switching from 1 DA to another can be helpful in some patients.
      - First line: Non-ergot DAs.
      - Second Line: Ergot DAs (association with lung, retroperitoneal, and heart valve fibrosis).
    - Standard levodopa can be switched to a CR formulation:
      - CR formulation of levodopa can improve wearing-" off".
      - CR formulation of levodopa is useful for the treatment of night-time akinesia (nocturnal end-of-dose akinesia).
    - Amantadine or an anticholinergic may be added: In patients with disabling recurrent "off" symptoms that fail to improve further with the aforementioned strategies, the addition of an anticholinergic (in younger patients) or amantadine may improve symptoms in some cases.
  - Dyskinesias: Peak-dose dyskinesia
    - Levodopa dose size may be reduced, with a risk of increasing "off" time; the latter can be compensated for by increasing the number of daily doses of levodopa or increasing the doses of a DA.
    - MAO-B inhibitors or COMT inhibitors may be discontinued or the dose may be reduced, with a risk of worsening of wearing-" off".
    - Amantadine may be added; benefit may last < 8 months.
    - In some cases, discontinuation of oral levodopa for a short period of time (3 days) with simultaneous continuous intravenous infusion of amantadine may temporarily improve dyskinesia.
    - Other interventions that may be considered include deep brain stimulation, internal globus pallidus stimulation, the addition of an atypical antipsychotic (clozapine or quetiapine), apomorphine continuous subcutaneous infusion, and intrajejunal levodopa infusion.

- The International Parkinson and MDS Evidence-Based Medicine Review Update: Treatments for the Motor Symptoms of PD *(Fox et al 2018)* (Refer to Appendix C for definitions of specific recommendations).
  - In patients with early PD, no treatment is considered clinically useful for the prevention or delay of disease progression. In patients requiring symptomatic monotherapy therapy, levodopa preparations (immediate release [IR], controlled release [CR], extended release [ER]), DAs (pramipexole IR and ER, ropinirole IR, rotigotine), MAO-B inhibitors (selegiline, rasagiline) or anticholinergics are considered clinically useful. However, inpatients with early or stable PD on levodopa, adjunct therapy can include DAs, COMT inhibitors, MAO-B inhibitors or surgery.

- In longer term follow-up, the available evidence suggests that there is no clinically relevant difference on motor function, troublesome motor complications, or mortality according to the choice of initial therapy.
  - Options for the treatment of motor fluctuations in patients that have been optimized on levodopa therapy, that have demonstrated efficacy and are considered clinically useful include:
    - DAs (pramipexole IR and ER, ropinirole IR and ER, and rotigotine)
    - Levodopa preparations (levodopa ER, levodopa/carbidopa IR, and levodopa/carbidopa/etacapone)
    - COMT inhibitors (entacapone, tolcapone, and opicapone)
    - MAO-B inhibitors (rasagiline, safinamide, and zonisamide)
    - Istradefylline, due to conflicting evidence is considered likely efficacious and possibly useful in patients.
    - For dyskinesia, clinically useful treatments include amantadine, clozapine, and surgery.

SAFETY SUMMARY

Contraindications

- All levodopa products are contraindicated in patients currently taking a nonselective MAO inhibitor or who have recently (within 2 weeks) taken a nonselective MAO inhibitor. Hypertension can occur if these drugs are used concurrently.
- Sinemet, Stalevo, and generic carbidopa-levodopa formulations are contraindicated in narrow-angle glaucoma.
- Lodosyn is contraindicated in patients with known hypersensitivity to the drug. Since it is used in conjunction with levodopa or carbidopa-levodopa combination products, contraindications for these products may also apply.

Warnings and Precautions

- Warnings and precautions for all of the levodopa products include falling asleep during activities of daily living, hallucinations/exacerbations of psychosis, impulse control disorders, causation or exacerbation of dyskinesia, and increased intraocular pressure in patients with glaucoma.
- Sudden discontinuation or rapid dose reduction should be avoided to reduce the risk of withdrawal-emergent hyperpyrexia and confusion resembling neuroleptic malignant syndrome (NMS).
- Cardiovascular ischemic events and arrhythmia have been reported in patients taking carbidopa/levodopa.
- Patients should be observed carefully for the development of depression with concomitant suicidal tendencies.
- Duopa has warnings for neuropathy and gastrointestinal or gastrointestinal procedure-related risks.
- Inbrija has a warning for bronchospasm in patients with lung disease; use in patients with asthma, chronic obstructive pulmonary disease (COPD), or other chronic underlying lung disease is not recommended.
- Due to the entacapone component, Stalevo has addition warnings for diarrhea, colitis, and rhabdomyolysis.
- Epidemiological studies have shown that patients with PD have a higher risk of developing melanoma than the general population. Whether the increased risk observed is due to PD or other factors, such as drugs used to treat PD, is unclear.
- Lodosyn has no antiparkinsonian effect when given alone. Lodosyn may decrease the peripheral effects of levodopa (eg, nausea, vomiting), but does not decrease central adverse effects. When Lodosyn is given in combination with levodopa, dyskinesias and other central adverse effects may occur sooner/at lower doses than with levodopa alone. Because Lodosyn is indicated for use with levodopa or carbidopa-levodopa combinations, warnings for these products may also apply.

Key Adverse Effects

- The most common AEs for the carbidopa/levodopa oral formulations include dyskinesias and nausea. Orthostatic hypotension, confusion, dizziness, and hallucinations also occur. Lodosyn has not been demonstrated to have any pharmacodynamic actions at recommended doses; the only AEs that have been observed have been with concomitant use of carbidopa with levodopa or carbidopa-levodopa combinations.
- The most common AEs for Duopa (incidence at least 7% greater than oral carbidopa/levodopa) are complication of device insertion, nausea, depression, peripheral edema, hypertension, upper respiratory tract infection, oropharyngeal pain, atelectasis, and incision site erythema.
- The most common AEs for Inbrija are cough, nausea, upper respiratory tract infection, and discolored sputum.
- The most common AEs for Stalevo are dyskinesias, urine discoloration, diarrhea, nausea, abdominal pain, vomiting, and dry mouth.

DOSING AND ADMINISTRATION

General dosing information

- The optimum daily dosage of the levodopa combination products must be determined by careful titration in each patient.
- Because PD is progressive, periodic clinical evaluations are recommended; adjustment of the carbidopa/levodopa dosage regimen may be required.
- Other antiparkinson medications (eg, anticholinergic agents, dopamine agonists, and amantadine) can be given with the carbidopa/levodopa products. Dosage adjustment of carbidopa/levodopa may be necessary when these agents are added.
- Studies show that peripheral dopa decarboxylase is saturated by carbidopa at approximately 70 to 100 mg a day. Patients receiving less than this amount of carbidopa are more likely to experience nausea and vomiting. Experience with total daily dosages of carbidopa greater than 200 mg is limited.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
carbidopa/levodopa	ODT	Oral	Usual initial dosage: 3 times daily; dosage may be increased by 1 tablet daily or every other day, as necessary, until a dosage of 8 tablets per day is reached	The ODT should be allowed to dissolve on top of the tongue, then swallowed with saliva; administration with liquid is not necessary.
Duopa (carbidopa/levodopa)	Enteral suspension	PEG-J	Continuous 16-hour infusion period composed of a morning dose, a continuous dose, and extra doses	Duopa must be administered with the CADD-Legacy 1400 portable infusion pump. At the end of the 16-hour infusion, patients will disconnect pump from the PEG-J and take their nighttime dose of oral IR carbidopa-levodopa tablets
Inbrija (levodopa)	Inhalation powder	Inhalation	Inhale 2 capsules as needed for OFF symptoms up to 5 times daily	Capsules for inhalation must be administered with the Inbrija inhaler.
Lodosyn (carbidopa)	Tablet	Oral	Patients receiving carbidopa/levodopa who require additional carbidopa: daily with the first dose of carbidopa/levodopa each day; additional doses may be given throughout the day with each carbidopa/levodopa dose as required for optimal response Patients requiring individual titration of carbidopa and levodopa dosage: 3 to 4 times daily, at the same time as levodopa	
Rytary (carbidopa/levodopa)	ER capsule	Oral	Patients naïve to levodopa therapy: 3 times daily; titrate as needed Converting from IR carbidopa/levodopa to Rytary: follow conversion based on total levodopa dose in prescribing information	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Sinemet (carbidopa/levodopa)	Tablet	Oral	Usual initial dosage: 3 times daily Dosage may be increased by 1 tablet every day or every other day, as necessary, until a dosage of 8 tablets per day is reached	
carbidopa/levodopa ER	ER tablet	Oral	Initial dose in patients not receiving levodopa: twice daily Initial dosage in patients treated with conventional carbidopa/levodopa preparations: carbidopa/levodopa ER should be substituted at an amount that provides ~10% more levodopa per day; the interval between doses should be 4 to 8 hours during the waking day	An interval of at least 3 days between dosage adjustments is recommended.
Stalevo (carbidopa/levodopa/ entacapone)	Tablet	Oral	Converting patients from carbidopa, levodopa, and entacapone to Stalevo: patients taking entacapone 200 mg with each dose of non-ER carbidopa/levodopa can switch to the corresponding strength of Stalevo containing the same amounts of levodopa and carbidopa Converting patients from carbidopa/levodopa products to Stalevo: there is no experience in transferring patients treated with ER formulations of carbidopa/levodopa	Tablets should not be split or fractionated. Patients with hepatic impairment should be treated with caution.

See the current prescribing information for full details

CONCLUSION

- The efficacy of levodopa in the treatment of symptomatic PD has been well established. It is generally the first choice for treatment if symptoms, especially bradykinesia, become troublesome. Levodopa is combined with the peripheral decarboxylase inhibitor carbidopa to block its conversion to dopamine in the systemic circulation and liver prior to crossing the blood-brain barrier.
  - Although highly effective in the treatment of PD symptoms, levodopa-induced complications develop within several years of starting levodopa in a substantial number of patients; complications include motor fluctuations (“wearing off” phenomenon), dyskinesia, and dystonia. Treatment strategies for managing levodopa-induced dyskinesia include adjusting the levodopa dose and dosing schedule or combination therapy.
- Carbidopa/levodopa combination products are available as IR tablets, ER tablets and capsules, and ODTs. Stalevo tablets include entacapone, a COMT inhibitor, to prolong and potentiate the levodopa effect in patients who experience “wearing off”. Duopa, an enteral carbidopa/levodopa suspension, is given as a continuous PEG-J infusion for patients with motor fluctuations in advanced PD. Inbrija is a levodopa inhalation powder intended to be used as an adjunct to carbidopa/levodopa therapy for the intermittent treatment of OFF episodes.
- The optimum daily dosage of the levodopa combination products must be determined by careful titration in each patient.
- Warnings and precautions for all of the levodopa products include falling asleep during activities of daily living, hallucinations/exacerbations of psychosis, impulse control disorders, and causation or exacerbation of dyskinesia. Duopa has additional warnings for gastrointestinal risk and neuropathy. Inbrija has a warning for bronchospasm in

patients with lung disease. Due to the entacapone component, Stalevo has additional warnings for diarrhea, colitis, and rhabdomyolysis. Common AEs for the levodopa products include dyskinesias and nausea.

- Guidelines for the treatment of PD recommend initiation of either a DA or carbidopa/levodopa product; either an IR or an ER product may be considered, as there appears to be no difference in the rate of motor complications. In late PD, motor fluctuations or dyskinesias can be managed by modifying the levodopa dose/schedule or adding an additional antiparkinson medication such as entacapone *(Fox et al 2018, Miyasaki et al 2002, Oertel et al 2011).*

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Publication Date: June 16, 2021

Therapeutic Class Overview
Calcitonin gene related peptide (CGRP) inhibitors

INTRODUCTION

- Migraine is a common, recurrent, incapacitating disorder characterized by moderate to severe headaches and disabling features, including nausea, vomiting, neurologic symptoms, photophobia, and phonophobia. Cluster headache is less prevalent than migraine and characterized by attacks of severe, unilateral pain with ipsilateral autonomic symptoms, which occur every other day to multiple times daily during a cluster period (*International Headache Society [IHS] 2018, Starling et al 2015).*
  - The goals for treatment of migraine are to reverse or stop the progression of a migraine attack. The goals for preventive treatment are to reduce the frequency, severity and duration of a migraine (*American Headache Society [AHS] 2019, Katsarava et al 2012*).
- The International Classification of Headache Disorders (ICHD) includes both cluster headache and migraine as part of a group of primary headache disorders (*IHS 2018*):
  - Chronic migraine is defined as ≥ 15 headache days per month for > 3 months with the features of migraine headache for at least 8 mean migraine days per month (MMD). The most common cause of symptoms suggestive of chronic migraine is medication overuse. According to the ICHD, around 50% of patients apparently with chronic migraine revert to an episodic migraine type after drug withdrawal; such patients are in a sense wrongly diagnosed with chronic migraine. In most clinical trials, migraine that is not chronic (ie, < 15 headache days per month) is considered to be episodic migraine, although the condition is not clearly defined in the ICHD.
  - Cluster headache is defined as ≥ 5 attacks lasting 15 to 180 minutes every other day to 8 times a day with severe unilateral orbital, supraorbital, and/or temporal pain. Episodic cluster headache attacks occur for a period of 7 days to 1 year and are separated by pain-free periods lasting at least 3 months. Common symptoms include nasal congestion, rhinorrhea, conjunctival injection and/or lacrimation, eyelid edema, sweating (forehead or face), miosis, ptosis, and/or a sense of restlessness or agitation.
- Cluster headache is more likely to occur in men, whereas migraines are more likely to occur in women. Migraines have a global prevalence of 15 to 18% and are a leading cause of disability worldwide. Chronic migraine is estimated to occur in 2 to 8% of patients with migraine, whereas episodic migraine occurs in more than 90% of patients. Cluster headache is rare compared to other primary headache disorders. It is estimated to have a prevalence of 0.1% within the general population (*Global Burden of Disease Study [GBD] 2016, Hoffman et al 2018, Lipton et al 2016, Ljubisavljevic et al 2019, Manack et al 2011*).
- Treatments for migraines and cluster headache are divided into acute and preventive therapies. Evidence and reputable guidelines clearly delineate appropriate therapies for episodic migraine treatment and prophylaxis; options stretch across a wide variety of therapeutic classes and are usually oral therapies. For the prevention of migraines, treatment options include oral prophylactic therapies, injectable prophylactic therapies, and neuromodulator devices. Oral prophylactic migraine therapies have modest efficacy, and certain oral therapies may not be appropriate for individual patients due to intolerability or eventual lack of efficacy. For the treatment of acute migraine, options include triptans, ergots, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, small molecule CGRP inhibitors, and a 5-hydroxytryptamine $(5\text{-HT})_{1F}$ receptor agonist. For the treatment of cluster headache, subcutaneous sumatriptan, zolmitriptan nasal spray, and oxygen have the most positive evidence for acute therapy, and suboccipital steroid injections are most effective for prevention (*American Migraine Foundation [AMF] 2020, Marmura et al 2015, Robbins et al 2016, Silberstein et al 2012, Simpson et al 2016 [guideline reaffirmed in 2019]).*
- The calcitonin gene-related peptide (CGRP) pathway is important in pain modulation and the Food and Drug Administration (FDA) has approved 6 CGRP inhibitors for prevention or treatment of migraine/headache disorder(s). Erenumab-aooe is a fully human monoclonal antibody, which potently binds to the CGRP receptor in a competitive and reversible manner with greater selectivity than to other human calcitonin family receptors. Fremanezumab-vfrm, eptinezumab-jjmr, and galcanezumab-gnlm are humanized monoclonal antibodies that bind to the CGRP ligand and block its binding to the receptor. Rimegepant and ubrogepant are small molecule oral CGRP receptor antagonists (*Dodick et al 2018[b], Edvinsson 2017, Goadsby et al 2017, Sun et al 2016, Tepper et al 2017*).
  - Two CGRP inhibitors known as the “gepants,” telcagepant and olcegepant, were previously investigated. In 2009, Merck withdrew the FDA application for telcagepant because of elevated liver enzymes and potential liver toxicity

observed with chronic use, which was likely related to the chemical structure of the compound. The manufacturer of olcegepant also ceased pursuing FDA approval; however, the manufacturer did not explicitly state the rationale. It has been widely speculated that olcegepant development ceased due to limitations associated with administration as an intravenous (IV)-only product (*Edvinsson et al 2017, Walker et al 2013*). No substantial issues with liver toxicity have been observed in trials with the currently marketed CGRP inhibitors.

- In April 2019, Teva announced that it would not pursue development of fremanezumab-vfrm for an episodic cluster headache indication due to results from the ENFORCE trial (*Teva Pharmaceuticals press release 2019*). Erenumab-aooe is not currently under clinical investigation for the indication of cluster headache; however, a trial has been initiated with eptinezumab-jjmr (*Clinicaltrials.gov 2021*).
- A CGRP inhibitor early in development is zavegepant, the first intranasally administered CGRP inhibitor in Phase 2/3 studies (*Biohaven Pharmaceutical 2021*). Atogepant, another oral CGRP inhibitor, was submitted for FDA approval in March 2021, with a decision anticipated for Q3 of 2021 *(AbbVie 2021)*.

- Medispan class: Migraine products – monoclonal antibodies; Calcitonin gene−related peptide (CGRP) receptor antagonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Aimovig (erenumab−aooe)	–
Ajovy (fremanezumab-vfrm)	–
Nurtec ODT (rimegepant sulfate)	–
Emgality (galcanezumab-gnlm)	–
Ubrelvy (ubrogepant)	–
Vyepti (eptinezumab-jjmr)	–

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021; Purple Book: Licensed Biological Products 2021*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	**Aimovig** (erenumab−aooe)	**Ajovy** (fremanezumab-vfrm)	**Emgality** (galcanezumab-gnlm)	**Nurtec ODT** (rimegepant)	**Ubrelvy** (ubrogepant)	**Vyepti** (eptinezumab-jjmr)
Acute treatment of migraine with or without aura in adults	-	-	-	✔	✔ *	-
Preventive treatment of migraine in adults	✔	✔	✔	-	-	✔
Preventive treatment of episodic migraine in adults	-	-	-	✔	-	-
Treatment of episodic cluster headache in adults	-	-	✔	-	-	-

* Limitation of use: Not indicated for the preventive treatment of migraine.

(*Prescribing information: Aimovig 2021, Ajovy 2021, Emgality 2019, Nurtec ODT 2021, Ubrelvy 2021, Vyepti 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

Prevention of episodic migraine

Eptinezumab-jjmr

- PROMISE-1 was a double-blind (DB), placebo-controlled (PC), multi-center (MC), Phase 3 trial in which adults with a history of episodic migraine were randomized to receive placebo (n = 222), eptinezumab-jjmr 100 mg (n = 221), or eptinezumab-jjmr 300 mg (n = 222) every 3 months for 12 months. The primary efficacy endpoint was the change in MMD from baseline to week 12. Eptinezumab-jjmr 100 mg and 300 mg significantly reduced MMDs across weeks 1 to 12 compared with placebo (placebo, −3.2; 100 mg, −3.9, p = 0.02; 300 mg, −4.3, p = 0.0001). The odds for a 50% reduction in MMD were approximately 1.7 to 2.2 times higher with eptinezumab-jjmr than placebo. Of note, the endpoints underwent a testing hierarchy and were not significant for 50% migraine responder rates in the 100 mg dose group (*Ashina et al 2020, Vyepti [dossier] 2020).*
  - The reduction in MMD was sustained through 1 year of follow-up for the eptinezumab-jjmr 300 mg group (-5.3 days), which was significant compared to placebo (-4.1 days) at weeks 37 to 48 (difference, -1.2; 95% CI, -1.95 to -0.46). The reduction in the 100 mg group was significantly greater compared to placebo at 25 to 36 weeks (-4.7 vs -4.0, respectively; difference, -0.72; 95% CI, -1.43 to -0.01), but not at 37 to 48 weeks (-4.5 vs -4.1; difference -0.38; 95% CI, -1.13 to 0.37) *(Smith et al 2020)*.

Erenumab-aooe

- The STRIVE trial was a 6-month, DB, PC, MC, Phase 3 trial in which 955 patients with episodic migraine were randomized to placebo (n = 319), erenumab-aooe 70 mg (n = 317), or erenumab-aooe 140 mg (n = 319) once monthly. The primary endpoint was the change in mean MMD from baseline to months 4 to 6, which favored treatment with erenumab−aooe 70 mg (mean change vs placebo, −1.4; 95% confidence interval [CI], −1.9 to −0.9; p < 0.001) and erenumab−aooe 140 mg (mean change vs placebo, −1.9; 95% CI, −2.3 to −1.4; p < 0.001). Erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 70 mg vs placebo, 16.7%; odds ratio [OR], 2.13; difference for 140 mg vs placebo, 23.4%; OR, 2.81). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 70 mg vs placebo, −0.9; difference for 140 mg vs placebo, −1.4) (*Goadsby et al 2017*). Data after 1 year of treatment found sustained efficacy in episodic migraine (*Goadsby et al 2020[a]*).
- The ARISE trial was a 12-week, DB, PC, MC, Phase 3 trial in which 577 patients with episodic migraine were randomized to placebo (n = 291) or erenumab-aooe 70 mg (n = 286) once monthly. The primary endpoint was the change in MMD from baseline to weeks 9 to 12, which favored treatment with erenumab−aooe 70 mg (mean change vs placebo, −1.0; 95% CI, −1.6 to −0.5; p < 0.001). Compared to placebo, erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference, 10.2%; OR, 1.59). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference, −0.6) (*Dodick et al 2018[a]*).
- The LIBERTY trial was a 12-week, DB, PC, MC, Phase 3b trial in which 246 patients with episodic migraine who failed 2 to 4 prior preventive migraine treatments were randomized to placebo (n = 125) or erenumab-aooe 140 mg (n = 121) once monthly. The primary endpoint was the proportion of patients with ≥ 50% reduction in MMD from baseline to the last 4 weeks of DB treatment (weeks 9 to 12), which erenumab−aooe significantly increased over placebo (difference, 16.6%; OR, 2.73; 95% CI, 1.43 to 5.19; p = 0.002). Compared to placebo, 5.9% more patients treated with erenumab−aooe 140 mg reported a 100% reduction in MMD, or migraine cessation. Erenumab-aooe 140 mg/month compared with placebo significantly reduced the MMD (difference, −1.61; 95% CI, −2.70 to −0.52; p = 0.004). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference, −1.73) (*Reuter et al 2018*).

