OPTUMRx®

Silver State Scripts Board Meeting

DECEMBER 9, 2021

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Agenda

NOTICE OF PUBLIC MEETING – SILVER STATE SCRIPTS BOARD

Date of Posting:	November 3, 2021
Date of Meeting:	Thursday, December 9, 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:	Teams Meeting OR https://tinyurl.com/SSSB-Dec-2021 The physical location for this meeting which is open to the public is at: JW Marriot Las Vegas Resort 221 N Rampart Blvd Las Vegas, NV 89145 (702) 869-7777 **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: 874 921 666#

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 September 23, 2021.
b. Status Update by DHCFP.

4. Proposed New Drug Classes

a. **For Possible Action:** Discussion and possible adoption of Cardiovascular Agents – Miscellaneous Cardiac 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.

b. **For Possible Action:** Discussion and possible adoption of Electrolytic and Renal Agents – Potassium Removing 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.

c. **For Possible Action:** Discussion and possible adoption of Neurological Agents – Movement Disorders.

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

a. **For Possible Action:** Discussion and possible adoption of Genitourinary Agents – Bladder Antispasmodics.

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

b. **For Possible Action:** Discussion and possible adoption of Hormones and Hormone Modifiers - Anti-Hypoglycemic 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.

c. **For Possible Action:** Discussion and possible adoption of Neurological Agents - Anti-Migraine Agents - Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists.

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 Ophthalmic Agents - Ophthalmic for Dry Eye Disease.

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 Psychotropic Agents - Antipsychotics - Atypical Antipsychotics, 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.

f. **For Possible Action:** Discussion and possible adoption of Psychotropic Agents - Antipsychotics - Atypical Antipsychotics, 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.

g. **For Possible Action:** Discussion and possible adoption of Toxicology Agents – Opiate Antagonists.

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

a. **For Possible Action:** Discussion and possible adoption of Analgesics - Analgesic/Miscellaneous - Neuropathic Pain/Fibromyalgia 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.

b. **For Possible Action:** Discussion and possible adoption of Cardiovascular Agents - Antihypertensive Agents - Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors).

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

7. Established Drug Classes

a. **For Possible Action:** Discussion and possible action of Hormones and Hormone Modifiers - Antidiabetic Agents - Incretin Mimetics.

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.

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. 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 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 three 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 2022

Date	Time	South Nevada Location	North Nevada Location
March 24, 2022	1:00 PM	TBD	None
June 23, 2022	1:00 PM	TBD	None

Web References

Preferred Drug List:

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

Medicaid Services Manual (MSM) Chapter 1200:

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

Silver State Scripts Board Bylaws:

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

The Division of Health Care Financing and Policy Public Notices:

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

Definition of "Therapeutic Alternative"

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

Standard Preferred Drug List Exception Criteria

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

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

Current Preferred Drug List

Preferred Products	PA Criteria	Non-Preferred Products
Analgesics		
Analgesic/Miscellaneous		
Neuropathic Pain/Fibromyalgia Agents		
DULOXETINE GABAPENTIN LYRICA® SAVELLA® *¥ (Fibromyalgia only)	* PA required *¥No PA required for drugs in this class if ICD-10 - M79.1; M60.0-M60.9, M61.1.*	CYMBALTA® GRALISE® 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 Scripts Board

Meeting Minutes

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 Scripts Board.

Agenda Item	Record	Notes
Closed Executive Session		
Financial Review of Drug Classes with Proposed Changes	Chairman Decerbo called the meeting to order at 1:00 PM on September 23, 2021. Roll was taken by Chairman Decerbo. Present / Absent Decerbo, Mark, Pharm.D. – Chair ☒ ☐ Adashek, Joseph, MD ☐ ☒ Crumby, Mark, Pharm.D. ☒ ☐ Hautekeet, Mike, R.Ph ☒ ☐ Khurana, Sapandeep, MD ☒ ☐ Passalacqua, Brian, MD ☐ ☒ Singh, Aditi, MD ☐ ☒ Ward, Kate, Pharm.D. ☒ ☐	**The DHCFP Staff Present were as follows:** Olsen, David, Social Services Chief III Gudino, Antonio, Social Services Program Specialist III Flowers, Ellen, Program Officer I Lither, Gabriel, Senior Deputy Attorney General (SDAG)

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 Third Quarter/Annual 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 Scripts Board meeting. Mr. Whittington presented the Financial Review of the Biologic Response Modifiers – Multiple Sclerosis Agents, Oral class noting the products with proposed changes in PDL status. Mr. Whittington presented the Financial Review of the Cardiovascular Agents – Antilipemics – HMG-CoA Reductase Inhibitors (Statins) class noting the products with proposed changes in PDL status. Mr. Whittington presented the Financial Review of the Dermatological Agents – Topical Antineoplastics – Topical Retinoids class noting the products with proposed changes in PDL status. Mr. Whittington presented the Financial Review of the Psychotropic Agents – ADHD Agents class noting the products with proposed changes in PDL status. Mr. Whittington presented the Financial Review of the Psychotropic Agents – Psychostimulants – Narcolepsy Agents class noting the products with proposed changes in PDL status. Mr. Whittington presented the Financial Review of the Respiratory Agents – Short-Acting/Rescue Therapy class noting the products with proposed changes in PDL status. Mr. Whittington presented the Financial Review of the Cardiovascular Agents – Antilipemics – Bile Acid Sequestrants class noting the products with proposed changes in PDL status.	**Gainwell Technologies 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. Earnest, Rob, R.Ph., J.D. Piccirilli, Annette

Agenda Item	Record	Notes
	Mr. Whittington presented the Financial Review of the Anti-infective Agents – Aminoglycosides – Inhaled Aminoglycosides class noting the products with proposed changes in PDL status. Mr. Whittington presented the Financial Review of the Biologic Response Modifiers – Immunomodulators – Targeted Immunomodulators class noting the products with proposed changes in PDL status. Mr. Whittington presented the Financial Review of the Biologic Response Modifiers – Multiple Sclerosis Agents, Injectable class noting the products with proposed changes in PDL status. Mr. Whittington presented the Financial Review of the Dermatological Agents – Topical Analgesics class noting the products with proposed changes in PDL status. Mr. Whittington presented the Financial Review of the Gastrointestinal Agents – Gastrointestinal Enzymes class noting the products with proposed changes in PDL status. Mr. Whittington presented the Financial Review of the Hormones and Hormone Modifiers – Antidiabetic Agents – Incretin Mimetics Agents class noting the products with proposed changes in PDL status. Mr. Whittington presented the Financial Review of the Hormones and Hormone Modifiers – Antidiabetic Agents – Insulins (Vials, Pens and Inhaled) class noting the products with proposed changes in PDL status. Mr. Whittington presented the Financial Review of the Musculoskeletal Agents – Antigout Agents class noting the products with proposed changes in PDL status. Mr. Whittington presented the Financial Review of the Neurological Agents – Antiparkinsonian Agents – Dopamine Precursors class noting the products with proposed changes in PDL status.	

<table>
<tr><th>Agenda Item</th><th>Record</th><th>Notes</th></tr>
<tr><td></td><td>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 Neurological Agents – Anti-Migraine Agents – Serotonin Receptor Agonists class noting the products with proposed changes in PDL status.

Mr. Whittington presented the Financial Review of the Ophthalmic Agents – Ophthalmic Antihistamines class noting the products with proposed changes in PDL status.

Mr. Whittington presented the Financial Review of the Respiratory Agents – Long-Acting/Maintenance Therapy 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 Scripts Board Meeting.</td><td></td></tr>
<tr><td colspan="3">Open Public Meeting</td></tr>
<tr><td>1. Call to Order and Roll Call</td><td>Chairman Decerbo called the meeting to order at 2:25 PM on September 23, 2021.

Roll was taken by Chairman Decerbo.