Fremanezumab-vfrm

- The HALO-EM trial was a 12-week, DB, PC, MC, Phase 3 trial in which 875 patients with episodic migraine were randomized to placebo (n = 294), fremanezumab-vfrm 225 mg once monthly (n = 290), or fremanezumab-vfrm 675 mg once quarterly (n = 291). The primary endpoint was the change in mean MMD, which favored treatment with fremanezumab-vfrm 225 mg (mean change vs placebo, −1.5; 95% CI, −2.0 to −0.9; p < 0.001) and fremanezumab-vfrm 675 mg (mean change vs placebo, −1.3; 95% CI, −1.8 to −0.7; p < 0.001). Of note, HALO-EM was powered to detect a 1.6-day difference in the MMD between the fremanezumab-vfrm and placebo groups, but effect sizes resulted in a 1.5-day reduction for the fremanezumab-vfrm monthly dosing group and a 1.3-day reduction for the fremanezumab-vfrm

quarterly dosing group. Although the threshold was not reached, a minimal clinically important difference has not been established for this particular outcome. Compared to placebo, greater MMD reductions were also observed in patients who were prescribed fremanezumab-vfrm 225 mg (mean change vs placebo, −1.3) and 675 mg (mean change vs placebo, −1.1) as monotherapy. Fremanezumab-vfrm significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 225 mg vs placebo, 19.8%; OR, 2.36; difference for 675 mg vs placebo, 16.5%; OR, 2.06). Additionally, fremanezumab-vfrm was associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 225 mg vs placebo, −1.4; difference for 675 mg vs placebo, −1.3) (*Dodick et al 2018[b]*). Data after 1 year of treatment found sustained efficacy in episodic migraine (*Goadsby et al 2020[b]*).

- FOCUS was a DB, PC, Phase 3b trial that evaluated 838 patients with episodic (39%) or chronic migraine (61%) who had previously not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, approximately 40% were classified as having episodic migraines and randomized to fremanezumab-vfrm 225 mg administered monthly with no loading dose (n = 110/283), fremanezumab-vfrm 675 mg administered quarterly (n = 107/276), or placebo (n = 112/279) for 12 weeks. Failure was defined as no clinically meaningful improvement after at least 3 months of therapy at a stable dose, as per the treating physician's judgment, discontinuation because of adverse events that made treatment intolerable, or treatment contraindicated or unsuitable for the preventive treatment of migraine for the patient. At baseline, the MMD was approximately 14.2 days and the MMHD (of at least moderate severity) was 12.6 days. For the overall population, the MMD reduction over 12 weeks was 0.6 (standard error [SE], 0.3) days for placebo, 4.1 (SE, 0.34) days for the monthly fremanezumab-vfrm group (least squares mean difference [LSMD] vs placebo, -3.5; 95% CI, -4.2 to -2.8 days; p < 0.0001), and 3.7 (SE, 0.3) for days for the quarterly fremanezumab-vfrm group (LSMD vs placebo, -3.1; 95% CI, -3.8 to -2.4 days; p < 0.0001). For episodic migraine and compared to placebo, the LSMD in MMD reduction over 12 weeks was 3.1 days for both dose groups (fremanezumab-vfrm monthly: LSMD, -3.1; 95% CI, -4.0 to -2.3 days; fremanezumab-vfrm quarterly: LSMD, -3.1; 95% CI, -3.9 to -2.2 days; p < 0.0001 for both). In the overall population, the proportions of patients with a ≥ 50% response over 12 weeks were 34% in both the quarterly and monthly fremanezumab-vfrm groups vs 9% with placebo (p < 0.0001). Only the monthly fremanezumab-vfrm arm achieved a ≥ 75% sustained responder rate that was statistically different from placebo (OR, 8.6; 95% CI, 2.0 to 37.9; p = 0.0045). Adverse events were similar for placebo and fremanezumab-vfrm. Serious adverse events were reported in 4 (1%) of 277 patients with placebo, 4 (1%) of 285 with monthly fremanezumab-vfrm, and 2 (< 1%) of 276 with quarterly fremanezumab-vfrm (*Ferrari et al 2019*).

Galcanezumab-gnlm

- The EVOLVE-1 and EVOLVE-2 trials were 6-month, DB, PC, MC, Phase 3 trials in 858 and 915 patients with episodic migraine, respectively. Patients were randomized to placebo (EVOLVE-1, n = 433; EVOLVE-2, n = 461), galcanezumab-gnlm 120 mg once monthly (EVOLVE-1, n = 213; EVOLVE-2, n = 231), or galcanezumab-gnlm 240 mg once monthly (EVOLVE-1, n = 212; EVOLVE-2, n = 223). Patients in the galcanezumab-gnlm 120 mg group received a loading dose of 240 mg at the first injection only. The EVOLVE-1 trial included a North American population and the EVOLVE-2 trial included a global population. The primary endpoint was the change in mean monthly migraine headache days (MMHD) (*Stauffer et al 2018, Skljarevski et al 2018*).
  - In EVOLVE-1, the primary endpoint outcome favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −1.9; 95% CI, −2.5 to −1.4; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.8; 95% CI, −2.3 to −1.2; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 23.7%; OR, 2.64; difference for 240 mg vs placebo, 22.3%; OR, 2.50). Compared to placebo, 9.4% more patients treated with galcanezumab-gnlm 120 mg and 9.4% more treated with galcanezumab-gnlm 240 mg reported a 100% reduction in MMHD, or migraine cessation. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −1.8; difference for 240 mg vs placebo, −1.6) (*Stauffer et al 2018*).
  - In EVOLVE-2, the primary endpoint outcome favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −2.0; 95% CI, −2.6 to −1.5; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.9; 95% CI, −2.4 to −1.4; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 23.0%; OR, 2.54; difference for 240 mg vs placebo, 21.0%; OR, 2.34). Compared to placebo, 5.8% more patients treated with galcanezumab-gnlm 120 mg and 8.1% more treated with galcanezumab-gnlm 240 mg reported migraine cessation. Galcanezumab-gnlm was also

associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −1.8; difference for 240 mg vs placebo, −1.7) (*Skljarevski et al 2018*).
  - In an analysis of persistence for patients with episodic migraine, 41.5 and 41.1% of galcanezumab-gnlm-treated patients (120 mg and 240 mg, respectively) had a ≥ 50% response for ≥ 3 months, which was greater than placebo (21.4%; p < 0.001). Approximately 6% of galcanezumab-gnlm-treated patients maintained ≥ 75% response all 6 months vs 2% of placebo-treated patients. Few galcanezumab-gnlm-treated patients maintained 100% response for all 6 months (< 1.5%) (*Förderreuther et al 2018*).
- CONQUER was a DB, PC, Phase 3b trial that evaluated 462 patients with episodic (58%) or chronic migraine (42%) who had previously not responded to 2 to 4 classes of migraine preventive medications for 12 weeks. All galcanezumab-gnlm patients were administered a 240 mg loading dose, then 120 mg per month. Failure was defined as discontinuation owing to no response or inadequate response, or safety or tolerability event. At baseline, the MMHD was approximately 13.2 days with 9.3 in the episodic migraine group and 18.7 in the chronic migraine group. For the overall population, the MMHD reduction over 12 weeks was 1.0 (SE, 0.3) days for placebo, 4.1 (SE, 0.3) days for the monthly galcanezumab-gnlm group (LSMD, -3.1; 95% CI, -3.9 to -2.3 days; p < 0.0001). For episodic migraine and compared to placebo, the LSMD in MMHD reduction over 12 weeks was 2.6 days for the galcanezumab-gnlm monthly group (95% CI, -3.4 to -1.7 days; p < 0.0001). In the overall population, the proportions of patients with a ≥ 50% response over 12 weeks were 41.8% in the monthly galcanezumab-gnlm group vs 17.1% with placebo (p < 0.0001). Compared to placebo, the monthly galcanezumab-gnlm arm achieved a statistically significant improvement of ≥ 75% sustained responder (3.7 vs 18.4%; OR, 5.9; 95% CI, 2.4 to 14.6; p = 0.0001) and 100% sustained responder (0 vs 7.7%; p < 0.0001). Treatment-emergent adverse events were similar for placebo and galcanezumab-gnlm (53 vs 51%). Serious adverse events were reported in 2 patients (1%) of each of the groups (*Mulleners et al 2020*).
  - A post-hoc analysis evaluated the time to treatment onset, which showed a significant reduction in headache days with galcanezumab-gnlm beginning during the first month, which was significant compared to placebo (-4.0 vs -0.7, respectively; p ≤ 0.001). There was also a significantly greater reduction in weekly headache days with galcanezumab-gnlm beginning week 1 compared to placebo (-1.1 vs -0.2; p < 0.01) *(Schwedt et al 2021)*.

Rimegepant

- Rimegepant was studied in a MC, DB, PC, Phase 2/3 trial in adults with migraine for ≥ 1 year and with 4 to 18 moderate-to-severe migraine attacks per month. A total of 747 adults with ≥ 6 migraine days were randomized to rimegepant 75 mg (n = 370) orally every other day vs placebo (n = 371) for 12 weeks. Patients were allowed to continue 1 preventive medication excluding another CGRP inhibitor (ie, topiramate, gabapentin, beta-blockers, and tricyclic antidepressants), and rescue medication (ie, triptans, NSAIDs, paracetamol, aspirin, caffeine, baclofen, antiemetics, and muscle relaxants). At baseline, patients had a mean of 7.8 moderate-to-severe attacks per month, 40% with aura, and 23% had a history of chronic migraine. After 12 weeks of treatment, a reduction from observation period in MMD during weeks 9 to 12 was 4.3 vs 3.5 days for rimegepant vs placebo, respectively (p = 0.0099). A ≥ 50% reduction in moderate-to-severe MMDs during weeks 9 to 12 were observed in 49 vs 41% for rimegepant vs placebo, respectively (p = 0.044). A reduction in mean number of total migraine days per month during weeks 1 to 12 was 3.6 vs 2.7 days, respectively (p = 0.0017). Treatment related adverse events were reported in 11% in the rimegepant arm vs 9% in the placebo arm. All other incidences of adverse events were similar between groups. Most common adverse events included nausea, nasopharyngitis, urinary tract infection, and upper respiratory tract infection (*Croop et al 2021*).

Prevention of chronic migraine

Eptinezumab-jjmr

- The PROMISE-2 trial was a 12-week, DB, PC, MC, Phase 3 trial in which 1121 patients with chronic migraine were randomized to placebo (n = 366), eptinezumab-jjmr 100 mg (n = 356), or eptinezumab-jjmr 300 mg (n = 350) once every 12 weeks (or quarterly). The primary endpoint was the change in mean MMD. Treatment with eptinezumab 100 and 300 mg was associated with significant reductions in MMDs across weeks 1 to 12 compared with placebo (placebo −5.6; 100 mg −7.7, p < 0.0001; 300mg −8.2, p < 0.0001). The odds for a 50% reduction in MMD were approximately 2.1 to 2.4 times higher with eptinezumab-jjmr than placebo (*Lipton et al 2020[a]*). Updated data from PROMISE-2 demonstrated similar responses at 24 weeks as were observed at 12 weeks (*Silberstein et al 2020[a]*).
- The PREVAIL trial was an OL, single-arm, Phase 3 trial evaluating long-term outcomes for eptinezumab-jjmr for 2 years. A total of 128 adults with chronic migraine received eptinezumab-jjmr 300 mg every 12 weeks for up to 8 doses. The percentage of patients with severe disability measured using the Migraine Disability Assessment tool (MIDAS) decreased from 84.4% to 26.8% at 12 weeks and 20.8% at week 104 (*Kudrow et al 2021)*.

Erenumab-aooe

- Erenumab-aooe was studied in a 12−week, DB, PC, MC, Phase 2 trial in which 667 patients with chronic migraine were randomized to placebo (n = 286), erenumab−aooe 70 mg (n = 191), or erenumab−aooe 140 mg (n = 190) once monthly. The primary endpoint was the change in MMD from baseline to weeks 9 to 12, which favored treatment with erenumab−aooe 70 mg and erenumab−aooe 140 mg (mean change for both doses vs placebo, −2.5; 95% CI, −3.5 to −1.4; p < 0.0001). Erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 70 mg vs placebo, 17%; OR, 2.2; difference for 140 mg vs placebo, 18%; OR, 2.3). Both erenumab−aooe 70 mg (difference, −1.9) and erenumab−aooe 140 mg (difference, −2.6) significantly reduced the mean acute migraine−specific medication days; however, the higher 140 mg dose had a greater reduction numerically over placebo and reductions may be dose−dependent (*Tepper et al 2017*).
  - An analysis of patient reported outcomes found patients with chronic migraine had clinically relevant improvements across a range of measures. Improvements were observed at month 3 for all endpoints regardless of erenumab−aooe dose, and minimally important clinical differences were achieved for certain measures with the erenumab−aooe 140 mg dose (*Lipton et al 2019[b]*).

Fremanezumab-vfrm

- Fremanezumab-vfrm was studied in a 12-week, DB, PC, MC, Phase 3 trial, HALO-CM, in which 1130 patients with chronic migraine were randomized to placebo (n = 375), fremanezumab-vfrm 225 mg once monthly (n = 379), or fremanezumab-vfrm 675 mg once quarterly (n = 376). Patients in the fremanezumab-vfrm 225 mg group received a loading dose of 675 mg at the first injection only. The primary endpoint was the change in mean headache days (MHD), which favored treatment with fremanezumab-vfrm 225 mg (mean change vs placebo, −2.1; SE, ± 0.3; p < 0.001) and fremanezumab-vfrm 675 mg (mean change vs placebo, −1.8; SE, ± 0.3; p < 0.001). Fremanezumab-vfrm significantly increased the proportion of patients achieving ≥ 50% reduction in MHD (difference for 225 mg vs placebo, 22.7%; OR, 2.73; difference for 675 mg vs placebo, 19.5%; OR, 3.13). Additionally, fremanezumab-vfrm was associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 225 mg vs placebo, −2.3; difference for 675 mg vs placebo, −1.8) (*Silberstein et al 2017*). Data after 1 year of treatment found sustained efficacy in chronic migraine (*Goadsby et al 2020[b]*).
  - A subgroup analysis evaluated the proportion of patients reverting to episodic migraine, defined as < 15 headache days per month. A total of 44.5% of patients in the placebo group reverted to episodic migraine compared to 50.5% in the quarterly fremanezumab-vfrm group (p = 0.108) and 53.7% in the monthly dosing group (p = 0.012) *(Lipton et al 2020[b])*.
- FOCUS was previously described as including 838 patients overall who had not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, 61% were diagnosed with chronic migraine and were randomized to fremanezumab-vfrm 675 mg administered quarterly (n = 169/276), a fremanezumab-vfrm 675 mg loading dose followed by 225 mg administered monthly (n = 173/283), or placebo (n = 167/279). Among patients classified as having chronic migraine and compared to placebo, the LSMD in MMD reduction over 12 weeks was 3.8 days for the fremanezumab-vfrm monthly group and 3.2 days for the fremanezumab-vfrm quarterly group (fremanezumab-vfrm monthly: LSMD, -3.8; 95% CI, -4.8 to -2.8 days; fremanezumab-vfrm quarterly: LSMD, -3.2; 95% CI, -4.2 to -2.2 days; p < 0.0001 for both) (*Ferrari et al 2019*).

Galcanezumab-gnlm

- Galcanezumab-gnlm was evaluated in a 12-week, DB, PC, MC, Phase 3 trial, REGAIN, in which 1113 patients with chronic migraine were randomized to placebo (n = 558), galcanezumab-gnlm 120 mg once monthly (n = 278), or galcanezumab-gnlm 240 mg once monthly (n = 277). Patients in the galcanezumab-gnlm 120 mg group received a loading dose of 240 mg at the first injection only. The primary endpoint was the change in MMHD, which favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −2.1; 95% CI, −2.9 to −1.3; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.9; 95% CI, −2.7 to −1.1; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 12.2%; OR, 2.10; difference for 240 mg vs placebo, 12.1%; OR, 2.10). Compared to placebo, 0.2% more patients treated with galcanezumab-gnlm 120 mg and 0.8% more treated with galcanezumab-gnlm 240 mg reported migraine cessation; this was not statistically different for either dose group. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −2.5; difference for 240 mg vs placebo, −2.1) (*Detke et al 2018*).
  - In an analysis of persistence for patients with chronic migraine, 29% of galcanezumab-gnlm-treated patients maintained ≥ 30% response all 3 months compared to 16% of placebo-treated patients. A total of 16.8 and 14.6%

of galcanezumab-gnlm-treated patients (120 mg and 240 mg, respectively) had a ≥ 50% response for ≥ 3 months, which was greater than placebo (6.3%; p < 0.001). Few patients maintained ≥ 75% response (< 3%) (*Förderreuther et al 2018*).

- CONQUER was previously described as including 462 patients overall who had not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, 42% were diagnosed with chronic migraine and were randomized to galcanezumab-gnlm 240 mg loading dose followed by 120 mg administered monthly (n = 95/193), or placebo (n = 98/193). Among patients classified as having chronic migraine and compared to placebo, the LSMD in MMHD reduction over 12 weeks was 3.7 days for the galcanezumab-gnlm monthly group (95% CI, -5.2 to -2.2 days; p < 0.0001) (*Mulleners et al 2020*).

Treatment of episodic cluster headache

Galcanezumab-gnlm

- Galcanezumab-gnlm was evaluated in an 8-week, DB trial, in which 106 patients with episodic cluster headache were randomized to placebo (n = 57) or galcanezumab-gnlm 300 mg once monthly (n = 49). A total of 90 (85%) patients completed the DB phase. Patients were allowed to use certain specified acute/abortive cluster headache treatments, including triptans, oxygen, acetaminophen (APAP), and NSAIDs during the study. At baseline, patients had a mean of 17.5 headache attacks/week, maximum of 8 attacks/day, minimum of 1 attack every other day, and at least 4 attacks during the prospective 7-day baseline period. For the primary endpoint, galcanezumab-gnlm significantly decreased the mean change from baseline in weekly cluster headache attack frequency during weeks 1 to 3 vs placebo (-8.7 vs -5.2 attacks; p = 0.036). Galcanezumab-gnlm was also associated with a significantly greater proportion of responders (≥ 50% reduction in weekly cluster headache attack frequency) at week 3 (71.4 vs 52.6%; p = 0.046). Adverse events did not differ between groups, except for a significant increase in the incidence of injection-site pain with galcanezumab-gnlm treated patients (8 vs 0%; p = 0.04) (*Clinicaltrials.gov [NCT02397473] 2021, Emgality prescribing information 2019, Goadsby et al 2019*).

Treatment of acute migraine (with or without aura)

Rimegepant ODT

- Rimegepant ODT was evaluated in a Phase 3, DB, MC, PC, randomized controlled trial (RCT) in 1466 patients (modified intention to treat, n = 1351) with migraine with or without aura. Patients were randomized to placebo (n = 682) or rimegepant ODT 75 mg (n = 669) and were not allowed a second dose of study treatment. Rescue medications allowed 2 hours post-dose included aspirin, ibuprofen, naproxen (or any other type of NSAID), APAP up to 1000 mg/day, antiemetics (eg, metoclopramide or promethazine), or baclofen. Approximately 14% of patients were taking preventive medications for migraine at baseline. The co-primary endpoints were pain freedom and most bothersome symptom (MBS) freedom at 2 hours post-dose. Among patients randomized, 92.2% were included in the efficacy analysis and 93.8% in the safety analysis (*Croop et al 2019, Nurtec ODT [dossier] 2020, Nurtec ODT prescribing information 2020*).
  - The percentage of patients achieving headache pain freedom and MBS freedom 2 hours after a single dose was statistically significantly greater in patients who received rimegepant ODT compared to those who received placebo.
    - *Pain-free at 2 hours*: 21.2% for rimegepant ODT 75 mg vs 10.9% for placebo (p < 0.0001)
    - *MBS-free at 2 hours*: 35.1% for rimegepant ODT 75 mg vs 26.8% for placebo (p = 0.0009)
  - Out of the 21 secondary endpoints tested hierarchically, significant results were achieved for the first 19 endpoints. Those endpoints that were considered not significant included freedom from nausea at 2 hours post-dose, and pain relapse from 2 to 48 hours.
  - The most common adverse events were nausea and urinary tract infection. No serious adverse events were reported.
- Three additional trials evaluating the efficacy and safety of rimegepant 75 mg in an oral tablet (non-ODT) formulation were considered supportive for approval.
  - A MC, DB, dose-ranging trial using an adaptive design was conducted to determine an effective and tolerable dose range of rimegepant for the acute treatment of migraine. A total of 885 adults with migraine with or without aura were randomized to 1 of 6 rimegepant dose groups (10, 25, 75, 150, 300, or 600 mg), sumatriptan 100 mg, or placebo. It was found that the proportion of patients who were pain-free 2 hours after receiving a single dose of rimegepant 75 mg oral tablet was significantly higher compared with placebo (31.4% [n = 27/86] vs 15.3% [n = 31/203]; p = 0.002). The most common adverse events were nausea, vomiting, and dizziness. No treatment-related serious AEs were reported (*Marcus et al 2014*).