<table>
<tr><th></th><th>Present</th><th>Absent</th></tr>
<tr><td>Decerbo, Mark, Pharm.D. – Chair</td><td>☒</td><td>☐</td></tr>
<tr><td>Adashek, Joseph, MD</td><td>☐</td><td>☒</td></tr>
<tr><td>Crumby, Mark, Pharm.D.</td><td>☒</td><td>☐</td></tr>
<tr><td>Hautekeet, Mike, R.Ph</td><td>☒</td><td>☐</td></tr>
<tr><td>Khurana, Sapandeep, MD</td><td>☒</td><td>☐</td></tr>
<tr><td>Passalacqua, Brian, MD</td><td>☐</td><td>☒</td></tr>
<tr><td>Singh, Aditi, MD</td><td>☐</td><td>☒</td></tr>
<tr><td>Ward, Kate, Pharm.D.</td><td>☒</td><td>☐</td></tr>
</table></td><td>The DHCFP Staff Present were as follows:
Olsen, David, Social Services Chief III
Gudino, Antonio, Social Services Program Specialist III
Flowers, Ellen, Program Officer I
Lither, Gabriel, SDAG

Gainwell Technologies Staff Present were as follows:
Leid, Jovanna, Pharm.D.</td></tr>
</table>

Agenda Item	Record	Notes
	A quorum was present.	**OptumRx Staff Present were as follows:** LeCheminant, Jill, Pharm.D. Kiriakopoulos, Amanda, Pharm.D. Whittington, Kevin, R.Ph. Piccirilli, Annette Medina, Daniel Hansen, Sean Lee, Cara, Pharm.D. Chien, Michael, Pharm.D. Earnest, Rob, R.Ph., J.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 July 29, 2021.	No corrections were offered. The minutes were approved by unanimous consent.	

Agenda Item	Record	Notes
b. Status Update by the DHCFP.	Chief David Olsen discussed the following dates for the upcoming Silver States Scripts Board meetings in the calendar year 2022. March 24, 2022, June 23, 2022, September 22, 2022, and December 15, 2022. Of the currently scheduled dates, the first two meetings have been posted online. Nevada Medicaid established contracts with managed care organizations, including a new managed care organization Molina which will begin starting January 1, 2022. Chief Olsen reviewed legislative updates, including Assembly Bill 177 that requires pharmacies to provide information regarding a prescription in languages other than English. Chief Olsen noted that the Board of Pharmacy is working on adopting the regulations. He covered Assembly Bill 178 that addresses early prescription renewals by pharmacists due to natural disasters effective earlier this month. Chief Olsen also provided information regarding the creation of a new provider type for pharmacists along with Senate Bill 190 that allows pharmacists to prescribe self-administered hormonal contraceptives and Senate Bill 325 which permits pharmacists to prescribe drugs to prevent the acquisition of human immunodeficiency virus (HIV) and to perform certain laboratory tests related to HIV testing. The public hearing for the State Plan Amendment for the new provider type is set for Tuesday, September 28 at 9 am to discuss the new provider type and pharmacist's enrollment. All of these are scheduled for implementation on January 1, 2022. He commented that for any information on public meetings to see the public notices website for additional information. Chief Olsen announced that Magellan Medicaid Administration will start on July 1, 2022, as Nevada's new pharmacy benefit manager (PBM). He noted that Magellan will begin facilitating the Silver State Scripts Board meetings at that time. Dr. Tina Hawkins from Magellan was present at the meeting to introduce herself and the team members. She commented that they were joining today to listen to the current process of meetings. Antonio Gudino announced that due to high levels of respiratory syncytial virus (RSV), Nevada Medicaid has extended the season beginning September 1, 2021, through March 31, 2022. He noted this is consistent with the	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/ The Division of Health Care Financing and Policy http://dhcfp.nv.gov/

Agenda Item	Record	Notes
	guidance of the AAP. RSV activity will continue to be monitored to determine if season length should be extended.	
4. Established Drug Classes Being Reviewed Due to the Release of New Drugs		
a. For Possible Action: Discussion and possible adoption of Biological Response Modifiers – Multiple Sclerosis Agents, Oral.		
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened. Comment was made by Sophia Yun, a pharmacist with Janssen Scientific Affairs. She provided clinical information regarding Ponvory. She noted that patients using this agent would not require the four-hour first dose monitoring. Ms. Yun provided indication information, efficacy, and safety data from Phase III clinical trials when compared to Aubagio. She noted superior efficacy when compared to Aubagio. Ms. Yun requested that Ponvory be added to the preferred drug list. Comment was provided by KayOnda Bayo from Bristol Myers Squibb representing Zeposia. Ms. Bayo provided indications for Zeposia and discussed clinical trials evaluating its safety and efficacy. She noted comparator studies with Avonex. Ms. Bayo requested that Zeposia be added to the formulary.	
ii. Drug class review presentation by OptumRx.	Dr. LeCheminant discussed the new product, Ponvory, the mechanism of action, indication, administration, and clinical trial demonstrating efficacy. She noted its significant reduction in annualized relapse rate and MRI endpoints when compared with Aubagio in a Phase 3 study.	

Agenda Item	Record	Notes
	Dr. LeCheminant 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 Khurana moved to accept the class as clinically and therapeutically equivalent. Board Member Hautekeet seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended adding Ponvory as non-preferred.	
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Board Member Ward moved to accept the proposed changes. Board Member Khurana seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
b. For Possible Action: Discussion and possible		

Agenda Item	Record	Notes
adoption of Cardiovascular Agents – Antilipemics – HMG-CoA Reductase Inhibitors (Statins)		
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. LeCheminant cited that this class is in the new drug sections because there was a new agent in the class; however, it is not yet part of the Medicaid Drug Rebate Program and will not be a part of the meeting today. Dr. LeCheminant 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 Khurana moved to accept the list is clinically and therapeutically equivalent. Board Member Ward seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended the Board move Vytorin to non-preferred and generic ezetimibe/simvastatin to preferred.	
v. Discussion by Board and action	Board Member Ward moved to accept the proposed updates as presented.	

Agenda Item	Record	Notes
by Board for approval of drugs for inclusion on the PDL.	Board Member Khurana seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
c. For Possible Action: Discussion and possible adoption of Dermatological Agents – Topical Antineoplastics – Topical Retinoids.		
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. LeCheminant discussed the new formulation of tazarotene 0.045% lotion available as Arazlo. She summarized noted indications. Dr. LeCheminant 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 Khurana 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. ☐	

Agenda Item	Record				Notes
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended Arazlo be added to the PDL as non-preferred and that Epiduo is moved to preferred.				
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Board Member Ward moved to accept the recommendation. Board Member Crumby seconded the motion. A vote was held:				
		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
d. For Possible Action: Discussion and possible adoption of Psychotropic Agents – ADHD Agents.					
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened. Comment was made by Justin Barnes, a medical science liaison with Ironshore Pharmaceuticals, regarding Jornay PM. Dr. Barnes discussed the differences of Jornay PM with other long-acting stimulants. He noted that there is no immediate release component to Jornay PM. Dr. Barnes				

<table>
<tr><th colspan="2">Agenda Item</th><th>Record</th><th>Notes</th></tr>
<tr><td colspan="2"></td><td>commented on administration times, clinical efficacy, and safety. He requested that Jornay PM be maintained as a preferred agent on the PDL.

Board Member Ward requested that in the interest of time that if no changes were being recommended to a preferred product to withhold comment at this time. Chairman Decerbo notified those in attendance how the slides are reviewed so that people wishing to provide comments can understand their product's status as preferred or non-preferred and what is being recommended.</td><td></td></tr>
<tr><td>ii.</td><td>Drug class review presentation by OptumRx.</td><td>Dr. LeCheminant discussed Qelbree, a new product within this class. She discussed the mechanism of action, clinical studies, and other available agents in the class.

Dr. LeCheminant recommended the Board consider the class clinically and therapeutically equivalent.</td><td></td></tr>
<tr><td>iii.</td><td>Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.</td><td>Board Member Ward moved to accept the class as clinically and therapeutically equivalent.

Board Member Khurana seconded the motion.