- A MC, DB, PC, Phase 3 trial (n = 1072 in efficacy analysis) evaluating rimegepant vs placebo for acute migraine treatment found that the proportion of patients who were pain-free 2 hours after receiving a single dose of rimegepant 75 mg oral tablet was significantly higher compared with placebo (19.6 vs 12.0%; absolute difference, 7.6%; 95% CI, 3.3 to 11.9; p < 0.001). In addition, the proportion of patients who were free from their MBS 2 hours post-dose was significantly higher with rimegepant 75 mg oral tablet compared with placebo (37.6 vs 25.2%; absolute difference, 12.4%; 95% CI, 6.9 to 17.9; p < 0.001). Nausea and urinary tract infection were the only AEs reported in > 1% of the patients in the rimegepant and placebo groups. A serious adverse event associated with rimegepant was back pain (n = 1) (*Lipton et al 2019[c]*, *Nurtec ODT [dossier] 2020*).
- A MC, DB, PC, Phase 3 trial (n = 1084 in efficacy analysis) evaluating rimegepant vs placebo for acute migraine treatment found that the proportion of patients who were pain-free 2 hours after receiving a single dose of rimegepant 75 mg oral tablet was significantly higher compared with placebo (19.2 vs 14.2%; p = 0.03). In addition, the proportion of patients who were free from their MBS 2 hours post-dose was significantly higher with rimegepant 75 mg oral tablet compared with placebo (36.6 vs 27.7%; p = 0.002). Nausea and dizziness were the most common adverse events reported in the rimegepant and placebo treatment groups, respectively. Serious adverse events were reported in 2 patients treated with rimegepant and 1 patient treated with placebo (*Lipton et al 2018 [poster], Nurtec ODT [dossier] 2020*).

- Data is emerging on the combination use of rimegepant with CGRP monoclonal antibodies. A sub-study nested within a MC, OL, long-term safety study evaluated outcomes of 13 patients on CGRP monoclonal antibodies (erenumab, n = 7; fremanezumab, n = 4; and galcanezumab, n = 2) who received rimegepant 75 mg as needed *(Berman et al 2020)*. An average of 7.8 rimegepant doses were administered over a 4-week period, and 5 patients experienced mild or moderate AEs and no patients experienced severe AEs *(Berman et al 2020; Mullin et al 2020)*. Of note, this data is only available in a very small number of patients.

Ubrogepant

- Ubrogepant was evaluated in 2 Phase 3, PC, DB trials (ACHIEVE I and II), in which 3358 patients (ACHIEVE I, n = 1672; ACHIEVE II, n =1686) were randomized to take 1 dose of placebo (n = 1122), ubrogepant 50 mg (n = 1118), or ubrogepant 100 mg (n = 557) (100 mg was evaluated in the ACHIEVE I trial only, and a 25 mg group was included in the ACHIEVE II trial only [n = 561]). Patients had 2 to 8 migraines/month with moderate to severe pain intensity in the past 3 months either with or without aura and had a history of migraine for ≥ 1 year. A second dose of study treatment (placebo or ubrogepant), or the patient's usual acute treatment for migraine, was allowed between 2 to 48 hours after the initial treatment for a non-responding or recurrent migraine headache. At baseline, 23% of patients were taking preventive medications for migraine, and approximately 23 to 27% were insufficient triptan responders. In ACHIEVE I, 79% were included in the efficacy analysis and 86% in the safety analysis, and in ACHIEVE II, 91.7% had a qualifying migraine event and 88% were included in the analysis (*Dodick et al 2019, Lipton et al 2019[a], Ubrelvy prescribing information 2021*).
  - Compared to placebo, significant improvements were demonstrated for the co-primary endpoints of pain freedom and the MBS freedom at 2 hours post-dose in the ubrogepant arms. MBS was a collection of selective, self-identified symptoms (ie, photophobia, phonophobia, or nausea). The following differences from placebo were demonstrated:
    - *Pain-free at 2 hours*: 7.4% (p = 0.002) and 7.5% (p = 0.007) for the ubrogepant 50 mg dose in ACHIEVE I and II trials, respectively, and 9.4% (p < 0.001) for ubrogepant 100 mg dose in ACHIEVE I trial.
    - *MBS-free at 2 hours*: 10.8% and 11.5% (p < 0.001 for both) for the ubrogepant 50 mg dose in ACHIEVE I and II trials, respectively, and 9.9% (p < 0.001) for ubrogepant 100 mg dose in ACHIEVE I trial.
  - The incidence of photo- and phonophobia was reduced following administration. Significantly more patients maintained pain freedom for 2 to 24 hours post-dose in the ubrogepant 100 mg arm (difference from placebo, 6.8%; p = 0.002) and the 50 mg arm for ACHIEVE II only (6.2%; p = 0.005).
  - In ACHIEVE I, the most common adverse events included nausea (1.5 to 4.7%), somnolence (0.6 to 2.5%), and dry mouth (0.6 to 2.1%). In ACHIEVE II, the most common adverse events within 48 hours were nausea (≤ 2.5% for all arms) and dizziness (≤ 2.1% for all arms). No serious adverse events or adverse events leading to discontinuation were reported 48 hours after the initial dose. In ACHIEVE II, the serious adverse events at 30 days included appendicitis, spontaneous abortion, pericardial effusion, and seizure.

Treatment of medication overuse headache

Eptinezumab-jjmr

- A subgroup, exploratory analysis of the PROMISE-2 trial, which was previously described, evaluated eptinezumab-jjmr 100 mg (n = 139), 300 mg (n = 147), or placebo (n = 145) in patients with chronic migraine and medication overuse headache at baseline screening. Patients receiving eptinezumab-jjmr had a significantly greater reduction in MMDs compared to placebo over weeks 1 to 12 (placebo: change from baseline, -5.4; 100 mg: change from baseline, -8.4, difference from placebo, -3.0, 95% CI, -4.56 to -1.52, p < 0.0001 vs placebo; 300 mg: change from baseline, -8.6, difference from placebo, -3.2, 95% CI, -4.66 to -1.78, p < 0.0001) *(Diener et al 2021)*.

Erenumab-aooe

- A subgroup analysis was performed to evaluate patients with chronic migraine and medication overuse included in a double-blind, placebo-controlled study of 667 patients, previously described by *Tepper et al*. A total of 274 patients had medication overuse at baseline screening and were randomized to erenumab-aooe 70 mg (n=79) or 140 mg (n = 78) or placebo (n = 117). At month 3, there was a significant reduction in MMD in both erenumab-aooe dosing groups (-6.6) compared to placebo (-3.5; difference, -3.1; 95% CI, -4.8 to -1.4; p < 0.001). The percentage of patients with ≥ 50% response rate was significantly higher in the 70 mg group (36%; OR, 2.67; 95% CI, 1.36 to 5.22) and the 140 mg group (35%; OR, 2.51; 95% CI, 1.28 to 4.94) compared to placebo (18%) *(Tepper et al 2019)*.

Fremanezumab-vfrm

- The impact of fremanezumab-vfrm on medication overuse headaches in patients with chronic migraine was evaluated through a subgroup analysis of the HALO CM study, which was previously described. Of the 1130 patients enrolled in HALO CM, 587 had medication overuse at baseline and were randomized to fremanezumab-vfrm quarterly (n = 201), monthly (n = 198), or placebo (n = 188). Compared with placebo, the reduction in MMD was greater for patients receiving fremanezumab-vfrm quarterly (-2.5 vs -4.7; difference, -2.2; 95% CI, -3.1 to -1.2; p < 0.0001) and monthly (-2.5 vs -5.2; difference, -2.7; 95% CI, -3.7 to -1.8; p < 0.0001) *(Silberstein et al 2020[b])*.

Galcanezumab-gnlm

- A post-hoc analysis of 3 previously described Phase 3 studies in patients with episodic migraine (EVOLVE-1 and EVOLVE-2) or chronic migraine (REGAIN) evaluated the efficacy of galcanezumab-gnlm in the prevention of migraine in patients with and without medication overuse *(Dodick et al 2021)*.
  - In the subgroup analysis of patients with medication overuse headaches and episodic migraine, there was a significantly greater reduction in MMD with both galcanezumab-gnlm 120 mg (-6.3; difference from placebo, -3.6; 95% CI, -4.7 to -2.4; p < 0.001) and 240 mg (-5.8; difference from placebo, -3.1; 95% CI, -4.2 to -2.0; p < 0.001) compared to placebo (-2.7).
  - In the subgroup analysis of patients with medication overuse headaches and chronic migraine, there was a significantly greater reduction in MMD with both galcanezumab-gnlm 120 mg (-4.8; difference from placebo, -2.5; 95% CI, -3.6 to -1.5; p < 0.001) and 240 mg (-5.6; difference from placebo, -2.3; 95% CI, -3.3 to -1.2; p < 0.001) compared to placebo (-2.5).

CLINICAL GUIDELINES

Acute treatment of migraine

- The American Headache Society (AHS) published updated consensus statement guidelines for migraine in 2018. The AHS recommends the use of APAP, NSAIDs, non-opioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans or dihydroergotamine (DHE) are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics. These guidelines do not differentiate the triptans, but recommend that non-oral routes be used when severe nausea or vomiting is present. Overall, the AHS designated the following drugs as having efficacy (*AHS 2019*):
  - Established efficacy:
    - Triptans
    - Ergotamine derivatives
    - NSAIDs (aspirin, diclofenac, ibuprofen, naproxen)
    - Opioids (butorphanol, although use is not recommended)
    - Combination medications
  - Probably effective
    - Ergotamine or other forms of DHE
    - NSAIDs (ketoprofen, ketorolac intramuscular or IV, flurbiprofen)
    - Magnesium IV

    - Isometheptene compounds
    - Combination medications (codeine/APAP, tramadol/APAP)
    - Antiemetics (prochlorperazine, promethazine, droperidol, chlorpromazine, metoclopramide)
  - The AHS recommends that rimegepant and ubrogepant may have a role in patients who have contraindications to the use of triptans or who have failed to respond to or tolerate ≥ 2 oral triptans, as determined by either a validated acute treatment patient reported outcome questionnaire or healthcare provider attestation. Coverage should be provided until ≥ 2 attacks are treated to determine efficacy and tolerability.
    - Other agents have had more established efficacy and safety relative to the newly FDA-approved migraine agents.
- There are a number of older guidelines/treatment recommendations for the treatment of migraine but, similar to the 2018 guidelines, they do not state a preference for a particular triptan or therapy (*Evers et al 2009, Francis et al 2010, Marmura et al 2015, Silberstein 2000, Silberstein et al 2012 [guideline reaffirmed in 2015]*).
- In 2019, the American Academy of Neurology (AAN) and the AHS published a guideline on the acute treatment of migraine in children and adolescents. The guideline states that there is evidence to support the efficacy of ibuprofen, APAP (in children and adolescents), and triptans (mainly in adolescents) for migraine relief, although confidence in the evidence varies between agents (*Oskoui et al 2019[a]*).
  - Of note, the CGRP inhibitors have not been adequately studied in children or adolescents and are not currently FDA-approved for use in these populations.

Prevention of migraine

- According to the AAN/AHS evidence−based guideline update on the pharmacologic treatment for episodic migraine prevention in adults, the following medications are effective preventive treatment options (see Appendix A for a definition of classifications) (*Silberstein et al 2012*):
  - Level A (established efficacy and > 2 Class I trials):
    - Antiepileptic drugs: divalproex sodium, sodium valproate, and topiramate
    - Beta blockers: metoprolol, propranolol, and timolol
    - Triptans (for menstrual related migraine [MRM]): for short−term prophylaxis, frovatriptan
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Antidepressants: amitriptyline and venlafaxine
    - Beta blockers: atenolol and nadolol
    - Triptans (for MRM): for short−term prophylaxis, naratriptan and zolmitriptan
  - Level C (possibly effective and 1 Class II trial):
    - Angiotensin−converting enzyme (ACE) inhibitors: lisinopril
    - Angiotensin II receptor blockers (ARBs): candesartan
    - Alpha agonists: clonidine and guanfacine
    - Antiepileptic drugs: carbamazepine
    - Beta blockers: nebivolol and pindolol
    - Antihistamines: cyproheptadine
- The AAN recommends onabotulinumtoxin A as an effective treatment option that should be offered for chronic migraine. However, onabotulinumtoxin A is considered ineffective for the treatment of episodic migraines and should not be offered. There is insufficient evidence to compare the effectiveness of botulinum neurotoxin A with that of oral prophylactic topiramate (*Simpson et al 2016 [guideline reaffirmed in 2019]*).
- In 2019, the AAN/AHS published a guideline on the preventive treatment of migraine in pediatric patients. The guideline states that the majority of preventive medications for pediatric migraine fail to demonstrate superiority to placebo. The guidelines make the following statements and recommendations for initial therapy (see Appendix B for a definition of classifications) (*Oskoui et al 2019[b]*):
  - It is possible that cognitive behavioral therapy (CBT) alone is effective in migraine prevention.
  - There is insufficient evidence to evaluate the effects of flunarizine, nimodipine, valproate, and onabotulinumtoxinA for use in migraine prevention in children and adolescents.
  - Acknowledging the limitations of currently available evidence, use of short-term treatment trials (a minimum of 2 months) may be warranted in those who could benefit from preventive treatment (Level B).
  - Consider amitriptyline combined with cognitive behavioral therapy (CBT) (inform of the potential adverse events, including risk of suicide) (Level B).

- Consider topiramate (Level B). Inform of side effects including decreased efficacy when combined with oral contraceptives and the teratogenic effect in patients of childbearing potential (Level A). In patients of childbearing potential, daily folic acid is recommended (Level A).
- Consider propranolol (Level B).
  - Of note, the CGRP inhibitors have not been adequately studied in children or adolescents and are not currently FDA-approved for use in these populations.

Cluster headache

- According to the AHS evidence-based guidelines for the treatment of cluster headache, there are a number of effective treatment options (AAN classifications were used for grading; see Appendix A for definitions) (*Robbins et al 2016*).
- For acute therapy of cluster headache, the following therapy options have positive evidence:
  - Level A (established efficacy and ≥ 2 Class I trials):
    - Certain triptans: sumatriptan subcutaneous and zolmitriptan nasal spray
    - Oxygen
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Certain triptans: sumatriptan nasal spray and zolmitriptan oral
    - Sphenopalatine ganglion stimulation
  - Level C (possibly effective and 1 Class II trial):
    - Cocaine/lidocaine nasal spray
    - Octreotide subcutaneous
- For preventive therapy of cluster headache, the following therapy options have positive evidence:
  - Level A (established efficacy and ≥ 2 Class I trials):
    - Suboccipital steroid injection
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Civamide nasal spray (not marketed in the US)
  - Level C (possibly effective and 1 Class II trial):
    - Lithium
    - Verapamil
    - Warfarin
    - Melatonin

SAFETY SUMMARY

- Ubrogepant is contraindicated with concomitant use of strong CYP3A4 inhibitors.
- Eptinezumab-jjmr, erenumab-aooe, fremanezumab-vfrm, galcanezumab-gnlm, and rimegepant are contraindicated in patients with serious hypersensitivity to the active ingredient or any of the excipients. Mild to moderate hypersensitivity reactions (eg, rash, dyspnea, pruritus, urticaria) were reported in trials. Cases of anaphylaxis and angioedema have been reported post-marketing. Delayed serious hypersensitivity has occurred with rimegepant. In cases of serious or severe reactions, treatment should be discontinued.
- Warnings and precautions associated with the CGRP inhibitors include hypersensitivity reactions, in some cases reactions were reported within hours to 1 month after administration. Erenumab-aooe has additional warnings and precautions associated with the following:
  - Constipation with serious complications: Constipation with serious complications has been reported post-marketing. Some cases have required hospitalization, including surgery. Constipation was a common adverse event reported in up to 3% of patients. Concurrent use of medication associated with decreased gastrointestinal motility may increase the risk for severe constipation.
  - Hypertension: Post-marketing reports of the development or worsening of hypertension have emerged. Some cases required pharmacological treatment to manage or, in other cases, hospitalization. Incidences of hypertension were most frequently reported within 7 days of treatment, and most cases were reported after the first dose.
- The CGRP inhibitors generally have a similar incidence of adverse events as placebo. Very few severe adverse events and treatment discontinuations due to adverse events were reported. Across studies, adverse events were generally mild and/or similar to placebo. The most common adverse events observed in studies of injectable CGRP inhibitors included injection site reactions (subcutaneous CGRP inhibitors), constipation (erenumab-aooe only), and

nasopharyngitis and hypersensitivity (eptinezumab-jjmr only). For the oral CGRP inhibitors, ubrogepant was associated with somnolence, and both ubrogepant and rimegepant were associated with nausea.

- There are no adequate data on the risks associated in patients who are pregnant or nursing, or in adolescent or pediatric populations.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Aimovig (erenumab−aooe)	Auto-injector (70 mg/mL or 140 mg/mL)	SC	*Prevention of migraine*: Once monthly (70 or 140 mg)	May be self−administered by patients in the abdomen, thigh, or back of upper arm. Latex−sensitive patients may have an allergic reaction to the needle shield within the white cap and the gray needle cap of the syringe. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, erenumab-aooe has a limited stability of 7 days.
Ajovy (fremanezumab−vfrm)	Auto-injector or prefilled syringe (225 mg/1.5 mL)	SC	*Prevention of migraine*: Once monthly (225 mg) or once every 3 months (675 mg)	May be self−administered by patients in the abdomen, thigh, or back of upper arm. The prefilled syringe cap is not made with natural rubber latex. Must be refrigerated and protected from light until time of use. If necessary, fremanezumab-vfrm may be stored at room temperature for a maximum of 7 days. After removal from the refrigerator, fremanezumab-vfrm must be used within 7 days or discarded.
Emgality (galcanezumab−gnlm)	Auto-injector (120 mg/mL) Prefilled syringe (100 mg/mL or 120 mg/mL)	SC	*Prevention of migraine*: 2 consecutive injections (120 mg each) as a loading dose, then once monthly (120 mg) *Episodic cluster headache*: 3 consecutive injections (100 mg each) at onset, and then once monthly until the end of the cluster period	May be self−administered by patients in the abdomen, thigh, back of upper arm or buttocks. The cap is not made with natural rubber latex. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, galcanezumab-gnlm has a limited stability of 7 days.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Nurtec ODT (rimegepant sulfate)	ODT (75 mg)	PO	*Acute migraine treatment:* As needed. Maximum dose: 75 mg in 24 hours. *Prevention of episodic migraine*: Every other day. Maximum dose: 75 mg in 24 hours.	The safety of using > 18 doses in a 30-day period has not been established. Avoid concomitant administration with strong or moderate inhibitors of CYP3A4 within 48 hours, moderate or strong inducers of CYP3A, or P-gp or BCRP inhibitors.
Ubrelvy (ubrogepant)	Oral tablets (50 and 100 mg)	PO	*Acute migraine treatment:* As needed. A second dose may be taken at least 2 hours after the initial dose. Maximum dose: 200 mg in 24 hours.	The safety of treating > 8 migraines in a 30 day period has not been established. Dose adjustments are warranted with certain concomitant drugs or in cases of metabolic impairment. Avoid use in patients with end stage renal disease (CrCL < 15 mL/min). Take with or without food
Vyepti (eptinezumab-jjmr)	Single-dose vial (100 mg/mL)	IV	*Prevention of migraine*: Once every 3 months (100 or 300 mg) The recommended dosage is 100 mg every 3 months; some patients may benefit from a dosage of 300 mg every 3 months.	Dilute with 0.9% sodium chloride injection. Following dilution, eptinezumab-jjmr must be infused within 8 hours. Infuse over approximately 30 minutes. Administered by a healthcare provider in a healthcare setting. Must be refrigerated and protected from light until time of use.

See the current prescribing information for full details.
Abbreviations: CrCL = creatinine clearance; CYP = cytochrome P450; BCRP = breast cancer resistance protein; IV = intravenous; ODT = orally disintegrating tablet; P-gp = P-glycoprotein; PO = oral; SC = subcutaneous
Note: With all of the CGRP inhibitors, there are no data in pregnant women or breastfed infants. A benefit/risk assessment should be taken into consideration prior to administering.

CONCLUSION

- Migraine is a common, recurrent, incapacitating disorder characterized by moderate to severe headaches and disabling features, including nausea, vomiting, neurologic symptoms, photophobia, and phonophobia. Migraines have a spectrum of frequency and severity that can significantly affect the quality of life of patients. Cluster headache is less prevalent than migraine and characterized by attacks of severe, unilateral pain with ipsilateral autonomic symptoms, which occur every other day to multiple times daily during a cluster period. Cluster headache is more likely to occur in men, whereas migraines are more likely to occur in women.
- Rimegepant and ubrogepant are oral CGRP inhibitors indicated for acute treatment of migraine with or without aura. Rimegepant is also indicated for the prevention of episodic migraine. The injectable CGRP inhibitors eptinezumab-jjmr, erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm are indicated for the prevention of migraine. Galcanezumab-gnlm has an additional indication for the treatment of episodic cluster headache. No CGRP inhibitor is

FDA-approved for use in patients aged < 18 years. Eptinezumab-jjmr is the only IV formulation and requires administration in a healthcare setting.