A vote was held:
<table><tr><th></th><th>Yes</th><th>No</th><th>Abst.</th></tr><tr><td>Decerbo, Mark, Pharm.D. – Chair</td><td>☒</td><td>☐</td><td>☐</td></tr><tr><td>Crumby, Mark, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr><tr><td>Hautekeet, Mike, R.Ph</td><td>☒</td><td>☐</td><td>☐</td></tr><tr><td>Khurana, Sapandeep, MD</td><td>☒</td><td>☐</td><td>☐</td></tr><tr><td>Ward, Kate, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr></table></td><td></td></tr>
<tr><td>iv.</td><td>Presentation of recommendations for PDL inclusion by OptumRx.</td><td>Dr. LeCheminant recommended adding Qelbree as non-preferred, to move atomoxetine to preferred status and Strattera to non-preferred status.</td><td></td></tr>
</table>

<table>
<tr><th>Agenda Item</th><th>Record</th><th>Notes</th></tr>
<tr><td>v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.</td><td>
Board Member Khurana moved to add Qelbree to preferred.

Chairman Decerbo seconded the motion.

Board Member Khurana stated that having another non-stimulant option available to patients with ADHD is needed. He noted concerns with stimulant options with aggression, irritability, and substance use disorder. He commented that atomoxetine was the only preferred non-stimulant option.

A vote was held:
<table>
<tr><th></th><th>Yes</th><th>No</th><th>Abst.</th></tr>
<tr><td>Decerbo, Mark, Pharm.D. – Chair</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Crumby, Mark, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Hautekeet, Mike, R.Ph</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Khurana, Sapandeep, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Ward, Kate, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
</table>

Board Member Khurana inquired about the use of the brand Strattera agent and if members could be grandfathered for use. Dr. LeCheminant commented that the preference would be for members to switch to the preferred generic agent, but that grandfathering could be put in place.

Board Member Khurana moved to maintain brand Strattera as preferred with atomoxetine as preferred.

Board Member Hautekeet seconded the motion.

Board Member Ward asked if Board Member Khurana was concerned about patients preferring the brand over the generic. Board Member Khurana commented on his concerns requiring failure with the generic and having to proceed through the various steps to obtain approval
</td><td></td></tr>
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<table>
<tr><th>Agenda Item</th><th>Record</th><th>Notes</th></tr>
<tr><td></td><td>through prior authorization for the brand product. Board Member Hautekeet noted that prescribers prefer to maintain patients on the brand product for certain agents. He notes that Strattera is one such product and his opinion that patients should be able to be maintained on whichever agent they start on.

A vote was held:

<table>
<tr><th></th><th>Yes</th><th>No</th><th>Abst.</th></tr>
<tr><td>Decerbo, Mark, Pharm.D. – Chair</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Crumby, Mark, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Hautekeet, Mike, R.Ph</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Khurana, Sapandeep, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Ward, Kate, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
</table>

Board Member Ward moved to maintain all other recommendations to this class on the PDL as presented.

Board Member Crumby seconded the motion.

A vote was held:

<table>
<tr><th></th><th>Yes</th><th>No</th><th>Abst.</th></tr>
<tr><td>Decerbo, Mark, Pharm.D. – Chair</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Crumby, Mark, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Hautekeet, Mike, R.Ph</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Khurana, Sapandeep, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Ward, Kate, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
</table>
</td><td></td></tr>
<tr><td>e. For Possible Action: Discussion and possible adoption of Psychotropic</td><td></td><td></td></tr>
</table>

Agenda Item	Record	Notes
Agents – Narcolepsy Agents.		
i. Public comment.	Dr. LeCheminant referenced submitted written public comment that was previously provided to the Board. She noted in the interest of time, she would not be reviewing individually during the meeting but that the Board had these comments prior to the meeting for their review. Telephonic and web comment was called for, and the phone lines were opened. Comment was provided by Deb Profant regarding Xywav. She provided new indications, dosing, and sodium intake. She provided clinical efficacy and safety information. Ms. Profant provided information on the REMS program for Xywav. She requested access to Xywav, similar to Xyrem.	
ii. Drug class review presentation by OptumRx.	Dr. LeCheminant discussed Xywav. She cited indications, efficacy, and that like Xyrem has less sodium content leading to favorability in narcolepsy patients with comorbid conditions such as hypertension and heart failure. Dr. LeCheminant 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 Khurana 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. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	

<table>
<tr><th>Agenda Item</th><th>Record</th><th>Notes</th></tr>
<tr><td>iv. Presentation of recommendations for PDL inclusion by OptumRx.</td><td>Dr. LeCheminant recommended adding Xywav to non-preferred and moving Wakix and armodafinil to non-preferred. Brand Nuvigil would be maintained as preferred.</td><td></td></tr>
<tr><td>v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.</td><td>Board Member Khurana moved to maintain Wakix as preferred and accept all other recommendations as presented.

Chairman Decerbo seconded the motion.

Board Member Khurana commented that the dopamine pathway for treatment could present challenges. As Wakix has a different mechanism of action, it permits the usage of a different type of agent as preferred. Chairman Decerbo noted that during the closed session, it did appear that it was being used judiciously. Board Member Ward inquired about the decision pathway between sodium oxybate and Wakix. Board Member Khurana noted that maintaining Wakix on the preferred side would provide a non-controlled substance as preferred. Board Member Ward noted that patients are also utilizing sodium oxybate.

A vote was held:
<table><tr><th></th><th>Yes</th><th>No</th><th>Abst.</th></tr><tr><td>Decerbo, Mark, Pharm.D. – Chair</td><td>☒</td><td>☐</td><td>☐</td></tr><tr><td>Crumby, Mark, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr><tr><td>Hautekeet, Mike, R.Ph</td><td>☒</td><td>☐</td><td>☐</td></tr><tr><td>Khurana, Sapandeep, MD</td><td>☒</td><td>☐</td><td>☐</td></tr><tr><td>Ward, Kate, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr></table></td><td></td></tr>
<tr><td>f. For Possible Action: Discussion and possible adoption of Respiratory Agents, Short-Acting/Rescue Therapy.</td><td></td><td></td></tr>
</table>

Agenda Item	Record	Notes
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. LeCheminant discussed indications of Proair Digihaler and its' built-in sensors to detect use and inspiratory flow. Dr. LeCheminant 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 Khurana 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. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended Proair Digihaler be added as 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 Ward motioned to accept the changes as presented. Board Member Khurana seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair ☒ Yes ☐ No ☐ Abst. Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
5. Classes Being Reviewed Due to New Generics		
a. For Possible Action: Discussion and possible adoption of Cardiovascular Agents – Antilipemics – Bile Acid Sequestrants		
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. LeCheminant discussed Welchol. Generic colesevelam is available. Dr. LeCheminant recommended the Board consider the class clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to	Chairman Decerbo moved to accept the class as clinically and therapeutically equivalent.	

Agenda Item	Record	Notes
approve clinical/therapeutic equivalency of agents in class.	Board Member Ward seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended adding colesevelam to non-preferred.	
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Board Member Khurana moved to accept the recommendation. Board Member Ward seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
6. Established drug classes		
a. For Possible Action: Discussion and possible adoption of Anti-infective Agents, Aminoglycosides, Inhaled Aminoglycosides.		

Agenda Item	Record	Notes
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. LeCheminant discussed available generic agents. Dr. LeCheminant 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 Ward moved to accept the class as clinically and therapeutically equivalent. Chairman Decerbo seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended moving tobramycin nebulizer 300mg/4mL to non-preferred.	
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Board Member Ward moved to accept the recommendation. Chairman Decerbo seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐	

Agenda Item	Record				Notes
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
b. For Possible Action: Discussion and possible adoption of Biologic Response Modifiers – Targeted Immunomodulators.					
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened. Comment was provided by Ben Droese, a pharmacist with Amgen Medical Affairs, regarding rituximab-arrx and its' newly assigned Q code effective July 1, 2021, of Q5123. Melissa Sommers, a medical science liaison with Novartis, provided public comment regarding Cosentyx. She provided indication information, clinical trial safety, and efficacy information. Ms. Sommers requested that Cosentyx be moved back to preferred status.				
ii. Drug class review presentation by OptumRx.	Dr. LeCheminant discussed Enspryng. She noted that this is a new agent in the class that became available after the agenda was already established. She discussed the mechanism of action, indication, efficacy studies, and other agents available in the class. Dr. LeCheminant 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 Khurana moved to accept the class as clinically and therapeutically equivalent. Board Member Ward seconded the motion. A vote was held:				