- Guidelines divide treatment recommendations according to age, prevention or treatment, and migraine type:
  - Current evidence−based prophylactic migraine treatment options and guidance are limited for chronic migraine, and oral prophylactic medications prescribed for episodic migraine are often used for the preventive treatment of chronic migraine. Prophylactic migraine treatment options include oral agents (mainly anti−seizure agents, antidepressants, and beta blockers), injectable agents (onabotulinumtoxin A for chronic subtypes only), or neuromodulation devices for migraine or headache attacks. Certain oral therapies may not be appropriate for individual patients due to intolerability or eventual lack of efficacy. There is no optimal prophylactic migraine therapy and head-to-head trials are lacking.
  - For the treatment of cluster headache, subcutaneous sumatriptan, zolmitriptan nasal spray, and oxygen have the most positive evidence for acute therapy according to the AHS guidelines. To date, only subcutaneous sumatriptan is FDA-approved for the acute treatment of cluster headache. Additionally, sumatriptan nasal spray, zolmitriptan oral formulations, and sphenopalatine ganglion stimulation are probably effective for acute treatment per guidelines. For prevention of cluster headaches, suboccipital steroid injections are most effective according to the guidelines; however, there is no preventive medication currently FDA-approved for cluster headache.
  - For acute treatment of migraine in adults, guidelines generally recommend the use of APAP, NSAIDs, non-opioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans or DHE are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics. Recent AHS guidelines state that rimegepant and ubrogepant may have a role in patients who have contraindications to the use of triptans or who have failed to respond to or tolerate ≥ 2 oral triptans.
- There are no head-to-head studies with the CGRP inhibitors, and no agent is clearly superior to others. Evidence for the CGRP inhibitors have demonstrated efficacy for the respective indications:
  - Like other preventive medications for migraine, the CGRP inhibitors are not likely to render patients migraine-free. Based on 3 to 6 month data, primary endpoint reductions are similar to many oral prophylactic therapies; however, comparisons are limited as endpoints have been inconsistently defined. There are limited analyses and trials examining efficacy in patients who failed ≥ 2 prior preventive therapies; however, available data suggest that these patients may achieve greater reductions in migraine/headache frequency. Further research is warranted.
    - Compared to placebo, the injectable CGRP inhibitors when prescribed for prophylactic migraine therapy consistently demonstrated modest but statistically significant reductions in primary endpoint measures (eg, MMD, MMH, or MMHD) ranged from 0.7 to 3.5 days after 3 to 6 months of treatment. The numbers needed to treat (NNTs) ranged from 3 to 10 in order to achieve a ≥ 50% reduction in MM(H)D. Subgroup analyses from Phase 3 CGRP inhibitor trials showed consistent benefit for prevention of migraine in patients with medication overuse headaches.
    - The only oral CGRP inhibitor indicated for prevention, although for only episodic migraine, had a significant reduction of 0.8 MMD after 3 months of treatment. The NNT was 13 in order to achieve a ≥ 50% reduction in moderate-to-severe MMDs.
  - For the treatment of cluster headaches, galcanezumab-gnlm demonstrated efficacy compared to placebo in an 8-week trial, which allowed for acute/abortive treatments during therapy. Galcanezumab-gnlm significantly decreased the mean change from baseline in weekly cluster headache attack frequency by 3.5 during weeks 1 to 3 vs placebo. Additionally, 18.8% more patients were classified as responders (≥ 50% reduction in weekly cluster headache attack frequency) with galcanezumab-gnlm at week 3 vs placebo (p = 0.046).
  - Ubrogepant and rimegepant are oral CGRP inhibitors FDA-approved for acute treatment of migraine with or without aura in adults. One differing characteristic is that ubrogepant allows for a second dose within 24 hours whereas rimegepant does not. Additionally, ubrogepant allows for 2 dosing options (50 or 100 mg), and rimegepant allows for one (75 mg).
    - Rimegepant ODT demonstrated efficacy compared to placebo for acute use. Patients were not allowed a second dose of study treatment (placebo or rimegepant). Rescue medications allowed 2 hours post-dose included aspirin, ibuprofen, naproxen (or any other type of NSAID), APAP up to 1000 mg/day, antiemetics (eg, metoclopramide or promethazine), or baclofen. Compared to placebo, significantly more patients treated with rimegepant were pain-free at 2 hours (difference vs placebo, 10.3%). For the co-primary endpoint of MBS, significantly more rimegepant-treated patients reported being MBS-free at 2 hours post-dose (difference vs placebo, 8.3%). Additional trials evaluating the efficacy and safety of rimegepant were considered supportive for approval.
    - Ubrogepant demonstrated efficacy compared to placebo for acute response to migraine treatment after 2 hours. A second dose of study treatment (placebo or ubrogepant), or the patient's usual acute treatment for migraine, was

allowed between 2 to 48 hours after the initial treatment for a non-responding or recurrent migraine headache. Compared to placebo, significantly more patients treated with ubrogepant were pain-free at 2 hours when administered the 50 mg (difference vs placebo, 7.4 to 7.5%) or 100 mg (difference vs placebo, 9.4%) dose. For the co-primary endpoint of MBS, significantly more ubrogepant-treated patients reported being MBS-free at 2 hours post dose for the 50 mg (difference vs placebo, 10.8 to 11.5%) and 100 mg (difference vs placebo, 9.9%) dose.

- Lack of information during pregnancy and breastfeeding is a consideration as many migraine patients are women of childbearing potential. The unknown risks of monoclonal antibodies and the effects on certain conditions are not fully characterized. Furthermore, rimegepant and ubrogepant have a number of drug interactions, and may not be appropriate with other medications. Important co-morbid populations were excluded from trials (eg, anxiety, depression, hypertension, and fibromyalgia), which also limits the generalizability to broader groups. There are no data in adolescents and children.
- The safety profiles of the subcutaneous CGRP inhibitors are generally mild with the most common adverse events observed being injection site reactions. Hypersensitivity and nasopharyngitis were the most commonly reported adverse events for the IV-administered agent, eptinezumab-jjmr. Mild to moderate hypersensitivity reactions, including rash, pruritus, drug hypersensitivity, and urticaria, were reported with all CGRP inhibitors. Post-marketing reports with erenumab-aooe have included hypertension and constipation with serious complications; some cases of constipation have required hospitalization and surgery. The oral CGRP inhibitors, ubrogepant and rimegepant, were associated with nausea; ubrogepant was additionally associated with somnolence.
- Overall for acute treatment, ubrogepant and rimegepant are alternatives to triptans and/or DHE in patients who are unable to tolerate or have an inadequate response or contraindication to established pharmacologic abortive migraine treatments. The injectable CGRP inhibitors represent another therapy option in the prevention of episodic or chronic migraine. Rimegepant is the only oral CGRP inhibitor that may be prescribed for the prevention of episodic migraines. Eptinezumab-jjmr and fremanezumab-vfrm are the only agents in the class that may be administered quarterly. Galcanezumab-gnlm is the only CGRP inhibitor indicated for the treatment of episodic cluster headaches. Dosage and administration vary by product and indication. Further long-term study is warranted.

APPENDICES

Appendix A. AAN levels of evidence classification *(AAN 2017, Gronseth et al 2011)*

Rating of recommendation	
A	Established as effective, ineffective, or harmful for the given condition in the specified population
B	Probably effective, ineffective, or harmful for the given condition in the specified population
C	Possibly effective, ineffective, or harmful for the given condition in the specified population
U	Data inadequate or conflicting; given current knowledge, treatment is unproven.
Rating of therapeutic article	
Class I	RCT in representative population with masked outcome assessment. The following are required: a) concealed allocation; b) primary outcome(s) is/are clearly defined; c) exclusion/inclusion criteria are clearly defined; d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias; e) certain requirements are needed for noninferiority or equivalence trials claiming to prove efficacy for 1 or both drugs.
Class II	Cohort study that meets a–e (Class I) or RCT that lacks 1 criterion from above (b−e).
Class III	Controlled trials (including well−defined natural history controls or patients serving as own controls), a description of major confounding differences between groups, and where outcome assessment is independent of patient treatment.
Class IV	Does not include patients with the disease, different interventions, undefined/unaccepted interventions or outcomes measures, and/or no measures of effectiveness or statistical precision presented or calculable.

Appendix B. AAN/AHS levels of evidence classification *(Oskoui et al 2019[b])*

Level of obligation; magnitude of benefit	
A	Must; large benefit relative to harm
B	Should; moderate benefit relative to harm
C	May; small benefit relative to harm
U	No recommendation supported; too close to call

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Publication Date: June 30, 2021

Therapeutic Class Overview
Triptans

INTRODUCTION

- Migraine is a common disabling primary headache disorder that can be divided into 2 major subtypes: without aura (the most common subtype associated with a higher average attack frequency) and with aura. According to the International Classification of Headache Disorder (IHS), migraine is a common primary headache disorder manifesting in attacks lasting 4 to 72 hours in adults and 1 to 72 hours in children. Migraines range from moderate to very severe and are sometimes debilitating. Typical characteristics of migraine include a unilateral location, pulsating quality, moderate or severe pain intensity, and aggravation by routine physical activity. Migraine without aura is also associated with at least 1 of the following: nausea, vomiting, or both and photophobia/phonophobia. Migraine with aura includes 1 or more of the following reversible aura symptoms: visual, sensory, speech and/or language, motor, brainstem, or retinal. When attacks occur ≥15 days/month for >3 months, patients are considered to have chronic migraines (*Cutrer et al 2020, Snow et al 2002, IHS 2018[a], IHS, 2018[b]*).
- Migraine affects approximately 12% of the US general population and occurs more frequently in women than men (17% of women and 6% of men each year) (*Cutrer et al 2020, Lipton et al 2001*).
- The Food and Drug Administration (FDA) Industry Guidance recommendations and the IHS recommend 2 co-primary endpoints for trials measuring efficacy of acute treatment of migraines. One is the proportion of patients who are pain-free at 2 hours and the other is the reduction of the most bothersome migraine-associated symptom at 2 hours (*FDA Industry Guidance [migraine] 2018, Tfelt-Hansen et al 2012*).
- The serotonin (5-HT1) receptor agonists, also referred to as triptans, work in the management of migraine via the promotion of vasoconstriction, inhibition of dural vasodilation and inflammation, and blockade of pain pathways in the brainstem (*Clinical Pharmacology 2021*). In contrast to analgesics, the triptans are considered to be "specific" migraine therapies because they act at the pathophysiologic mechanisms of headaches (*Smith 2021*).
- There is well-established evidence demonstrating the triptans to be an effective option for acute treatment of migraine; however, there is inconsistent head-to-head data demonstrating the superiority of any triptan, making it difficult to recommend the use of 1 over another (*Smith 2021*).
- In adults, all triptans are FDA-approved for the acute treatment of migraines with or without aura. In addition to the acute treatment of migraines, subcutaneous sumatriptan (with the exception of Zembrace SymTouch) is also approved for cluster headaches. The agents FDA-approved in pediatric patients include almotriptan, sumatriptan/naproxen, zolmitriptan nasal spray (for ≥12 years of age), and rizatriptan (for ≥6 years of age).
- FDA-approved triptans are available as an oral tablet (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, sumatriptan/naproxen combination, zolmitriptan), orally disintegrating tablet (ODT) (rizatriptan, zolmitriptan), nasal spray (sumatriptan, zolmitriptan), nasal powder (sumatriptan), and subcutaneous injection (sumatriptan) (*Drugs@FDA 2021*).
- According to Drugs@FDA, the marketing status of Alsuma and Sumavel DosePro is discontinued; therefore, these products have been removed from the therapeutic class overview (*Drugs@FDA 2021*).
- In October 2017, the FDA announced Teva's voluntary discontinuation of Zecuity (sumatriptan iontophoretic transdermal system) due to post-marketing reports of application site reactions, including severe redness, cracked skin, blistering/welts, and burns/scars associated with the product (*FDA Drug Shortages and Discontinuations 2017*). Therefore, this product has also been removed from the therapeutic class overview.
- Medispan class: Migraine Products – Selective Serotonin Agonists 5-HT(1); Selective Serotonin Agonist-NSAID Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Amerge (naratriptan hydrochloride tablet)	✔
Axert (almotriptan malate tablet)†	✔
Frova (frovatriptan succinate tablet)	✔
Imitrex (sumatriptan tablet, nasal spray, injection)	✔

Drug	Generic Availability
Imitrex Statdose (sumatriptan cartridges for injection)	✔
Maxalt (rizatriptan benzoate tablet)	✔
Maxalt MLT (rizatriptan benzoate ODT)	✔
Migranow* (sumatriptan tablet + camphor/menthol gel)	-
Onzetra Xsail (sumatriptan nasal powder)	-
Relpax (eletriptan hydrobromide tablet)	✔
Tosymra (sumatriptan nasal spray)	-
Treximet (sumatriptan/naproxen sodium tablet)	✔
Zembrace SymTouch (sumatriptan injection)	-
Zomig (zolmitriptan nasal spray, tablet)	✔ ‡
Zomig-ZMT (zolmitriptan ODT)	✔

*This product is not approved by the FDA.
†The brand name product has been discontinued; only generic availability.
‡ Generic zolmitriptan tablets are available. Zolmitriptan nasal spray is available as an authorized generic.

(Drugs@FDA 2021; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Amerge (naratriptan) tablet	Axert (almotriptan) tablet	Frova (frovatriptan) tablet	Imitrex (sumatriptan) tablets, nasal spray, injection	Imitrex Statdose (sumatriptan) cartridges (injection)	Maxalt (rizatriptan) tablet	Maxalt MLT (rizatriptan) ODT	Migranow (sumatriptan) tablet and (camphor/menthol) gel	Onzetra Xsail (sumatriptan) nasal powder	Relpax (eletriptan) tablet	Tosymra (sumatriptan) nasal spray	Treximet (sumatriptan/naproxen) tablet	Zembrace SymTouch (sumatriptan) injection	Zomig (zolmitriptan) tablet; nasal spray	Zomig ZMT (zolmitriptan) ODT
Acute treatment of migraine with or without aura in adults	✔	✔	✔	✔	✔	✔	✔	✔ ‖	✔	✔	✔	✔	✔	✔ ‡	✔
Acute treatment of cluster headache in adults				✔ *	✔										
Acute treatment of migraine with or without aura (aged ≥ 6 years)						✔	✔								
Acute treatment of migraine headache pain in adolescents with a history of migraine with or without aura, and who have migraine attacks usually lasting ≥ 4 hours when untreated (aged ≥ 12 years)		✔ §													
Acute treatment of migraine with or without aura (aged ≥ 12 years)												✔		✔ †‡	

Abbreviation: ODT = orally disintegrating tablet

Class Limitations of Use: No agents in this class are intended to be used as prophylactic migraine therapy. Use is recommended only after a clear diagnosis of migraine (or cluster headache, if FDA-approved for use) has been established. Agents are not indicated for the treatment of cluster headache unless FDA-approved.
Additional Limitations of Use:
*Indication applies only to the injection formulation
†Indication applies only to the nasal spray formulation
‡Nasal spray is not recommended in patients with moderate to severe hepatic impairment
§For adolescents aged 12 to 17 years, efficacy on migraine-associated symptoms was not established
‖ Indication applies only to the sumatriptan component

(*Prescribing information: Amerge 2020; Axert 2017; Frova 2018; Imitrex injection 2020; Imitrex nasal spray 2017; Imitrex tablets 2020; Maxalt 2020; Maxalt MLT 2020; Migranow 2021; Onzetra Xsail 2019; Relpax 2020; Tosymra 2019; Treximet 2021; Zembrace SymTouch 2021; Zomig nasal spray 2019; Zomig tablets 2019; Zomig ZMT 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

- In general, clinical trial data consistently demonstrate the superiority of the triptans over placebo in achieving headache pain relief and freedom from pain at 2 hours, sustained pain-free response, reducing rescue medication use, and improving migraine-associated symptoms such as nausea, photophobia and phonophobia (*Bird et al 2014, Brandes et al 2007, Cady et al 2015, Derry et al 2012 [a], Derry et al 2012[b], Derry et al 2012[c], Derry et al 2014, Ferrari et al 2002, Law et al 2016, Oldman et al 2002, Pascual et al 2007, Poolsup et al 2005, Zembrace SymTouch Prescribing Information 2021, Richer et al 2016*).
- While there appear to be differences in the relative efficacies among the triptans, direct head-to-head trials do not consistently support the use of 1 over another, suggesting that individual variations in response to different triptans exist. Triptans have been evaluated in numerous meta-analyses and comparative trials, with sumatriptan often used as the benchmark standard as it has the most clinical experience available. All triptans are effective at treating migraines and are well tolerated; however, there are some notable differences between the different agents and formulations. Based on older evidence and reviews, the following conclusions were drawn (*Derry et al 2012[a], Derry et al 2012[b], Derry et al 2012[c], Derry et al 2014, Ferrari et al 2002, Oldman et al 2002, Pascual et al 2007*):
  - Rizatriptan 10 mg has the fastest onset of action and the highest efficacy rates of pain-freedom and headache relief at 2 hours post-dose for oral agents (*Oldman et al 2002*); however, the rate of recurrence at 24 hours appears to be higher with rizatriptan (*Ferrari et al 2002, Pascual et al 2007*). Naratriptan 2.5 mg has lower efficacy rates of pain-freedom and headache relief at 2 hours (*Pascual et al 2007*) while eletriptan has a lower rate of recurrence (*Ferrari et al 2002*).
  - Subcutaneous sumatriptan is the most effective for acute migraine treatment but is associated with more adverse events (AEs) relative to the other triptan formulations (*Oldman et al 2002, Derry et al 2012[c]).*
  - Frovatriptan has the least number of head-to-head trials with active comparators. A pooled analysis of 3 studies showed similar efficacy at 2 hours post-dose with pain-free and pain relief responses between frovatriptan and the comparator group (consisting of almotriptan, rizatriptan, and zolmitriptan); however, frovatriptan had less recurrent episodes at 48 hours post-dose than the comparator group ($p < 0.001$) (*Cortelli et al 2011*).
  - Sumatriptan/naproxen fixed-dose combination is more effective for migraine treatment than monotherapy or placebo when measuring headache relief at 2 hours and associated symptoms of migraine, with a similar AE profile to sumatriptan monotherapy (*Brandes et al 2007*).
  - Most triptans are well tolerated; however, naratriptan 2.5 mg and almotriptan 12.5 mg appear to have the lowest risk of causing an AE (*Ferrari et al 2002*).
- Recent evidence is summarized below:
  - Novel sumatriptan nasal formulations have been studied in placebo-controlled (PC) clinical trials. Onzetra Xsail was evaluated in 2 double-blind (DB), randomized trials in 498 patients with moderate to severe migraines (ie, TARGET and COMPASS). The TARGET study (n = 230) resulted in significantly more patients who experienced headache relief at 2 hours post-dose among those who received nasal powder sumatriptan 22 mg compared to placebo (68% vs 45%, respectively; p = 0.002). At 30 minutes post-dose, a significant difference in relief was maintained between treatment groups (42% vs 27%; p = 0.03) (Cady et al 2015). The COMPASS study was a cross-over study with a high drop-out rate, which compared nasal powder sumatriptan 22 mg to oral sumatriptan 100 mg (n = 275; 1531 migraines

assessed) in patients with 2 to 8 migraines/month at baseline. Primary endpoint results demonstrated a significant reduction in the adjusted mean difference in pain intensity scores ($p < 0.001$). At 2 hours, the rates of pain relief (freedom) were comparable (*Tepper et al 2015*).

- A phase 2 trial of Tosymra in 107 patients with 2 to 8 migraines/month found improved response (freedom from headache pain at 2 hours post-dose) compared with placebo (43.8% vs 22.5%; $p = 0.044$). Tosymra was also significantly better than placebo at alleviating bothersome symptoms such as nausea, photophobia, and phonophobia 2 hours post-dose (70.7% vs 39.5%; $p = 0.004$) (*Lipton et al 2018*).
- Data to support the approval of Zembrace SymTouch were based on subcutaneous sumatriptan succinate bioequivalence studies. The safety and efficacy of subcutaneous sumatriptan succinate were evaluated in 3 controlled, unpublished studies in over 1,000 patients with moderate to severe migraines. Studies demonstrated that the onset of relief began as early as 10 minutes following a 6 mg sumatriptan injection. Within 2 hours, headache relief was achieved in 82% of patients treated with a sumatriptan 6 mg injection, and 65% were pain free (*Zembrace SymTouch Prescribing Information 2021, Imitrex Prescribing Information 2020*).
- In a randomized, DB, crossover study, the efficacy and tolerability of 3 mg subcutaneous sumatriptan (Zembrace SymTouch) and 6 mg subcutaneous sumatriptan (Sumavel DosePro – now discontinued) were compared in 20 patients with rapidly escalating migraine attacks. The proportion of patients who were pain-free at 1-hour post-dose was similar following treatment with 3 mg and 6 mg subcutaneous sumatriptan (50% vs 52.6%, respectively; $p = 0.87$). Tolerability was also similar for both doses; although, sumatriptan 3 mg was associated with fewer triptan sensations (ie, paresthesia, neck pain, flushing, and involuntary muscle contractions of the neck) when compared to the 6 mg dose (1 patient vs 4 patients) (*Cady et al 2017*).
- A summary of Cochrane Reviews evaluating the various routes of administration for sumatriptan demonstrated that the injectable (particularly the 6 mg subcutaneous dose) routes of administration were most effective in reducing pain within the first 2 hours of treatment compared to placebo (number needed to treat [NNT], 2.3) and sustained pain-freedom after 24 hours (NNT, 6.1). Efficacy was dose-related with the oral sumatriptan 50 mg dose demonstrating the highest NNT for most endpoints. Compared to other triptans, only rizatriptan 5 mg (vs sumatriptan 25 mg), rizatriptan 10 mg (vs sumatriptan 25 to 100 mg), and eletriptan 40 to 80 mg (vs sumatriptan 50 to 100 mg) were superior to sumatriptan for various endpoints. No differences in the incidence of AEs were found (*Derry et al 2014*).
- A Cochrane Review of zolmitriptan trials concluded that zolmitriptan 2.5 to 5 mg benefited the same proportion of patients as sumatriptan 50 mg for headache relief at 2 hours (range 66 to 68%) with no significant difference in safety (*Bird et al 2014*).
- The TEENZ study assessed the efficacy and safety of zolmitriptan nasal spray for the acute treatment of a single migraine headache in 798 adolescents aged 12 to 17 years. This DB, 4-arm parallel study randomized patients in a ratio of 5:3:3:5 to placebo or zolmitriptan nasal spray in doses of 0.5 mg, 2.5 mg, or 5 mg, respectively. Zolmitriptan 5 mg nasal spray was statistically superior to placebo for the primary endpoint of pain-free status after 2 hours (29.7% vs 16.6%, respectively; $p < 0.001$). Dysgeusia was the most frequently reported AE with zolmitriptan 5 mg nasal spray (occurring in 11.4% of patients) (*Winner et al 2016*).
- In pediatric patients, a Cochrane review concluded that triptans (moderate quality of evidence) and ibuprofen (low quality evidence) are effective at providing freedom from pain in children and adolescents. There are limited safety data available for AEs associated with ibuprofen use, and there may be higher rates of minor AEs associated with triptan use. Further studies are needed in this population to validate conclusions (*Richer et al 2016*).

CLINICAL GUIDELINES

- The American Headache Society (AHS) published updated treatment guidelines for migraine in 2018 (*AHS 2019*). The Society recommends the use of acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), nonopioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans or dihydroergotamine (DHE) are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics. These guidelines do not differentiate the triptans but recommend that non-oral routes are used when severe nausea or vomiting is present.
- There are a number of older guidelines/treatment recommendations for the treatment of migraine but, similar to the 2018 guidelines, they do not state a preference for a particular triptan (*Evers et al 2009, Francis et al 2010, Marmura et al 2015, Silberstein 2000, Silberstein et al 2012 [guideline reaffirmed in 2015]).* For the treatment of cluster headaches, the 2016 AHS guidelines recommend subcutaneous sumatriptan and zolmitriptan nasal spray (*Robbins et al 2016*).