<table>
<tr><th>Agenda Item</th><th>Record</th><th>Notes</th></tr>
<tr><td></td><td>
<table>
<tr><th></th><th>Yes</th><th>No</th><th>Abst.</th></tr>
<tr><td>Decerbo, Mark, Pharm.D. – Chair</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Crumby, Mark, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Hautekeet, Mike, R.Ph</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Khurana, Sapandeep, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Ward, Kate, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
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</td><td></td></tr>
<tr><td>iv. Presentation of recommendations for PDL inclusion by OptumRx.</td><td>Dr. LeCheminant recommended adding Enspryng as non-preferred and moving Cosentyx, Inflectra, Renflexis, Stelara, and Xeljanz XR to non-preferred.</td><td></td></tr>
<tr><td>v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.</td><td>Board Member Ward noted the multiple indications for each of the agents. She moved to permit continued use of agents of therapy, moving from preferred to non-preferred indefinitely (Cosentyx, Stelara, Xeljanz XR).

Board Member Hautekeet seconded the motion.

Chairman Decerbo noted that he is not fully supportive of moving Stelara and Cosentyx to non-preferred. He did not ask to change any motion but wanted to make those aware of his thoughts.

A vote was held:
<table>
<tr><th></th><th>Yes</th><th>No</th><th>Abst.</th></tr>
<tr><td>Decerbo, Mark, Pharm.D. – Chair</td><td>☐</td><td>☐</td><td>☒</td></tr>
<tr><td>Crumby, Mark, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Hautekeet, Mike, R.Ph</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Khurana, Sapandeep, MD</td><td>☐</td><td>☒</td><td>☐</td></tr>
<tr><td>Ward, Kate, Pharm.D.</td><td>☐</td><td>☐</td><td>☒</td></tr>
</table>
Chairman Decerbo motioned to have Cosentyx and Stelara maintained as preferred and Xeljanz XR moved to non-preferred.</td><td></td></tr>
</table>

Agenda Item	Record	Notes
	Board Member Ward seconded the motion. A vote was held: Yes / No / Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐ Board Member Ward motioned to maintain Inflectra and Renflexis as preferred. She noted potential access issues with formularies at different infusion centers. Chairperson Decerbo seconded the motion. A vote was held: Yes / No / Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐ Board Member Khurana inquired if there was a need to grandfather utilizers of Xeljanz XR. Chairman Decerbo did not see a need to grandfather utilizers of this product but would welcome a motion if others felt differently.	

Agenda Item	Record	Notes
	Board Member Khurana motioned to accept all other recommendations to this class as presented. Board Member Ward seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
c. For Possible Action: Discussion and possible adoption of Biologic Response Modifiers – Multiple Sclerosis Agents, Injectable		
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened. Comment was provided by Melissa Sommers from Novartis for Kesimpta. She provided agent indications and requested that the product be added as preferred to the PDL. She noted administration of Kesimpta along with clinical trial efficacy.	
ii. Drug class review presentation by OptumRx.	Dr. LeCheminant discussed current generic availability. Dr. LeCheminant recommended the Board consider the class clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to approve	Chairperson Decerbo moved to accept the class as clinically and therapeutically equivalent.	

Agenda Item		Record				Notes
	clinical/therapeutic equivalency of agents in class.	Board Member Ward seconded the motion. A vote was held:				
			Yes	No	Abst.	
		Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
		Crumby, Mark, Pharm.D.	☒	☐	☐	
		Hautekeet, Mike, R.Ph	☒	☐	☐	
		Khurana, Sapandeep, MD	☒	☐	☐	
		Ward, Kate, Pharm.D.	☒	☐	☐	
iv.	Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended moving Rebif to non-preferred.				
v.	Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Chairman Decerbo noted that interferon utilization is low. He noted that the two beta-1a products are not interchangeable. Chairman Decerbo stated that it would be reasonable to grandfather Rebif utilizers. Chairman Decerbo motioned that current utilizers of Rebif be grandfathered when moved to non-preferred. Board Member Hautekeet seconded the motion. Board Member Ward asked that Kesimpta, Lemtrada, and Ocrevus be reviewed for access regarding PA criteria. Dr. LeCheminant noted that she would review these criteria with the DUR Board. A vote was held:				
			Yes	No	Abst.	
		Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
		Crumby, Mark, Pharm.D.	☒	☐	☐	
		Hautekeet, Mike, R.Ph	☒	☐	☐	