- In 2019, the American Academy of Neurology and AHS published a guideline on the acute treatment of migraine in children and adolescents (*Oskoui et al 2019*). The guideline states that there is evidence to support the efficacy of ibuprofen, acetaminophen (in children and adolescents), and triptans (mainly in adolescents) for migraine relief, although confidence in the evidence varies between agents.

SAFETY SUMMARY

- All triptans are contraindicated in patients with significant underlying cardiovascular (CV) disease (eg, angina pectoris, history of myocardial infarction, documented silent ischemia, or coronary artery vasospasm); peripheral vascular disease; ischemic bowel disease; uncontrolled hypertension; a history of stroke, transient ischemic attack or history of hemiplegic or basilar migraine because these patients are at a higher risk of stroke; and recent use (ie, within 24 hours) of ergotamine-containing medication, ergot-type medication (such as DHE or methysergide) or another 5-HT1 receptor agonist. Additional contraindications include:
  - Naratriptan, sumatriptan and sumatriptan/naproxen are contraindicated in severe hepatic impairment. Naratriptan is also contraindicated in severe renal impairment (creatinine clearance [CrCL] < 15 mL/min).
  - Frovatriptan, naratriptan, eletriptan, sumatriptan, sumatriptan/naproxen, or zolmitriptan are contraindicated in patients with Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders.
  - Concurrent administration of rizatriptan, sumatriptan, sumatriptan/naproxen, or zolmitriptan with a monoamine oxidase (MAO)-A inhibitor or recent (within 2 weeks) use of a MAO-A inhibitor.
  - Eletriptan is contraindicated in patients with recent use (within at least 72 hours) of potent cytochrome P450 (CYP) 3A4 inhibitors including ketoconazole, itraconazole, nefazodone, clarithromycin, ritonavir, or nelfinavir.
  - Sumatriptan/naproxen is contraindicated in the setting of coronary artery bypass graft (CABG) surgery; use during the third trimester of pregnancy; and in those patients with a history of asthma, urticaria, rhinitis, nasal polyp syndrome, or allergic-type reactions after taking aspirin (ASA) or NSAIDs.
- Sumatriptan/naproxen has a boxed warning of potentially fatal CV and gastrointestinal (GI) risks associated with NSAID use. NSAIDs can increase CV thrombotic events (eg, myocardial infarction and stroke); use is contraindicated in the setting of CABG; and increased reports of GI events such as bleeding, ulceration, and perforation of the stomach or intestines have been reported, including fatal events.
- The following warnings and precautions are associated with medications in the class:
  - Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, sumatriptan/naproxen, and zolmitriptan have a higher risk of myocardial ischemia, infarction, Prinzmetal angina, arrhythmias, and other adverse cardiac events in certain patients; cerebrovascular events and associated fatalities in certain patients; other vasospasm-related events (ie, GI ischemic and peripheral vasospastic); chest, throat, neck, and jaw pain, tightness and pressure; exacerbation of headache with medication overuse; and serotonin syndrome.
  - Almotriptan has additional warnings of corneal opacities and possible accumulation and subsequent toxicity due to the binding of melanin-containing tissues in certain patients. Almotriptan should be used with caution in patients with hypersensitivity to sulfonamides.
  - Almotriptan, rizatriptan, and zolmitriptan have reports of significant elevations of blood pressure.
  - All sumatriptan-containing products have reports of seizures following administration. Sumatriptan/naproxen also has warnings associated with NSAID use, which include: increased exacerbations of asthma, nasal polyps, or fatal bronchospasm due to ASA-sensitivity or cross-reactivity; increases in fluid retention and edema that may worsen heart failure; hyperkalemia; renal toxicity; serious skin reactions (eg, exfoliative dermatitis, Stevens-Johnson syndrome, and toxic epidermal necrolysis); drug reaction with eosinophilia and systemic symptoms (DRESS); the potential to mask inflammation and fever; elevated liver enzymes; fetal toxicity (including premature closure of fetal ductus arteriosis and oligohydramnios/neonatal renal impairment); and hematologic toxicity (eg, anemia).
  - Naratriptan, frovatriptan, sumatriptan, sumatriptan/naproxen, eletriptan, and zolmitriptan nasal spray have a warning for hypersensitivity reactions, including anaphylaxis and angioedema. In addition, the needle shield of the prefilled syringe of injectable sumatriptan (Imitrex and Imitrex Statdose) contains a latex derivative that has the potential to cause allergic reactions in patients sensitive to latex.
  - Zolmitriptan ODT contains phenylalanine; the labeling warns of use in patients with phenylketonuria.
- Triptan-containing medications have a large number of potential AEs, but the incidence of most individual reactions is relatively low and often dose-related. Among the oral preparations, no triptan is clearly safer. In general, the injectable triptans are associated with more AEs compared with the oral/topical dosage forms. Triptans are often associated with

atypical sensations, including numbness, tingling, flushing, heaviness/tightness of the chest and throat, heat, burning, cold, or pressure.
  - Generally, the most common AEs associated with 5-HT1 receptor agonists are dizziness, numbness, tingling, flushing, sleepiness, and fatigue.
  - Serious cardiac events, including myocardial infarction and coronary artery vasospasm, have occurred following use of 5-HT1 receptor agonists. These events are extremely rare and have been reported in patients with risk factors predictive of coronary artery disease. Other cardiac events reported in association with drugs in this class have included ventricular tachycardia and fibrillation.
- A 2017 meta-analysis including 141 trials compared the tolerability of 14 oral treatments for acute migraine. In indirect comparisons of PC trials utilizing triptans, naratriptan had the lowest odds of any AE (odds ratio [OR] = 1.11; 95% confidence interval [CI], 0.84 to 1.43) and treatment-related AE (OR = 0.86, 95% CI, 0.51 to 1.55); zolmitriptan had the highest odds of any AE (OR = 2.22; 95% CI, 1.83 to 2.70) and sumatriptan had the highest odds of treatment-related AE (OR = 2.23, 95% CI, 1.83 to 2.73). Results from the meta-regression reported that the dose of triptans had a significant effect on the occurrence of any AE and treatment-related AE, with higher doses yielding a higher probability of AE occurrence and lower doses lessening the risk (*Thorlund 2017*).

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Amerge (naratriptan)	Tablets	Oral	Adults: Given as a single dose; may repeat administration in 4 hours Maximum daily dose: 5 mg	Safety of treating >4 migraines in 1 month has not been established Mild or moderate renal or hepatic impairment: recommended starting dose is 1 mg not to exceed 2.5 mg in any 24-hour period Contraindicated for use in severe renal and hepatic impairment
Axert (almotriptan)	Tablets	Oral	Adults and adolescents (≥12 years): Given as a single dose; may repeat administration in 2 hours Maximum daily dose: 25 mg	Safety of treating >4 migraines in 1 month has not been established In adults, 12.5 mg dose is more effective Hepatic impairment and severe renal impairment: recommended starting dose is 6.25 mg not to exceed 12.5 mg in any 24-hour period
Frova (frovatriptan)	Tablets	Oral	Adults: Given as a single dose; may repeat administration in 2 hours Maximum daily dose: 7.5 mg	Safety of treating >4 migraines in 1 month has not been established

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Imitrex, Imitrex Statdose (sumatriptan)	Tablets, nasal spray, single dose vial, single dose prefilled cartridges for pen use	Oral, intranasal, SC	Tablets (adults): Given as a single dose; may repeat administration in 2 hours Maximum daily dose: 200 mg Intranasal (adults): Given as a single dose; may repeat administration in 2 hours Maximum daily dose: 40 mg Maximum single dose: 20 mg SC injection (adults): Given as a single dose; may repeat administration in 1 hour Maximum daily dose: 12 mg Maximum single dose: 6 mg, particularly for cluster headaches; however, lower doses (1 to 5 mg) may be administered for the treatment of migraine	Tablets and nasal spray: safety of treating >4 migraines in 1 month has not been established Contraindicated for use in severe hepatic impairment (all formulations) Mild or moderate hepatic impairment (tablets): maximum single dose should not exceed 50 mg Administer the needle only to the skin; IM or IV delivery should be avoided
Maxalt, Maxalt MLT (rizatriptan)	Tablets, ODT	Oral	Adults: Given as a single dose; may repeat administration in 2 hours Maximum daily dose: 30 mg Pediatric (≥6 years): Weight based dosing: 5 mg for <40 kg and 10 mg for ≥40 kg	Safety of treating >4 migraines in 1 month in adults and >1 dose within 24 hours in patients 6 to 17 years of age have not been established For ODT, administration with liquid is not necessary Dosage adjustments for patients on concurrent propranolol is required
Migranow (sumatriptan + camphor/ menthol)	Tablet (sumatriptan) + gel (4% camphor/10% menthol)	Oral + topical	Adults: Sumatriptan: Given as a single dose; may repeat administration in 2 hours Maximum daily dose: 200 mg Camphor/menthol: Apply to affected area up to 3 or 4 times daily	Safety of treating >4 migraines in 1 month has not been established Gels should not be applied to wounds, damaged skin, mucous membranes, or eyes Hepatic impairment: maximum single dose of sumatriptan should in general not exceed 50 mg; contraindicated for use in severe hepatic impairment
Onzetra Xsail (sumatriptan)	Capsule in disposable nosepiece for use with breath-powered delivery device only	Intranasal	Adults: 2 nosepieces (1 nosepiece in each nostril) administered using the breath-powered delivery device; may repeat administration in 2 hours	Safety of treating >4 migraines in 1 month has not been established Breath-powered powder delivery requires a forceful blow through the

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Maximum daily dose: 2 doses (44 mg/4 nosepieces) or 1 dose (22 mg/2 nosepieces) of Onzetra Xsail and 1 dose of another sumatriptan product, separated by at least 2 hours	mouthpiece to deliver the powder into each nostril Contraindicated for use in severe hepatic impairment
Relpax (eletriptan)	Tablets	Oral	Adults: Given as a single dose; may repeat administration in 2 hours Maximum daily dose: 80 mg Maximum single dose: 40 mg	Safety of treating >3 migraines in 1 month has not been established
Tosymra (sumatriptan)	Nasal spray	Intranasal	Adults: Given as a single dose; may repeat after 1 hour Maximum daily dose: 30 mg	Administered as a single spray to 1 nostril May be administered 1 hour after another sumatriptan product
Treximet (sumatriptan/ naproxen)	Tablets	Oral	Adults and adolescents (≥12 years): Given as a single dose (85/500 mg for adults and 10/60 mg for adolescents) Maximum daily dose: 2 tablets in 24 hours, taken at least 2 hours apart for adults and 1 tablet in a 24-hour period for adolescents	May be administered with or without food; tablets should not be split, crushed, or chewed Safety of treating >5 migraines in adults and >2 migraines in pediatric patients over the span of 1 month has not been established Mild or moderate hepatic impairment: recommended dose is 1 tablet (10/60 mg) in a 24-hour period Contraindicated for use in severe hepatic impairment
Zembrace SymTouch (sumatriptan)	Single dose prefilled autoinjector	SC	Adults: Injected as a single dose; each dose should be separated by at least 1 hour Maximum daily dose: 12 mg Maximum single dose: 3 mg	The needle penetrates ¼ inch of skin; IM or IV delivery should be avoided Administer dose to the upper arm or thigh May be administered 1 hour after another sumatriptan product Contraindicated for use in severe hepatic impairment
Zomig, Zomig-ZMT (zolmitriptan)	Tablets, ODT, nasal spray	Oral; intranasal	Tablets (adults): Given as a single dose; may repeat administration in 2 hours	Safety of treating >3 migraines (oral) or >4 migraines (intranasal) in 1 month has not been established

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Nasal spray: (adults and adolescents (≥12 years): Given as a single dose; may repeat administration in 2 hours Maximum daily dose: 10 mg Maximum single dose: 5 mg	For ODT, administration with liquid is not necessary Do not break ODT because they are not functionally scored. Moderate to severe hepatic impairment: recommended dose is 1.25 mg (one-half of one 2.5 mg tablet); limit the total daily dose in severe hepatic impairment to no more than 5 mg/day ODTs are not recommended in moderate or severe hepatic impairment as these tablets should not be broken in half Nasal spray is not recommended in moderate to severe hepatic impairment Dosage adjustments for patients on concurrent cimetidine is required

See the current prescribing information for full details

CONCLUSION

- The 5-HT_1 receptor agonists, commonly referred to as triptans, are a well-established therapy for the acute treatment of migraine attacks with or without aura. These agents work via the promotion of vasoconstriction, inhibition of dural vasodilation and inflammation, and blockade of pain pathways in the brainstem. In contrast to analgesics, the triptans are considered to be specific migraine therapies because they act at the pathophysiologic mechanisms of headaches (*Smith 2021, Clinical Pharmacology 2021*).
- Currently, there are 7 single-entity triptans (almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, and zolmitriptan) and 1 fixed-dose triptan/NSAID (sumatriptan/naproxen) available. All triptans are available as a tablet; however, some are available in a variety of other dosage formulations. Specifically, sumatriptan (nasal spray, nasal powder, subcutaneous injection, and tablet) and zolmitriptan (nasal spray, ODT, and tablet) are available in the greatest number of dosage formulations. While it is noted that the subcutaneous sumatriptan injection has the fastest onset of action, there is no evidence to suggest that different oral triptan formulations have a faster onset of action than others (*Francis et al 2010*). Almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, sumatriptan, sumatriptan/naproxen, and zolmitriptan are available generically in at least 1 dosage form or strength (*Drugs@FDA 2021*).
- Triptan selection is based on the characteristics of the headache, dosing convenience, and patient preference. All available triptans are FDA-approved for the acute treatment of migraine with or without aura. The subcutaneous sumatriptan injections (with the exception of Zembrace SymTouch) are also FDA-approved for the acute treatment of cluster headache episodes. In pediatric patients, almotriptan, zolmitriptan nasal spray (fastest onset), and sumatriptan/naproxen are approved for use in children 12 years of age and older, while rizatriptan is approved for use in children as young as 6 years of age.
- While there are data to suggest that the available triptans differ in comparative efficacy, because of the lack of consistent superiority of 1 triptan over another in direct head-to-head comparisons, it appears that individual variations in response to the different triptans exist. There are no pediatric comparative effectiveness data and studies are sparse. Based on pharmacokinetic and pharmacodynamic data, subcutaneous and intranasal formulations generally have a

quicker onset of action and subcutaneous formulations generally have a lower NNT, but more AEs. Frovatriptan and naratriptan have the longest onset of action, which may be responsible for lower incidences of AE. Meta-analyses and systematic reviews point to a potential for lower efficacy with naratriptan and frovatriptan; however, more studies are needed to validate findings.

- Triptan-containing medications have a large number of potential AEs, but the incidence of most individual reactions is relatively low and often dose-related. Among the oral preparations, no triptan is clearly safer. A 2017 meta-analysis including 141 trials compared the tolerability of 14 oral treatments for acute migraine. In indirect comparisons of PC trials utilizing triptans, naratriptan had the lowest odds of any AE (OR = 1.11; 95% CI, 0.84 to 1.43) and treatment-related AE (OR = 0.86, 95% CI, 0.51 to 1.55); zolmitriptan had the highest odds of any AE (OR = 2.22; 95% CI, 1.83 to 2.70) and sumatriptan had the highest odds of treatment-related AE (OR = 2.23, 95% CI, 1.83 to 2.73). Results from the meta-regression reported that the dose of triptans had a significant effect on the occurrence of any AE and treatment-related AE, with higher doses yielding a higher probability of AE occurrence and lower doses lessening the risk (*Thorlund 2017*).
- In general, the injectable triptans are associated with more AEs compared with the oral dosage forms. Triptans are often associated with atypical sensations, including numbness, tingling, flushing, heaviness/tightness in the chest and throat, heat, burning, cold, or pressure.
- The American Headache Society (AHS) published updated treatment guidelines for migraine in 2018 (AHS, 2019). They recommend the triptans or dihydroergotamine (DHE) for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics. These guidelines do not differentiate the triptans but recommend that non-oral routes be used when severe nausea or vomiting is present. There are a number of older guidelines/treatment recommendations for the treatment of migraine but, similar to the 2018 guidelines, they do not state a preference for a particular triptan (*Evers et al 2009, Francis et al 2010, Marmura et al 2015, Silberstein 2000, Silberstein et al 2012 [guideline reaffirmed in 2015]*).
- For the treatment of cluster headaches, the 2016 AHS guideline provides an update to the 2010 AAN guidelines (*Francis et al 2010, Robbins et al 2016*). For acute treatment, subcutaneous sumatriptan and zolmitriptan nasal spray are recommended with a higher level of evidence; although zolmitriptan nasal spray is not FDA-approved for use (*Robbins et al 2016*).
- In 2019, the American Academy of Neurology and AHS published a guideline on the acute treatment of migraine in children and adolescents (*Oskoui et al 2019*). The guideline states that there is evidence to support the efficacy of ibuprofen, acetaminophen (in children and adolescents), and triptans (mainly in adolescents) for migraine relief, although confidence in the evidence varies between agents.
- All triptans are generally effective for the acute treatment of migraine attacks and are well tolerated with a similar safety profile. Although some triptans have been shown to be significantly superior to other 5-HT_1 receptor agonists in direct comparator studies, these results may not translate to significant differences within meta-analyses and systematic reviews. Additionally, clinical superiority cannot be determined as an individual patient's response to a particular drug may vary. In general, injectable treatments have been associated with the fastest onset of action; therefore, they are amenable for quick relief. However, injectable triptans are associated with more AEs compared to oral or nasal dosage forms. Treatment guidelines do not recommend 1 agent over another; rather, choice of treatment should be individualized based on patient need, response, preference, migraine severity, and tolerability.

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Publication date: July 1, 2021

Therapeutic Class Overview
Ophthalmic Anti-Allergy

INTRODUCTION

- Conjunctivitis can be classified as noninfectious or infectious, and as acute, chronic, or recurrent. Types of noninfectious conjunctivitis are allergic, mechanical/irritative/toxic, immune-mediated, and neoplastic. Causes of infectious conjunctivitis are viruses and bacteria *(American Academy of Ophthalmology [AAO] 2018)*.
- Types of allergic conjunctivitis include atopic keratoconjunctivitis, seasonal or perennial conjunctivitis, vernal conjunctivitis, and giant papillary conjunctivitis. Atopic keratoconjunctivitis is a severe, chronic, external ocular inflammation associated with atopic dermatitis. Vernal conjunctivitis is a severe form of allergic conjunctivitis that may involve the cornea *(AAO 2018, Bielory et al 2020)*.
- Allergic conjunctivitis results from classic Type I immunoglobulin E (IgE)-mediated hypersensitivity, where the immediate response to allergens is mediated predominantly by mast cells. The mast cells are present in the conjunctiva in high concentrations and release chemical mediators when activated by allergen-IgE cross-linkage. During the early response, histamine is the main mediator, and it causes itching, vasodilation, and vasopermeability. During the late phase of the allergic reaction, mast cells release chemokines and cytokines, which results in the influx of other inflammatory cells and continued inflammation (*Bielory et al 2020, Bielory et al 2012*). Symptoms of allergic conjunctivitis include itching, tearing, mucoid discharge, chemosis, hyperemia, and redness. Most commonly, symptoms are present in both eyes, but they may also occur unilaterally *(Hamrah and Dana 2020a, Bielory et al 2012)*.
- The ophthalmic anti-allergy therapeutic class overview details the efficacy and safety of the ophthalmic antihistamines and ophthalmic mast cell stabilizers.
  - The ophthalmic antihistamines are Food and Drug Administration (FDA)-approved for the management of the signs and symptoms associated with allergic conjunctivitis *(Micromedex 2.0 2021, Facts & Comparisons 2021)*.
    - All ophthalmic antihistamines are available by prescription with the exception of ketotifen. OTC products include ketotifen and olopatadine and are indicated for the temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair, and dander.
  - The ophthalmic mast cell stabilizers include cromolyn sodium (previously marketed under the brand name, Opticrom), Alomide (lodoxamide) and Alocril (nedocromil). Nedocromil is approved for the treatment of itching associated with allergic conjunctivitis while cromolyn and lodoxamide are the only agents in this review that are FDA-approved for the treatment of vernal conjunctivitis (*Drugs@FDA 2021, Hamrah and Dana 2020b*).
  - Alrex (loteprednol etabonate 0.2%) ophthalmic suspension, an ophthalmic corticosteroid, is also indicated for the temporary relief of the signs and symptoms of seasonal allergic conjunctivitis in adults. Acular (ketorolac 0.5%) ophthalmic solution, an ophthalmic non-steroid anti-inflammatory drug (NSAID), is also FDA-approved for the treatment of ocular pruritus due to seasonal allergic conjunctivitis (ages ≥ 2 years) (*Micromedex 2.0 2021*). These 2 agents are reviewed in separate class reviews.
- Medispan Therapeutic Class: Ophthalmic Antiallergic

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Ophthalmic Antihistamines	
Alaway†, Zaditor† (ketotifen 0.025% ophthalmic solution)	✔
Bepreve (bepotastine besilate 1.5% ophthalmic solution)	-§
Elestat (epinastine HCl 0.05% ophthalmic solution)	✔
Lastacaft (alcaftadine 0.25% ophthalmic solution)	-
Optivar* (azelastine HCl 0.05% ophthalmic solution)	✔
Pataday* (olopatadine HCl 0.2% ophthalmic solution) Patanol* (olopatadine HCl 0.1% ophthalmic solution)	✔ ‡ ✔ ‡
Pataday Once Daily Relief† (olopatadine HCl 0.2%, 0.7%** ophthalmic solution)	-

Drug	Generic Availability
Pataday Twice Daily Relief† (olopatadine HCl 0.1% ophthalmic solution)	-
Zerviate (cetirizine 0.24% ophthalmic solution)	-
Ophthalmic Mast Cell Stabilizers	
Alocril (nedocromil 2% ophthalmic solution)	-§
Alomide (lodoxamide 0.1% ophthalmic solution)	-
cromolyn sodium 4% ophthalmic solution	✔

Key: HCl = hydrochloride
* Brand name has been discontinued; generics are available.
† Available over-the-counter.
‡ Generic prescription products containing olopatadine HCl 0.1% or 0.2% remain available.
** This prescription brand, Pazeo, has been discontinued; olopatadine HCl 0.7% became available over-the-counter as Pataday Once Daily Relief in September 2020.
§ A generic product has received FDA approval but is not yet commercially available.

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications – Ophthalmic Antihistamines

Indication	**Alaway, Zaditor** (ketotifen)	**Bepreve** (bepotastine)	**Elestat** (epinastine)	**Lastacaft** (alcaftadine)	**Optivar** (azelastine)	olopatadine prescription	**Pataday Once or Twice Daily Relief** (olopatadine) OTC	**Zerviate** (cetirizine)
Prevention of ocular itching associated with allergic conjunctivitis			✔	✔				
Treatment of ocular itching associated with allergic conjunctivitis		✔			✔	✔ (0.2%)		✔
Treatment of signs and symptoms of allergic conjunctivitis						✔ (0.1%)		
Temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair, and dander	✔						✔	

(Prescribing information: Alaway 2020, Azelastine 2019, Bepreve 2019, Elestat 2011, Lastacaft 2020, Pataday 2010, Pataday Once Daily Relief 2020, Pataday Twice Daily Relief 2020, Patanol 2018, Zaditor 2020, Zerviate 2020)

Table 3. Food and Drug Administration Approved Indications – Ophthalmic Mast Cell Stabilizers

Indication	Alocril (nedocromil)	Alomide (lodoxamide)	cromolyn sodium
Treatment of itching associated with allergic conjunctivitis	✔		
Treatment of vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis		✔	✔

(*Prescribing information: Alocril 2018, Alomide 2020, cromolyn sodium ophthalmic solution 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

Ophthalmic Antihistamines

- Due to the rapid onset of action of the ophthalmic antihistamines, most trials used the conjunctival allergen challenge model to establish the relative efficacy of these formulations compared to placebo. The results of these trials demonstrated improvements in symptoms, especially for itching, in those treated with ophthalmic antihistamines and antihistamines/mast cell stabilizers compared to placebo.
- Several studies have been conducted to directly compare ophthalmic ketotifen and ophthalmic olopatadine. These studies have produced mixed results, generally demonstrating no difference between the agents. Results of some studies suggest that ophthalmic olopatadine may be preferred and better tolerated by patients *(Avunduk et al 2005, Berdy et al 2000, Borazan et al 2009, Ganz et al 2003, Leonardi et al 2004)*. There are limited head-to-head studies that compare the clinical efficacy of the other ophthalmic antihistamines to one another, and all are considered equally efficacious at improving ocular allergy symptoms. While some studies reported statistically significant differences in symptom scores, the overall clinical significance of these differences is not known, as many of these trials were conducted using single doses of study medication (in the conjunctival allergen challenge model) and generally enrolled a small number of patients. A Cochrane review of topical antihistamines for treatment of allergic conjunctivitis concluded that topical antihistamines and mast cell stabilizers reduce symptoms temporarily. Data for the long-term use of topical antihistamines are lacking *(Castillo et al 2015)*.
- A study compared efficacy of daily use of alcaftadine (n = 60), olopatadine (n = 60), and bepotastine (n = 60) for 14 days in 180 patients with mild-to-moderate allergic conjunctivitis. At day 14, the total ocular symptom score (TOSS) had significantly reduced from baseline scores in all 3 groups. Although the authors describe a statistically significant difference between groups in mean TOSS score at day 14, this was a post hoc assessment and the clinical significance of this difference is unclear. No significant differences in adverse events were observed between the 3 groups (*Ayyappanavar et al 2021*).
- Clinical data supporting the FDA approval of cetirizine ophthalmic solution were from two Phase 3 studies that evaluated the efficacy and safety of the drug compared with vehicle in the treatment of allergen-induced conjunctivitis using a conjunctival allergen challenge model (*Malhotra et al 2019, Meier et al 2018*). Approximately 100 subjects were randomized in each study. Results revealed that ophthalmic cetirizine administered 15 minutes or 8 hours before the challenge results in significantly reduced ocular itching at all time points post-challenge ($p < 0.0001$) compared to vehicle in both studies. Additionally, significant improvement in chemosis, eyelid swelling, tearing, ciliary redness, episcleral redness, and nasal symptoms were observed with cetirizine. The ophthalmic solution was well-tolerated and was associated with a low incidence of mild adverse events.

Ophthalmic Mast Cell Stabilizers

- Clinical studies have demonstrated that ophthalmic mast cell stabilizers are safe and effective for their FDA-approved indications.
- Ophthalmic formulations of cromolyn and lodoxamide are FDA-approved for the treatment of vernal conjunctivitis, which is a severe form of allergic conjunctivitis that may involve the cornea. A study confirmed that ophthalmic cromolyn 4% was significantly more effective than placebo in treating the signs and symptoms of vernal conjunctivitis, such as conjunctival and limbal injection, limbal edema, and tearing (n = 65) (*Foster et al 1988*). In a few small studies (N = 30 to 120) conducted over 10 to 28 days, ophthalmic lodoxamide was reported to be more effective than ophthalmic cromolyn 4% in improving clinical signs and symptoms of vernal conjunctivitis (*Avunduk et al 2000, Caldwell et al 1992, Leonardi et al 1997*).
- Clinical studies have shown that ophthalmic formulations of cromolyn, lodoxamide, azelastine, and nedocromil were more effective than placebo for managing symptoms of seasonal and perennial allergic conjunctivitis (*James et al 2003, Kjellman et al 1995, Leino et al 1992, Orfeo et al 2002, Owen et al 2004*). Pooled data showed that patients using ophthalmic mast-cell stabilizers were 4.9 times more likely to perceive benefit than those using placebo (*Owen et al 2004*).
- A meta-analysis of 4 trials found that patients were 1.3 times more likely to perceive their treatment response as “good” with ophthalmic antihistamines and ophthalmic antihistamines/mast-cell stabilizers compared to patients receiving pure

ophthalmic mast-cell stabilizers. However, this difference in response failed to reach statistical significance (*Owen et al 2004*).

- Single-acting mast cell stabilizers are now rarely used in the treatment of acute allergic conjunctivitis because of their slow onset of action (ie, 3 to 5 days may be required for symptom abatement). Dual-acting antihistamine/mast cell stabilizers reduce allergic inflammation by preventing mast cell release of inflammatory mediators and by selectively blocking the H_1-receptor, thus countering the effects of histamine that has already been released and enabling a relatively rapid onset of action and an effect on the late-phase response (*Bielory et al 2013*).

CLINICAL GUIDELINES

- According to the AAO, mild allergic conjunctivitis may be treated with an OTC antihistamine/vasoconstrictor or with the more effective second-generation topical histamine H_1 receptor antagonists (*AAO 2018*). Because ophthalmic vasoconstrictors have a short duration of action and may cause rebound hyperemia and conjunctivitis medicamentosa, they should only be used short-term. Ophthalmic mast-cell stabilizers can be utilized if the condition is recurrent or persistent. Newer medications that combine antihistamine activity with mast cell stabilizing properties can be utilized for either acute or chronic disease. If symptoms are not adequately controlled, a brief course of low-potency topical corticosteroids can be added. Additional measures include artificial tears, cool compresses, and allergen avoidance. Oral antihistamines are commonly used as well but may induce or worsen dry eye syndrome, impair the tear film's protective barrier, and worsen allergic conjunctivitis.
- For vernal/atopic conjunctivitis, general treatment measures include minimizing exposure to allergens or irritants and using cool compresses and ocular lubricants. Topical and oral antihistamines and topical mast cell stabilizers can be used to maintain comfort. For acute exacerbations of vernal/atopic conjunctivitis, topical corticosteroids are usually necessary to control severe symptoms (*AAO 2018*).
- The guideline does not recommend one specific ophthalmic antihistamine or mast cell stabilizer over another (*AAO 2018*). There are limited head-to-head trials comparing the agents in these classes to each other. While a few studies reported some differences, the overall clinical significance of these differences is not known since many trials were conducted using single doses of study medication (conjunctival allergen challenge model), in a small number of patients, and/or with comparisons to products that are no longer commercially available.

SAFETY SUMMARY

Ophthalmic Antihistamines

- Contact lens use: patients should not wear a contact lens if the eye is red; remove contact lenses prior to instilling this product, as the preservative, benzalkonium chloride, may be absorbed by soft contact lenses.
- Contamination of tip and solution: do not touch eyelids or surrounding areas with the dropper tip of the bottle.
- Products are for ophthalmic use only.
- Adverse events are primarily ocular in nature with burning/stinging upon instillation, ocular irritation, ocular pruritus, and redness. Systemic adverse events include mild taste upon instillation, headache, rhinitis, and potential hypersensitivity reactions.
- Due to the topical application of the ophthalmic antihistamines, drug interactions have not been reported.

Ophthalmic Mast Cell Stabilizers

- Contraindications to these products include hypersensitivity to any component of the medications.
- Contact lenses should not be worn during use of these medications.
- Contact of dropper tip to any surface should be avoided to minimize risk of contamination and ocular infection.
- Products are for ophthalmic use only.
- The most common adverse effects of the ophthalmic mast cell stabilizers are ocular burning, stinging and headache. In general, drug interactions are limited due to low systemic bioavailability by the ocular route.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ophthalmic Antihistamines				

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Alaway, Zaditor (ketotifen)	Ophthalmic solution	Ophthalmic	Twice daily	Instill 1 drop into affected eye(s) twice daily, every 8 to 12 hours, no more than twice per day. For children ≥ 3 years of age, refer to adult dose; safety and effectiveness in children < 3 years of age have not been established. Not studied in pregnancy.
Bepreve (bepotastine)	Ophthalmic solution	Ophthalmic	Twice daily	Instill 1 drop into affected eye(s) twice daily. For children ≥ 2 years of age, refer to adult dose; safety and effectiveness in children < 2 years of age have not been established. Pregnancy: Unclassified†
Elestat (epinastine)	Ophthalmic solution	Ophthalmic	Twice daily	Instill 1 drop in each eye twice daily. Treatment should be continued throughout the period of exposure (ie, until the pollen season is over or until exposure to the offending allergen is terminated), even when symptoms are absent. For children ≥ 2 years of age, refer to adult dose; safety and effectiveness in children < 2 years of age have not been established. Pregnancy Category C*
Lastacaft (alcaftadine)	Ophthalmic solution	Ophthalmic	Once daily	Instill 1 drop in each eye once daily. If more than 1 topical ophthalmic medicinal product is being used, each one should be administered at least 5 minutes apart. For children ≥ 2 years of age, refer to adult dose; safety and effectiveness in children < 2 years of age have not been established.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Pregnancy: Unclassified†
Optivar (azelastine)	Ophthalmic solution	Ophthalmic	Twice daily	Instill 1 drop into affected eye(s) twice daily. For children ≥ 3 years of age, refer to adult dose; safety and effectiveness in children < 3 years of age have not been established. Pregnancy Category C*
Pataday, Patanol, (olopatadine)	Ophthalmic solution	Ophthalmic	Once or twice daily (varies by product)	Patanol 0.1%: Instill 1 drop into affected eye(s) twice daily at an interval of 6 to 8 hours. Pataday 0.2%, 0.7%: Instill 1 drop into affected eye(s) once daily For children ≥ 2 (0.2%, 0.7%) and ≥ 3 (0.1%) years of age, refer to adult dose; safety and effectiveness in children < 3 years (0.1%) and < 2 years (0.2%, 0.7%) of age have not been established. Pregnancy Pataday: Pregnancy Category C* Patanol: Unclassified†
Pataday Once Daily Relief and Pataday Twice Daily Relief (olopatadine)	Ophthalmic solution	Ophthalmic	Once or twice daily (varies by product)	Pataday Twice Daily Relief 0.1%: Instill 1 drop into affected eye(s) twice daily at an interval of 6 to 8 hours, no more than twice per day Pataday Once Daily Relief 0.2%, 0.7%: Instill 1 drop into affected eye(s) once daily, no more than once daily and for the 0.7% formulation, no more than 1 drop in each eye For aged ≥ 2 years, use adult dosage for either OTC Pataday product. Not studied in pregnancy.
Zerviate (cetirizine)	Ophthalmic solution	Ophthalmic	Twice daily	Instill 1 drop into affected eye(s) twice daily.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				For children ≥ 2 years of age, refer to adult dose; safety and effectiveness in children < 2 years of age have not been established. Pregnancy: Unclassified†
Ophthalmic Mast Cell Stabilizers				
Alocril (nedocromil)	Ophthalmic Solution	Ophthalmic	Twice daily	Instill 1 or 2 drops into each affected eye(s) twice daily. Use at regular intervals. Treatment should be continued throughout the period of exposure, even when symptoms are absent. For children ≥ 3 years of age, refer to adult dose; safety and effectiveness in children < 3 years of age have not been established Pregnancy: Unclassified†
Alomide (lodoxamide)	Ophthalmic solution	Ophthalmic	4 times a day for up to 3 months	Instill 1 to 2 drops into each affected eye(s) four times daily for up to 3 months. For children > 2 years of age, refer to adult dose; safety and effectiveness in children ≤ 2 years of age have not been established. Pregnancy: Unclassified†
cromolyn sodium	Ophthalmic solution	Ophthalmic	4 to 6 times daily	Instill 1 or 2 drops into each affected eye(s) 4 to 6 times daily at regular intervals. Symptomatic response is usually evident within a few days, but up to 6 weeks may be required; therapy should be continued if needed to sustain improvement. For children ≥ 4 years of age, refer to adult dose; safety and effectiveness in children < 4

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				years of age have not been established. Pregnancy Category B*.

†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.

*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women. Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

See the current prescribing information for full details.

CONCLUSION

- The most common form of ocular allergy is allergic conjunctivitis (*Bielory et al 2012, Hamrah and Dana 2020a*). Ophthalmic mast cell stabilizers and antihistamines are FDA-approved for the management of signs and symptoms associated with allergic conjunctivitis. The ophthalmic mast cell stabilizers cromolyn and lodoxamide are the only agents in this class that are FDA-approved for the treatment of vernal conjunctivitis.
- Few distinguishing characteristics exist among the available ophthalmic antihistamines, but alcaftadine and olopatadine 0.2% and 0.7% may be administered once daily, while the remaining ophthalmic antihistamines are administered 2 to 4 times daily. Currently, ophthalmic formulations of azelastine, epinastine, ketotifen, and olopatadine are available generically. Ophthalmic formulations of ketotifen and olopatadine are also available in OTC formulations. Due to the ophthalmic administration of these agents, relatively few adverse effects have been reported; the most common adverse reactions are ocular burning and stinging and headache.
- Regarding the ophthalmic mast cell stabilizers, all are approved for use in children (> 2 to 4 years of age depending on the product). The most common adverse effects of these agents are ocular burning, stinging, and headache. The administration schedule of these ophthalmic products ranges from twice daily to 6 times daily. Ophthalmic cromolyn is the only mast cell stabilizer currently available as a generic formulation.
- The AAO conjunctivitis guideline does not recommend one specific ophthalmic antihistamine or mast cell stabilizer over another (*AAO 2018*). There are limited head-to-head trials comparing the agents in these classes to each other. While a few studies reported some differences, the overall clinical significance of these differences is not known since many trials were conducted using single doses of study medication (conjunctival allergen challenge model), in a small number of patients, and/or with comparisons to products that are no longer commercially available.

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Publication Date: March 30, 2021

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.
  - The 2 available triple combination agents (consisting of LAMA/LABA/ICS) are indicated for COPD and one is also indicated for asthma.
  - 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 in the lungs. 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 2019, asthma affected an estimated 20 million adults and 5.1 million children in the United States (U.S.) (*Centers for Disease Control and Prevention [CDC] 2021, National Heart, Lung, and Blood Institute [NHLBI] Web site*).
- 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] 2021*). COPD affects 6.4% of the U.S. population and is a major contributor to mortality from chronic lower respiratory diseases, the third leading cause of death in the U.S. (*CDC 2019*).
- Utibron Neohaler (glycopyrrolate/indacaterol) was previously available but was discontinued in March 2020 (*FDA Drug Shortages 2020*).
- 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 & AirDuo Digihaler (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)	-

Drug	Generic Availability
ipratropium/albuterol solution	✔
Stiolto Respimat (tiotropium/olodaterol)	-
Triple combination	
Breztri Aerosphere (glycopyrrolate/formoterol/budesonide)	-
Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol)	-

* Branded product DuoNeb is no longer marketed.
† Authorized generic (for AirDuo RespiClick and Symbicort only)
‡ Wixela Inhub is the generic of Advair Diskus. No generic is available for Advair HFA.

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

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

Indication	Advair Diskus	Advair HFA	AirDuo RespiClick & Digihaler	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)

*Should only be used in patients not adequately controlled on an ICS or whose disease warrants initiation of both an ICS and a LABA.

(*Prescribing information: Advair HFA 2021, Advair Diskus 2020, AirDuo Digihaler 2020, AirDuo RespiClick 2020, Breo Ellipta 2019, Dulera 2020, Symbicort 2019, Wixela Inhub 2021*)

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
Long-term, once-daily, maintenance treatment of patients with COPD	✔					
Long-term, twice-daily, maintenance treatment of patients with COPD		✔		✔		
Long-term, once-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			✔			

Indication	Anoro Ellipta	Bevespi Aerosphere	Combivent Respimat	Duaklir Pressair	ipratropium/ albuterol solution	Stiolto Respimat
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 2020, Bevespi Aerosphere 2020, Combivent Respimat 2020, Duaklir Pressair 2020, ipratropium/albuterol solution 2018, Stiolto Respimat 2020*)

Table 2C. FDA-Approved Indications for Triple Combination Agents

Indication	Breztri Aerosphere	Trelegy Ellipta
Maintenance treatment of patients with COPD	✔	✔ (100/62.5/25 strength only)
Maintenance treatment of asthma		✔ (age ≥ 18 years)

(*Prescribing information: Breztri Aerosphere 2020, Trelegy Ellipta 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

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*).
- The efficacy of the AirDuo Digihaler (fluticasone propionate/salmeterol) was based primarily on the dose-ranging trials and the confirmatory trials for the AirDuo RespiClick (fluticasone propionate/salmeterol). The AirDuo Digihaler contains a built-in electronic module which detects, records, and stores data on inhaler events, including peak inspiratory flow rate (L/minute), for transmission a mobile App. There is no evidence the use of the App leads to improved clinical outcomes, including safety and effectiveness (*AirDuo Prescribing information 2020*)
- 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 50/5 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 2020*).
- 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 experienced ≥ 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 experienced 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 experienced ≥ 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*).

Comparisons between different ICS/LABA combinations

- There are some data available comparing different combination ICS/LABA products for the treatment of COPD.
  - One crossover study comparing budesonide/formoterol to fluticasone propionate/salmeterol demonstrated no significant difference between products for the primary endpoint, the increase from baseline in peak expiratory flow 5 minutes after the morning dose (*Partridge et al 2009*). However, the mean morning 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*).

- A Cochrane systematic review evaluated if there were differences in the risk for mortality or serious adverse events in patients with asthma receiving formoterol with an ICS compared to salmeterol with an ICS. A total of 12 studies (n = 11,572) in adults and adolescents and 2 studies (n = 723) children were included in the review. The risk for mortality was not assessed due to the low number of events. Evidence on all-cause non-fatal serious adverse events indicated that there is no difference between formoterol/budesonide and salmeterol/fluticasone inhalers (OR, 1.14; 95% CI, 0.82 to 1.59) (*O'Shea et al 2021*).

ICS/LABA compared to tiotropium or in combination with tiotropium for COPD

- 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 = 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, 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 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 2017*). 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 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*).
- 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 ICS/LABAs for maintenance treatment of COPD. At 12 and 24 weeks, LAMA, LAMA/LABA, and ICS/ALBA 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 ICS/LABA 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 TDI 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% (rate ratio, 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).*

<u>Comparisons of combination $beta_2$-agonist/anticholinergic products to each other or to other bronchodilator combinations</u>

- 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.
  - 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 (no longer available), 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*).
- Several systematic reviews/meta-analyses compared various LAMA/LABA combinations (*Calzetta et al 2016, Lee et al 2020, Schlueter et al 2016, Siddiqui et al 2019, 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 did not include the more recently approved products in some cases. Additionally, 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 (no longer available) 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 (*Sion et al 2017*).
  - The *Schlueter et al* meta-analysis of 27 trials (N = 30,361) including 4 LAMA/LABA fixed-dose combination agents (aclidinium/formoterol 400/12 mcg, glycopyrrolate/indacaterol 110/50 mcg [no longer available], 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. The only statistically significant result indicated that umeclidinium/vilanterol appeared to improve lung function to a greater extent than aclidinium/formoterol at 24 to 26 weeks (difference of 61 mL; 95% CrI, 18 to 103; in favor of umeclidinium/vilanterol).
  - The network meta-analysis by *Lee et al* included 16 randomized controlled trials evaluating 6 LAMA/LABA fixed-dose combination agents (tiotropium/salmeterol [not FDA approved], glycopyrrolate/indacaterol [no longer available], umeclidinium/vilanterol, tiotropium/olodaterol, aclidinium/formoterol, and glycopyrrolate/formoterol). No significant differences were found between the LAMA/LABA combinations for moderate to severe exacerbations, all-cause mortality, or major adverse cardiovascular events (*Lee et al 2020*).

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, 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 vs ICS/LABA. The analysis showed that umeclidinium/vilanterol, glycopyrrolate/indacaterol (no longer

available), 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 combinations for COPD and asthma

- Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol) inhalation powder was the first FDA-approved "closed triple" inhaler – an inhaler containing 3 active ingredients from 3 different therapeutic classes: an ICS, a LAMA, and a LABA.
  - 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 for the treatment of patients with COPD (*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 in patients with COPD (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 for COPD 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).
    - An updated, post hoc mortality analysis of IMPACT was published after the collection of additional vital status data. With known vital status for 99.6% of the intention-to-treat population (n = 10,335), there were 98 deaths (2.36%) in patients on umeclidinium/vilanterol/fluticasone furoate, 109 (2.64%) on vilanterol/fluticasone furoate, and 66 (3.19%) on umeclidinium/vilanterol. For triple therapy, the HR for death was 0.72 (95% CI, 0.53 to 0.99; $p = 0.042$) vs umeclidinium/vilanterol and 0.89 (95% CI, 0.67 to 1.16; $p = 0.387$) vs vilanterol/fluticasone furoate (*Lipson et al 2020*). The FDA noted several statistical and clinical issues with respect to interpretation of the mortality data, and the FDA Pulmonary-Allergy Drugs Advisory Committee voted 14-1 against a proposed labeling claim that Trelegy Ellipta reduces all-cause mortality in patients with COPD (*FDA Trelegy Ellipta briefing document 2020, Healio 2020*).
  - The 24- to 52-week double-blind CAPTAIN trial evaluated the safety and efficacy of triple therapy with Trelegy Ellipta (umeclidinium/vilanterol/fluticasone furoate) for the treatment of asthma in adult patients. Umeclidinium/vilanterol/fluticasone furoate was compared to Breo Ellipta (vilanterol/fluticasone furoate). For the comparison of triple vs dual therapy using the lower strength (100 mcg) of fluticasone furoate, there was a significant improvement in the primary endpoint of change in trough FEV_1 at week 24, with a difference of 110 mL (95% CI, 66 to 153; $p < 0.0001$). The corresponding improvement for the higher strength (200 mcg fluticasone furoate) was also significant at 92 mL (95% CI, 49 to 135) (*Lee LA et al 2021*).
    - A numerical improvement in the annualized rate of moderate/severe exacerbations was seen between triple and dual therapy with the lower strength, but the difference did not reach statistical significance (rate ratio, 0.78 [95% CI, 0.61 to 1.01]; $p = 0.060$). The exacerbation rate was comparable between triple and dual therapy for the higher strength comparison (rate ratio, 0.97; 95% CI, 0.73 to 1.28; $p = 0.80$).

- An additional triple therapy product, Breztri Aerosphere (glycopyrrolate/formoterol/budesonide) inhalation aerosol, was FDA-approved in 2020. Safety and efficacy were demonstrated in 2 double-blind trials comparing triple therapy to dual therapy with glycopyrrolate/formoterol (Bevespi Aerosphere) or formoterol/budesonide in patients with COPD (*Ferguson et al 2018, Rabe et al 2020*).
  - In the 24-week KRONOS study (N = 1902), the FEV_1 AUC (0 to 4 hr) was significantly improved for triple therapy vs formoterol/budesonide, with a difference of 116 mL (95% CI, 80 to 152; p < 0.0001); the difference in change from baseline in pre-dose trough FEV_1 was nominally significant, with a difference of 74 mL (95% CI, 47 to 102; p < 0.0001). These lung function endpoints were not significantly improved for the triple therapy vs glycopyrrolate/formoterol; however, improvements were demonstrated in some secondary endpoints including SGRQ and the incidence of moderate or severe COPD exacerbations for this comparison (*Ferguson et al 2018*).
  - The 52-week ETHOS study (N = 8588) enrolled patients with a documented history of COPD exacerbation(s) in the preceding year. The primary endpoint of annualized rate of moderate or severe COPD exacerbations was significantly improved for triple therapy (with the marketed dose) compared to the corresponding doses of either dual therapy. For triple therapy vs glycopyrrolate/formoterol, the rate ratio was 0.76 (95% CI, 0.69 to 0.83; p < 0.001), and for triple therapy vs formoterol/budesonide, the rate ratio was 0.87 (95% CI, 0.79 to 0.96; p = 0.003) (*Rabe et al 2020*).
    - An updated analysis of ETHOS data evaluated the risk for all-cause mortality after the collection of additional vital status data. With known vital status for 99.6% of the intention-to-treat population, the risk of death was significantly lower with triple therapy compared to glycopyrrolate/formoterol (HR, 0.51; 95% CI, 0.33 to 0.80), but triple therapy did not significantly reduce the risk of death compared to formoterol/budesonide (HR, 0.72; 95% CI, 0.44 to 1.16) (*Martinez et al 2021*)
- A meta-analysis evaluated 20 randomized controlled trials (N = 11,894) that compared triple therapy (ICS/LABA/LAMA) vs dual therapy with an ICS plus LABA in children and adults with persistent uncontrolled asthma. Triple therapy was associated with significant reductions in severe exacerbation risk (risk ratio, 0.83; 95% CI, 0.77 to 0.90) and improvement in asthma control (ACQ or ACT scores: standardized mean difference, -0.06; 95% CI, -0.10 to -0.02), but no significant differences were found between triple versus dual therapy in mortality (risk ratio, 0.96; 95% CI, 0.33 to 2.75) (*Kim et al 2021*).
- A network meta-analysis evaluated if there were significant differences between different triple therapy combinations for the treatment of COPD. Nine different combinations of triple therapy were identified in 21 randomized controlled trials (N = 29,892). The analysis found no significant differences between different triple therapies in clinical outcomes, including acute exacerbation risk and all-cause mortality (*Lee HW et al 2021*). A limitation to this analysis was inclusion of trials that evaluated some formulations/dose regimens not available in the U.S.

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.
  - A 2020 focused update of the 2007 NAEPP guideline provided updated recommendations on the use of intermittent ICSs and the use of LAMAs as add-on therapy (*Cloutier et al 2020*). The update did not address use of ICS-formoterol as an option for intermittent asthma. For mild, persistent asthma, the use of as needed concomitant ICS and SABA was added as an alternative to daily low-dose ICS with as needed SABA for management of mild, persistent asthma. Additionally, ICS-formoterol in a single inhaler used as both a daily controller and reliever therapy in moderate to severe persistent asthma was recommended over the use of a higher-dose ICS/LABA therapy with a SABA as

needed. Finally, the addition of a LAMA can be considered for patients who have uncontrolled, persistent asthma despite ICS/LABA therapy.

- The 2021 GINA report also provides a stepwise approach to asthma management. Treatment recommendations are based on 2 tracks stratified by the choice of reliever. Track 1 includes ICS-formoterol as the reliever, and it is the preferred approach for most patients because it reduces the risk of severe exacerbations. Track 2 uses a SABA as the reliever. Treatment in adults and adolescents with a SABA only is not recommended. For Step 1 and 2 therapy, the preferred (track 1) approach is low dose ICS-formoterol as needed for symptom relief or if needed for exercise for patients with mild asthma. For Step 3, the preferred treatment is low dose ICS-formoterol as both maintenance and reliever therapy. Preferred therapy for Step 4 is a medium dose ICS-formoterol with as needed low dose ICS-formoterol as the reliever therapy. For patients with persistent symptoms or exacerbations despite Step 4 therapy, referral to a specialist with expertise in severe asthma management is recommended. Treatment options may include any of the following options: high dose ICS-LABA therapy, add-on LAMA (tiotropium or triple combination [ICS/LABA/LAMA] inhaler), azithromycin, low-dose oral corticosteroids, and biologic agents for severe allergic or severe Type 2 asthma (*GINA 2021*).
  - Tiotropium by mist inhaler (age ≥ 6 years) may be considered as an add-on controller option in patients with persistently uncontrolled asthma despite use of a medium or high dose ICS/LABA; alternatively a triple combination ICS/LABA/LAMA inhaler can be used in patients ≥18 years of age. In step 4 therapy, it is recommended under track 2 (less preferred), and at step 5, it is recommended as one of several preferred add-on treatment options.
  - The 2021 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 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. Vaccination for COVID-19 is recommended for people with asthma (*GINA 2021*).
- Recommendations have also been made for stepping down therapy among patients with asthma that has been well-controlled for an extended period of time. Reasons for stepping down therapy include reducing excess drug exposure (and potential adverse effects), improving adherence by simplifying a treatment regimen, and reducing cost (*Chipps et al 2019, GINA 2021*). Prior to stepping down therapy, patients need to be assessed for risk of asthma exacerbation, lung function, symptom control, and adherence to current therapy. Recommendations for step-to-step reductions include decreasing dose or frequency of ICS with concurrent use of LABA, switching to an oral agent (ie, an LTRA such as montelukast), or use of ICS-formoterol as needed, depending on the current step of therapy. During step-down therapy, patients need to be evaluated for asthma symptoms, use of rescue medications, and lung function.
- 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 2021, NHLBI 2007*).
  - A meta-analysis of 16 randomized controlled trials evaluating the use of a ICS/LABA 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 (rate ratio, 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 ICS/LABA and in comparison with ICS controller therapy only.
- 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 2021 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. Historically, "asthma-COPD overlap" was addressed, but they are now recognized as separate unique disease states with some similar signs and symptoms. Key recommendations from the GOLD guidelines are as follows (*GOLD 2021*):
  - 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 or ICS/LABA.
    - Increases FEV_1 and reduces symptoms compared to monotherapy.
- Long-term monotherapy with ICS is not recommended. Long-term treatment with ICS may be considered in association with LABAs for patients with a history of exacerbations despite treatment with long-acting bronchodilators. 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 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.

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

- American Thoracic Society clinical practice guidelines recommend the following pharmacologic treatment for patients with COPD (Strong to conditional Strength of Recommendation/moderate Level of Evidence) (*Nici et al 2020*)

- Those who complain of dyspnea or exercise intolerance: LAMA/LABA combination therapy is recommended over LABA or LAMA monotherapy.
- Those who complain of dyspnea or exercise intolerance despite dual therapy with LAMA/LABA: use of triple therapy with LAMA/LABA/ICS is recommended over dual therapy with LAMA/LABA in those patients with a history of ≥ 1 exacerbation(s) in the past year requiring antibiotics or oral steroids or hospitalization.
- Those receiving triple therapy (LAMA/LABA/ICS): it is suggested that the ICS can be withdrawn if the patient has had no exacerbations in the past year.
- No recommendation is made for or against ICS as an additive therapy to long-acting bronchodilators in patients with COPD and blood eosinophilia, except for those patients with a history of ≥ 1 exacerbation(s) in the past year requiring antibiotics or oral steroids or hospitalization, for whom ICS as an additive therapy is suggested.

- 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, and Stiolto Respimat are contraindicated without ICS in patients with asthma.
- Anoro Ellipta, Bevespi Aerosphere, Duaklir Pressair, and Stiolto Respimat 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), 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, and Stiolto Respimat 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 events 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 events were very similar between groups. In a 48-week safety trial, most adverse events 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 [LAMA/LABA/ICS])

- Contraindications with Trelegy Ellipta include:
  - Severe hypersensitivity to milk proteins or any ingredients in the formulation.
  - Primary treatment of status asthmaticus or acute episodes of COPD or asthma requiring intensive measures

- Similar to other combination agents for COPD (and/or asthma), Trelegy Ellipta and Breztri Aerosphere have a number of additional warnings and precautions including:
  - 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 events with Trelegy Ellipta include:
  - COPD (incidence ≥ 1%): upper respiratory tract infection, pneumonia, bronchitis, oral candidiasis, headache, back pain, arthralgia, influenza, sinusitis, pharyngitis, rhinitis, dysgeusia, constipation, urinary tract infection, diarrhea, gastroenteritis, oropharyngeal pain, cough, and dysphonia.
  - Asthma (incidence ≥ 2%): pharyngitis/nasopharyngitis, upper respiratory tract infection/viral upper respiratory tract infection, bronchitis, respiratory tract infection/viral respiratory tract infection, sinusitis/acute sinusitis, urinary tract infection, rhinitis, influenza, headache, and back pain.
- The most common adverse events (incidence ≥ 2%) with Breztri Aerosphere include upper respiratory tract infection, pneumonia, back pain, oral candidiasis, influenza, muscle spasm, urinary tract infection, cough, sinusitis, and diarrhea.

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
AirDuo Digihaler (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
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

Drug	Available Formulations	Route	Usual Recommended Frequency
Stiolto Respimat (tiotropium bromide/olodaterol)	Inhalation spray	Inhalation	Once daily
Triple combination			
Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol)	Inhalation powder	Inhalation	Once daily
Breztri Aerosphere (glycopyrrolate/formoterol/budesonide)	Inhalation spray	Inhalation	2 times daily

*The AirDuo Digihaler contains a built-in electronic module which detects, records, and stores data on inhaler events, including peak inspiratory flow rate (L/minute), for transmission to mobile App. Use of the App is not required for administration of medication to the patient.

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 and Breztri Aerosphere are fixed-dose “triple therapy” combination inhalers combining a LAMA, a LABA, and an ICS. Both agents provide an alternative to the use of multiple inhalers for patients with COPD in whom triple therapy is indicated; Trelegy Ellipta is also an option for adult patients with asthma who require triple therapy.
- 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. Triple combination inhalers are a treatment option for patients with persistent symptoms or exacerbations despite Step 4 therapy.
  - 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. Use of daily and as-needed combination ICS-formoterol is the preferred treatment approach for adults and adolescents.
- The 2020 focused update of the NAEPP guideline recommends the use of ICS-formoterol in a single inhaler used as both a daily controller and reliever therapy in moderate to severe persistent asthma.
- 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 maintenance and as-needed ICS/formoterol combination for asthma treatment.
  - Administration instructions and inhalation devices vary among products and should be considered in product selection.

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Publication Date: June 30, 2021

OPTUMRx

Therapeutic Class Overview
Respiratory Corticosteroids

INTRODUCTION

- Inhaled corticosteroids (ICSs) are approved by the Food & Drug Administration (FDA) for the treatment of asthma. These agents are effective in the treatment of asthma due to their wide range of inhibitory activities against multiple cell types (eg, mast cells and eosinophils) and mediators (eg, histamine and cytokines) involved in the asthmatic response.
- 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 2019, asthma affected an estimated 20 million adults and 5.1 million children in the United States (*Centers for Disease Control and Prevention 2021, National Heart, Lung, and Blood Institute [NHLBI] Web site*).
- 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 (*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] 2021*).
  - Control medications include:
    - Corticosteroids (ICSs, or oral corticosteroids for severe exacerbations)
    - Long-acting β-agonists (LABAs)
    - Leukotriene receptor antagonists (LTRAs) in select patients
    - Methylxanthines (ie, theophylline) in select patients
    - 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 high dose ICS/LABA
  - Quick-relief/reliever medications include:
    - Short-acting β-agonists (SABAs) for relief of acute symptoms and prevention of exercise-induced bronchospasm
    - ICS-formoterol for relief of acute symptoms and if needed before exercise
    - 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 2021, Fasenra 2021, Nucala 2020*) or with oral corticosteroid dependent asthma (*Dupixent prescribing information 2021*). Additionally, tiotropium, long used for chronic obstructive pulmonary disease (COPD), is FDA-approved for the maintenance treatment of asthma (*Spiriva Respimat prescribing information 2020*).
- ICSs are the most effective and most commonly recommended long-term control medications used for the treatment of asthma. The updated 2021 GINA Report on Global Strategy for Asthma Management and Prevention recommends initial treatment based on a patient's presenting symptoms. The preferred track for Step 1 and Step 2 therapy in adults and adolescents is low dose combination ICS-formoterol as needed. (*GINA 2021*).
- LABAs should not be used as monotherapy for the management of asthma due to an increased risk for serious adverse events including death; however, they are part of combination ICS-formoterol therapy and can be used as adjunctive therapy in patients who are not adequately controlled with an ICS alone (*GINA 2021, NHLBI 2007*).
- The preferred reliever medication recommended by GINA is low dose ICS-formoterol. SABA-only treatment is not recommended for the treatment of asthma in adults or adolescents. Children can be managed with as needed SABA or ICS-formoterol. (*GINA 2021*).

- 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 but are not recommended. An additional controller option is LTRAs. Add-on options for severe asthma include tiotropium, low dose macrolides, and biologic agents for severe allergic or severe Type 2 asthma (*GINA 2021*).
- This review includes single-agent ICSs (ie, respiratory corticosteroids). While respiratory corticosteroids are commonly available in combination with other bronchodilators such as LABAs, combination agents are not included within this review. Although inflammation is also a component of COPD pathogenesis, no single-entity ICS has been FDA-approved for use in COPD (*Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2021*).
- Of note, QVAR RediHaler, a breath-actuated inhalation formulation of beclomethasone dipropionate manufactured by Teva Pharmaceuticals, was approved by the FDA in August 2017 and was launched in February 2018, replacing the previous QVAR product (*Teva Pharmaceuticals 2018*). Additionally, in January 2018, Mylan informed the FDA of the discontinuation of Aerospan (flunisolide) due to business reasons (*FDA Drug Shortages Web site*). ArmonAir RespiClick (fluticasone propionate) was also discontinued in 2018.
- Medispan class: Steroid Inhalants

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Alvesco (ciclesonide) inhalation aerosol	-
ArmonAir Digihaler (fluticasone propionate) dry powder inhaler	-
Arnuity Ellipta (fluticasone furoate) dry powder inhaler	-
Asmanex HFA (mometasone furoate) inhalation aerosol	-
Asmanex Twisthaler (mometasone furoate) dry powder inhaler	-
Flovent Diskus (fluticasone propionate) dry powder inhaler	-
Flovent HFA (fluticasone propionate) inhalation aerosol	-
Pulmicort Flexhaler (budesonide) dry powder inhaler	-
Pulmicort Respules (budesonide) suspension for nebulization	✔
QVAR RediHaler (beclomethasone dipropionate) inhalation aerosol	-

(*Drugs@FDA 2021, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drug	Maintenance treatment of asthma as prophylactic therapy
Alvesco (ciclesonide) inhalation aerosol	✔ (age ≥ 12 years)
ArmonAir Digihaler (fluticasone propionate) dry powder inhaler	✔ (age ≥ 12 years)
Arnuity Ellipta (fluticasone furoate) dry powder inhaler	✔ (age ≥ 5 years)
Asmanex HFA (mometasone furoate) inhalation aerosol	✔ (age ≥ 5 years)
Asmanex Twisthaler (mometasone furoate) dry powder inhaler	✔ (age ≥ 4 years)
Flovent Diskus (fluticasone propionate) dry powder inhaler; Flovent HFA (fluticasone propionate) inhalation aerosol	✔ (age ≥ 4 years)
Pulmicort Flexhaler (budesonide) dry powder inhaler	✔ (age ≥ 6 years)
Pulmicort Respules (budesonide) suspension for nebulization	✔ (age 12 months to 8 years)
QVAR RediHaler (beclomethasone dipropionate) inhalation aerosol	✔ (age ≥ 4 years)

(*Prescribing information: Alvesco 2020, ArmonAir Digihaler 2020, Arnuity Ellipta 2020, Asmanex HFA 2020, Asmanex Twisthaler 2021, Flovent Diskus 2020, Flovent HFA 2021, Pulmicort Flexhaler 2019, Pulmicort Respules 2019, QVAR RediHaler 2021*)

- 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

- Several trials demonstrate the efficacy of ICSs compared to placebo for preventing exacerbations, improving forced expiratory volume (FEV_1) and peak expiratory flow (PEF), improving symptoms, reducing use of SABAs, reducing oral corticosteroid requirements, and/or improving quality of life (*Amar et al 2017, Baker et al 1999, Bleecker et al 2014, Fish et al 2000, Karpel et al 2007, Lotvall et al 2014, Meltzer et al 2009, Meltzer et al 2012, Nathan et al 2010, Nelson et al 1999, Rowe et al 1999, Sheffer et al 2005*).
- Numerous head-to-head trials have compared various ICS regimens to one another. Several clinical trials demonstrated no significant differences between different ICSs:
  - A trial comparing budesonide 750 mcg twice daily to fluticasone propionate 375 mcg twice daily in children 5 to 16 years of age demonstrated no statistically significant differences between treatment groups in PEF, symptom scores, physician/patient/parent assessment of efficacy, or frequency of exacerbations (*Fitzgerald et al 1998*).
  - A trial comparing fluticasone propionate 250 mcg twice daily to various doses of mometasone furoate twice daily demonstrated comparable efficacy between fluticasone propionate and mometasone furoate for improvement in FEV_1, forced expiratory flow at 25 to 75% ($FEF_{25\ to\ 75\%}$) of forced vital capacity (FVC), and PEF (*O'Connor et al 2001*).
  - A trial comparing fluticasone propionate 250 mcg twice daily to mometasone furoate 400 mcg every evening demonstrated no significant differences between groups in FEV_1, FVC, PEF, albuterol use, or asthma symptom scores (*Wardlaw et al 2004*).
  - A trial comparing fluticasone propionate 500 mcg twice daily to mometasone furoate 500 mcg twice daily demonstrated no significant differences in PEF, FEV_1, symptom scores, or rescue albuterol use (*Harnest et al 2008*).
  - A trial comparing beclomethasone dipropionate 168 mcg twice daily to mometasone furoate 100 or 200 mcg twice daily demonstrated no significant differences in FEV_1, PEF, asthma symptoms, nocturnal awakenings, or albuterol use (*Nathan et al 2001*). The beclomethasone product evaluated in the trial is no longer commercially available.
  - A trial comparing ciclesonide 160 mcg every evening to budesonide 400 mcg every evening in children aged 6 to 11 years demonstrated no significant differences between groups in FEV_1, morning PEF, asthma symptom score, or need for rescue medication (*Von Berg et al 2007*).
  - A trial comparing fluticasone furoate 100 mcg daily to placebo also included fluticasone propionate 250 mcg twice daily as a reference arm; comparable results were seen between fluticasone propionate and fluticasone furoate for FEV_1, percentage of rescue-free days, and severe asthma exacerbations (*Lotvall* et al 2014).
  - A trial comparing fluticasone furoate 200 mcg daily to fluticasone propionate 500 mcg twice daily demonstrated that fluticasone furoate was non-inferior to fluticasone propionate based on effect on FEV_1 (*O'Byrne et al 2014*).
- Overall, comparative trials have not conclusively demonstrated one ICS to be significantly more effective than another. However, in several individual trials, significant differences in some endpoints were observed. For example, comparative trials have demonstrated:
  - In a trial comparing fluticasone propionate 200 mcg twice daily to budesonide 400 mcg twice daily in children 4 to 12 years of age, patients treated with fluticasone propionate had superior results for mean morning PEF compared to patients receiving budesonide (271 ± 82 and 259 ± 75 L/minute, respectively, p = 0.002) (*Ferguson et al 1999*).
  - In a trial comparing budesonide 200 mcg twice daily to fluticasone propionate 100 mcg twice daily in children 6 to 9 years of age, effectiveness measures were comparable between groups; however, the mean growth velocity was significantly greater in the fluticasone propionate group (5.5 cm/year) compared to the budesonide group (4.6 cm/year) (*Ferguson et al 2007*).
    - A 2019 Cochrane review that included the 2007 study by Ferguson et al in addition to 5 other studies also concluded that fluticasone may have a less suppressive effect on growth when compared to budesonide. When pooling data from 2 studies, the mean difference in change in height over a period from 20 weeks to 1 year was 0.97 cm (95% confidence interval [CI], 0.62 to 1.32); however, there was no significant difference in linear growth velocity with comparing the 2 agents (mean difference, 0.39 cm/year; 95% CI, -0.94 to 1.73) (*Axelsson et al 2019*).

- A trial comparing beclomethasone dipropionate 168 or 336 mcg twice daily to fluticasone propionate 88 to 220 mcg twice daily demonstrated greater improvement in FEV_1 for fluticasone propionate-treated patients than beclomethasone dipropionate-treated patients. At endpoint, mean FEV_1 values in the low- and medium-dose fluticasone propionate groups improved by 0.31 (14%) and 0.36 L (15%), respectively, compared to improvements of 0.18 (8%) and 0.21 L (9%) in the low-and medium-dose beclomethasone dipropionate treatment groups, respectively. Improvements were also superior in the fluticasone propionate group for $FEF_{25\ to\ 75\%}$, FVC, morning PEF, and use of albuterol (*Raphael et al 1999*). Of note, the beclomethasone product evaluated in the trial is no longer commercially available.
- In a trial comparing budesonide 400 mcg twice daily to various doses of mometasone furoate twice daily, the FEV_1 was significantly improved from baseline in the mometasone furoate 200 and 400 mcg treatment groups compared to the budesonide treatment group. In addition, morning wheezing scores were significantly improved in the mometasone furoate 400 mcg twice daily group compared to the budesonide group, and patients treated with mometasone furoate 200 or 400 mcg twice daily required significantly less albuterol compared to patients treated with budesonide (*Bousquet et al 2000*).
- In a trial comparing budesonide 400 mcg once daily to mometasone furoate 440 mcg once daily, the mometasone furoate group had superior results for the percent change in FEV_1, $FEF_{25\ to\ 75\%}$, FVC, evening asthma symptom scores, albuterol use, percentage of asthma symptom-free days, and physician-evaluated response to therapy (*Corren et al 2003*).

- Meta-analyses have evaluated ciclesonide and mometasone furoate compared to other ICS agents:
  - A meta-analysis comparing ciclesonide to other ICS agents (budesonide or fluticasone propionate) in children with asthma demonstrated no significant differences between ciclesonide and budesonide on asthma symptom scores, symptom-free days, rescue medication-free days, or exacerbations. When ciclesonide and fluticasone propionate were compared, no significant differences were found in asthma symptoms or rescue medication-free days. One of the 4 studies of ciclesonide versus fluticasone propionate demonstrated a higher incidence of exacerbations with ciclesonide; however, the dose of fluticasone propionate was relatively higher in this study (*Kramer et al 2013*).
  - A meta-analysis comparing mometasone furoate to other ICS agents (beclomethasone dipropionate [QVAR formulation which is no longer marketed], budesonide, or fluticasone propionate) in patients with moderate to severe asthma demonstrated superior results with mometasone furoate for pulmonary function measures (FEV_1, FVC, $FEF_{25\ to\ 75\%}$, and morning PEF). Mometasone furoate was also shown to be superior on some symptom indices (morning difficulty breathing scores and rescue medication use), but not others (morning wheeze scores, morning cough scores, and nocturnal awakenings). However, based on the pooled results for the comparative arms, it is not possible to make conclusions about the relative efficacy of mometasone furoate compared to other individual agents (*Yang et al 2012*).
- Fluticasone propionate has also been compared to a LTRA, montelukast, in several randomized controlled trials in both adults and children. Although differences were not detected for all endpoints, in general these trials demonstrated superior outcomes for fluticasone propionate for FEV_1, symptom-free days, asthma symptom scores, nighttime awakenings, rescue albuterol use, physician's global assessments, frequency of exacerbations, and/or quality of life measures (*Busse et al 2001, Garcia et al 2005, Sorkness et al 2007, Szefler et al 2005, Zeiger et al 2006*).
- The safety and efficacy of QVAR RediHaler were evaluated in 1858 patients with persistent symptomatic asthma, including two 12-week and one 6-week Phase 3 confirmatory trials in patients ≥12 years of age, and one 12-week Phase 3 confirmatory trial in patients 4 to 11 years of age (*Amar et al 2016, Hampel et al 2017, Vandewalker et al 2017*).
  - The first 12-week Phase 3 trial (N = 270) was a randomized, double-blind, placebo-controlled trial study that compared QVAR RediHaler 40 mcg and 80 mcg twice daily versus placebo in patients who previously used low-dose ICS or non-corticosteroid therapy. For the primary endpoint of change from baseline in trough FEV_1 area under the effect curve 0 to 12 weeks ($AUEC_{0\text{-}12wk}$), a significantly greater improvement was seen with QVAR RediHaler 80 mcg and 160 mcg as compared to placebo (difference of least square means [LSM] from placebo of 0.124 L and 0.116 L, respectively). Both doses of QVAR RediHaler demonstrated improvements in asthma control as supported by significantly greater improvements in morning PEF and a reduction in asthma symptoms versus placebo (*Hampel et al 2017*).
  - The second 12-week Phase 3 trial (N = 532) was a randomized, double-blind, placebo-controlled trial that compared QVAR RediHaler 160 mcg and 320 mcg twice daily versus QVAR 160 mcg and 320 mcg twice daily and placebo in patients who previously used mid- to high-dose ICS or ICS/LABA therapy. The baseline-adjusted trough morning

FEV_1 $AUEC_{0\text{-}12wk}$ increased in all active treatment groups versus placebo, although the differences were not significant. Overall, the safety profiles of QVAR and QVAR RediHaler were comparable (*Amar et al 2016*).
  - A 6-week randomized, double-blind, parallel-group, placebo-controlled trial compared QVAR RediHaler 160 mcg and 320 mcg twice daily versus placebo, with a QVAR 160 mcg twice daily reference arm, in patients previously using non-corticosteroid, ICS ± LABA, or combination asthma therapy. For the primary endpoint of change from baseline in trough FEV_1 $AUEC_{0\text{-}6wk}$, a significantly greater improvement was seen with QVAR RespiClick 160 mcg and 320 mcg versus placebo (difference of LSM from placebo of 0.144 L and 0.150 L, respectively). Both doses of QVAR RediHaler demonstrated improvements in asthma control as supported by significantly greater improvements in morning PEF, reduced rescue medication use, and a reduction in asthma symptoms versus placebo, with similar results demonstrated with QVAR 160 mcg treatment (*Ostrom et al 2018*).
  - A 12-week randomized, double-blind, parallel-group, placebo-controlled trial in pediatric patients compared QVAR RediHaler 40 mcg and 80 mcg twice daily versus placebo in patients who previously used non-corticosteroid or low-dose ICS ± LABA therapy. Treatment with the QVAR RediHaler did not demonstrate a statistically significant difference versus placebo for the primary endpoint of FEV_1 $AUEC_{0\text{-}12wk}$; however, the change in weekly average of daily morning PEF was 11.3 L/min and 8.5 L/min for the 80 mcg/day and 160 mcg/day doses of QVAR RediHaler, respectively, with nominal significance (*Vandewalker et al 2017*).
- The FDA approval of ArmonAir Digihaler was based on trials of the fluticasone propionate (ArmonAir RespiClick) dry powder inhaler. The safety and efficacy of ArmonAir RespiClick was evaluated in 2130 patients with asthma, including two 12-week Phase 3 confirmatory trials (*ArmonAir Digihaler prescribing information 2020*).
  - The first 12-week Phase 3 trial (N = 647) was a randomized, double-blind, placebo-controlled trial in patients > 12 years of age previously treated with low-dose or medium-dose ICS or ICS/LABA combinations. Patients were randomized to 1 of 5 different groups: placebo, fluticasone propionate 50 mcg, fluticasone propionate 100 mcg, fluticasone propionate/salmeterol 50/12.5 mcg, or fluticasone propionate/salmeterol 100/12.5 mcg. Each treatment was administered twice daily. The efficacy of all active treatment groups was superior to placebo in terms of change from baseline in trough FEV_1 and the standardized baseline-adjusted area under the effect curve for FEV_1 from time 0 to 12 hours after the dose (FEV_1 $AUEC_{0\text{–}12h}$). Change from baseline in trough morning PEF was greater with fluticasone propionate 100 mcg versus placebo, but a significant difference was not seen for fluticasone propionate 50 mcg versus placebo. Change from baseline in total daily asthma symptom scores was greater for all active treatment groups versus placebo (*Raphael et al 2018*).
  - The second 12-week Phase 3 trial (N = 728) was a randomized, double-blind, placebo-controlled trial in patients > 12 years of age previously treated with an ICS ± LABA. Patients were randomized to 1 of 5 different groups: placebo, fluticasone propionate 100 mcg, fluticasone propionate 200 mcg, fluticasone propionate/salmeterol 100/12.5 mcg, or fluticasone propionate/salmeterol 200/12.5 mcg. Each treatment was administered twice daily. All active treatment groups were superior to placebo in terms of change from baseline in trough FEV_1 and the standardized baseline-adjusted area under the effect curve for FEV_1 from time 0 to 12 hours after the dose (FEV_1 $AUEC_{0\text{–}12h}$). Daily asthma symptoms scores and trough morning PEF were also improved for all active treatment groups versus placebo (*Sher et al 2017*).

CLINICAL GUIDELINES

- 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, LTRAs, 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.

- A 2020 focused update of the 2007 NAEPP guideline provided updated recommendations on the use of intermittent ICSs and the use of LAMAs as add-on therapy (*Cloutier et al 2020*). The update did not address use of ICS-formoterol as an option for intermittent asthma. For mild, persistent asthma, the use of as needed concomitant ICS and SABA was added as an alternative to daily low-dose ICS with as needed SABA for management of mild, persistent asthma. Additionally, ICS-formoterol in a single inhaler used as both a daily controller and reliever therapy in moderate to severe persistent asthma was recommended over the use of a higher-dose ICS/LABA therapy with a SABA as needed. Finally, the addition of a LAMA can be considered for patients who have uncontrolled, persistent asthma despite ICS/LABA therapy.

- The 2021 GINA report also provides a stepwise approach to asthma management. Treatment recommendations are based on 2 tracks stratified by the choice of reliever. Track 1 includes ICS-formoterol as the reliever, and it is the preferred approach for most patients because it reduces the risk of severe exacerbations. Track 2 uses a SABA as the reliever. Treatment in adults and adolescents with a SABA only is not recommended. For Step 1 and 2 therapy, the preferred (track 1) approach is low dose ICS-formoterol as needed for symptom relief or if needed for exercise for patients with mild asthma. For Step 3, the preferred treatment is low dose ICS-formoterol as both maintenance and reliever therapy. Preferred therapy for Step 4 is a medium dose ICS-formoterol with as needed low dose ICS-formoterol as the reliever therapy. For patients with persistent symptoms or exacerbations despite Step 4 therapy, referral to a specialist with expertise in severe asthma management is recommended. Treatment options may include any of the following options: high dose ICS-LABA therapy, add-on LAMA (tiotropium or triple combination [ICS/LABA/LAMA] inhaler), azithromycin, low-dose oral corticosteroids, and biologic agents for severe allergic or severe Type 2 asthma (*GINA 2021*).
  - The 2021 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 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. Vaccination for COVID-19 is recommended for people with asthma (*GINA 2021*).
- Recommendations have also been made for stepping down therapy among patients with asthma that has been well-controlled for an extended period of time. Reasons for stepping down therapy include reducing excess drug exposure (and potential adverse effects), improving adherence by simplifying a treatment regimen, and reducing cost (*Chipps et al 2019, GINA 2021*). Prior to stepping down therapy, patients need to be assessed for risk of asthma exacerbation, lung function, symptom control, and adherence to current therapy. Recommendations for step-to-step reductions include decreasing dose or frequency of ICS with concurrent use of LABA, switching to an oral agent (ie, an LTRA such as montelukast), or use of ICS-formoterol as needed, depending on the current step of therapy. During step-down therapy, patients need to be evaluated for asthma symptoms, use of rescue medications, and lung function.
- 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*).

SAFETY SUMMARY

- ICS agents are generally contraindicated in patients with hypersensitivity to components of the product. ArmonAir Digihaler, Arnuity Ellipta, Asmanex Twisthaler, Flovent Diskus, and Pulmicort Flexhaler are also contraindicated in patients with hypersensitivity to milk proteins. All ICSs are contraindicated as primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.
- ICSs have no boxed warnings. Key warnings and precautions are similar among products, and generally include:
  - The occurrence of *Candida albicans* infections in the mouth and pharynx
  - Eosinophilic conditions and Churg-Strauss Syndrome
  - Glaucoma, increased intraocular pressure, and cataracts
  - Hypercorticism and adrenal suppression
  - The risk of oral corticosteroid withdrawal or adrenal insufficiency in patients transitioning from oral to ICS agents
  - Paradoxical bronchospasm
  - Reduction in bone mineral density with long-term use
  - Reduction in growth velocity in pediatric patients

- Adverse effects are similar among products. Common adverse effects include allergic rhinitis, back pain, conjunctivitis, cough, bronchitis, diarrhea, dyspepsia, dysmenorrhea, dysphonia, ear infections, epistaxis, fever, gastrointestinal discomfort, gastroenteritis, headache, increased asthma symptoms, musculoskeletal pain, nasal congestion, nasopharyngitis/pharyngitis, nausea and vomiting, oral candidiasis, otitis media, pharyngolaryngeal pain, rash, sinusitis, throat irritation, and upper respiratory infection.
- Asmanex HFA and Twisthaler, ArmonAir Digihaler, Arnuity Ellipta, Flovent Diskus and HFA, and Pulmicort Flexhaler and Respules carry warnings regarding coadministration with strong inhibitors of cytochrome P450 3A4 (eg, ketoconazole, itraconazole, nefazodone); coadministration with these agents may increase systemic corticosteroid exposure.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Alvesco (ciclesonide)	Inhalation aerosol (HFA): 80 or 160 mcg per actuation	Inhalation	Patients treated previously with only bronchodilators: initial, 80 mcg twice daily; maximum, 160 mcg twice daily Patients treated previously with an ICS: initial, 80 mcg twice daily; maximum, 320 mcg twice daily Patients treated previously with oral corticosteroids: initial, 320 mcg twice daily; maximum, 320 mcg twice daily	Not indicated for children < 12 years of age.
ArmonAir Digihaler (fluticasone propionate)	Dry powder inhaler: 55, 113, or 232 mcg per actuation	Inhalation	Patients not previously on an ICS, with less severe asthma: initial, 55 mcg twice daily; maximum, 232 mcg twice daily Patients with greater asthma severity: initial, 113 to 232 mcg twice daily; maximum, 232 mcg twice daily Patients switching from another ICS: Starting dose should be based on previous asthma drug therapy and disease severity, either 55, 113, or 232 mcg twice daily For patients who do not respond adequately to the starting dose after 2 weeks, higher dosages may provide additional control.	Not indicated in children < 12 years of age. The ArmonAir Digihaler is a digital dry powder device with built-in sensors to detect when it is used and to measure inspiratory flow. It is designed to be used with a companion mobile app.
Arnuity Ellipta (fluticasone furoate)	Dry powder inhaler: 50, 100 or 200 mcg per actuation	Inhalation	Patients not previously on an ICS: initial, 100 mcg once daily; maximum, 200 mcg once daily	Age 5 to 11 years: 50 mcg once daily

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Patients treated previously with an ICS: Starting dose should be based on previous asthma drug therapy and disease severity, 100 mcg or 200 mcg once daily For patients ≥ 12 years of age who do not respond adequately to the starting dose after 2 weeks, higher dosages may provide additional control.	
Asmanex HFA (mometasone furoate)	Inhalation aerosol (HFA): 50, 100, or 200 mcg per actuation	Inhalation	Patients not previously on an ICS: initial, 100 mcg, 2 inhalations twice daily; maximum 200 mcg, 2 inhalations twice daily Patients treated previously with oral corticosteroids: 200 mcg, 2 inhalations twice daily For patients ≥ 12 years of age who do not respond adequately to the starting dose after 2 weeks, higher dosages may provide additional control.	Children 5 to 11 years of age: 50 mcg, 2 inhalations twice daily
Asmanex Twisthaler (mometasone furoate)	Dry powder inhaler: 110 or 220 mcg per actuation	Inhalation	Patients treated previously with bronchodilators alone or an ICS: initial, 220 mcg once daily in the evening; maximum, 440 mcg administered as once daily in the evening or as 220 mcg twice daily Patients treated previously with oral corticosteroids: initial, 440 mcg twice daily; maximum, 880 mcg per day For patients ≥ 12 years of age who do not respond adequately to the starting dose after 2 weeks, higher dosages may provide additional control.	Children 4 to 11 years of age: initial, 110 mcg once daily in the evening; maximum, 110 mcg per day. When administered once daily, should be taken only in the evening.
Flovent Diskus (fluticasone propionate)	Dry powder inhaler: 50, 100, or 250 mcg per actuation	Inhalation	Patients who are not on an ICS: initial, 100 mcg twice daily; maximum, 1000 mcg twice daily For other patients and those who do not respond adequately to the starting dose after 2 weeks, higher	Children 4 to 11 years of age: initial, 50 mcg twice daily; maximum, 100 mcg twice daily

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			dosages may provide additional control.	
Flovent HFA (fluticasone propionate)	Inhalation aerosol (HFA): 44, 110, or 220 mcg per actuation	Inhalation	Patients who are not on an ICS: initial, 88 mcg twice daily; maximum, 880 mcg twice daily For other patients and those who do not respond adequately to the starting dose after 2 weeks, higher dosages may provide additional control.	Children 4 to 11 years of age: 88 mcg twice daily
Pulmicort Flexhaler (budesonide)	Dry powder inhaler: 90 or 180 mcg per actuation	Inhalation	Patients ≥ 18 years of age: initial, 360 mcg twice daily (selected patients can be initiated at 180 mcg twice daily); maximum, 720 mcg twice daily For patients who do not respond adequately to the starting dose after 1 to 2 weeks, higher dosages may provide additional control.	Children 6 to 17 years of age: initial, 180 mcg twice daily (selected patients can be initiated at 360 mcg twice daily); maximum, 360 mcg twice daily
Pulmicort Respules (budesonide)	Suspension for nebulization: 0.25 mg/2 mL, 0.5 mg/2 mL, or 1 mg/2 mL	Inhalation	Children 12 months to 8 years of age treated previously with only bronchodilators: initial, 0.5 mg total daily dose administered either once daily or divided into 2 doses; maximum, 0.5 mg total daily dose Children 12 months to 8 years of age treated previously with an ICS: initial, 0.5 mg total daily dose administered either once daily or divided into 2 doses; maximum, 1 mg total daily dose Children 12 months to 8 years of age treated previously with an oral corticosteroid: initial, 1 mg total daily dose administered either as 0.5 mg twice daily or 1 mg once daily; maximum, 1 mg total daily dose	Not indicated in adults.
QVAR RediHaler (beclomethasone dipropionate)	Inhalation aerosol: 40 or 80 mcg per actuation	Inhalation	Patients ≥ 12 years of age, not previously on an ICS: 40 to 80 mcg twice daily; maximum, 320 mcg twice daily Patients ≥ 12 years of age, previously treated with an ICS: initial, 40, 80, 160, or 320 mcg	Children 4 to 11 years of age: initial, 40 mcg twice daily; maximum, 80 mcg twice daily

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			twice daily (dependent on prior asthma therapy and asthma severity); maximum, 320 mcg twice daily For patients who do not respond adequately to the starting dose after 2 weeks, higher dosages may provide additional control.	

See the current prescribing information for full details.

CONCLUSION

- ICS agents are considered the cornerstone of drug therapy for long-term asthma control. Consensus guidelines emphasize the important role of ICS agents as controller medications. The NHLBI and GINA asthma guidelines agree that ICSs are the preferred treatment for therapy in children and adults with asthma to prevent exacerbation and control symptoms. The 2021 GINA Global Strategy for Asthma Management and Prevention report recommends initial treatment based on a patient's presenting symptoms. Treatment recommendations are based on 2 tracks stratified by the choice of reliever. Track 1 includes ICS-formoterol as the reliever, and it is the preferred approach for most patients because it reduces the risk of severe exacerbations. For Step 1 and 2 therapy, the preferred (track 1) approach is low dose ICS-formoterol as needed. Step-wise adjustments to the ICS dose are recommended based on control of asthma symptoms.
- Although individual head-to-head clinical trials have demonstrated some differences among ICS agents on certain endpoints, results have not conclusively demonstrated one agent to be significantly more effective than another in the management of asthma. Contraindications, warnings/precautions, and adverse effects are also similar among products.
- There are differences among products with respect to their available formulations, dosing schedule, and use in the pediatric population. Notably, some products are available as dry powder formulations, while others are available as inhalation aerosols. Most ICSs are dosed twice daily; however, Arnuity Ellipta is administered once daily. Asmanex Twisthaler and Pulmicort Respules may be administered either once or twice daily. ArmonAir Digihaler offers built-in sensors and connects with a companion mobile application that allows tracking and information on usage and inspiratory flow rates.
  - The appropriate choice of an ICS agent for an individual patient may depend on ease of use of the ICS device, dosing schedule, and contraindications such as hypersensitivity to milk proteins.
  - The inhaler device is an important component of treatment, and the patient's response, preference, and ability to use the inhaler device should be considered in product selection.

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Publication Date: June 30, 2021