Agenda Item	Record				Notes
	Khurana, Sapandeep, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
d. For Possible Action: Discussion and possible adoption of Dermatological Agents – Topical Analgesics.					
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened. Comment was provided by Kalpana Patel, PharmD and VP of Medical Affairs of Scilex Pharmaceuticals, representing ZTLido. Dr. Patel provided indications for ZTLido, disease state background, mechanism of action, and clinical efficacy studies. She noted adverse events with lidocaine patches and patch adhesion studies when compared to Lidoderm and generic patches. Dr. Patel requested ZTLido to be moved to preferred on the PDL.				
ii. Drug class review presentation by OptumRx.	Dr. LeCheminant discussed a new product, Lenzapro. She noted the formulation of lidocaine 4% with a 4% menthol OTC patch. She reviewed the generic options within this class. Dr. LeCheminant 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 Khurana moved to accept the class as clinically and therapeutically equivalent. Board Member Crumby seconded the motion. A vote was held:				
		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	

Agenda Item	Record	Notes
	Khurana, Sapandeep, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended adding Lenzapro to non-preferred and moving Lidocaine 5% patch to non-preferred. Lidoderm was recommended to move to preferred.	
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Board Member Ward moved to accept the recommendation. Board Member Hautekeet seconded the motion. Board Member Ward noted the substantial number of claims due to non-preferred agents and wanted clarification of the use of the non-preferred claims (generic diclofenac gel and ZTLido). Dr. LeCheminant noted potential dual coverage with a different insurance that requires the generic version. Mr. Whittington also noted the availability of some of the branded products leading to increased utilization of the generic non-preferred agents. A vote was held: Yes No Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
e. For Possible Action: Discussion and possible adoption of Gastrointestinal Agents – Gastrointestinal Enzymes.		
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. LeCheminant discussed current generic availability within this drug class. Dr. LeCheminant 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 Ward 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. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
iv.	Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended moving Pancreaze to preferred.	
v.	Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Chairperson Decerbo moved to accept the recommendation. Board Member Ward seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐	

Agenda Item	Record	Notes
	Ward, Kate, Pharm.D. ☒ ☐ ☐	
f. For Possible Action: Discussion and possible adoption of Hormone and Hormone Modifiers – Antidiabetic Agents – Incretin Mimetics Agents.		
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened. Comment was provided by Dr. Dewan regarding glucagon and GLP1 agents. Dr. Dewan requested that no PA be required for patients exhibiting signs of insulin resistance to prevent movement to Type 2 Diabetes. Dr. Dewan also requested that pre-formulated glucagon agents be added as preferred for ease of administration with different caregivers. He noted phone calls he receives in the ER due to caregivers not being able to administer the current preferred glucagon formulations. Chairman Decerbo noted that requests regarding PA criteria for the GLP1 would be best served with the DUR Board as they determine the PA criteria. He also noted that glucagon is not on the agenda today for review but that this class could be reviewed in December. Chairman Decerbo encouraged Dr. Dewan to return at that time to discuss these classes. Gabriel Lither noted that all drugs could have action reviewed since it is the annual meeting. Chairman Decerbo deferred to the Board due to the lack of cost information previously reviewed. Board Member Ward agreed that a December agenda item would be more appropriate for a cost review. Dr. Dewan also requested that Rybelsus be added to preferred as an oral formulation due to potential patient needle phobia. Comment was provided by Justin Calecc with Novo Nordisk regarding Rybelsus. He noted that it is the first and only oral GLP1 agonist. Mr. Calecc	

Agenda Item	Record	Notes
	provided guideline information. He stated that it is the same molecule as the injectable Ozempic formulation. He specified that the safety profiles were similar between both agents. Mr. Calecc provided safety and efficacy clinical trial information.	
ii. Drug class review presentation by OptumRx.	Dr. LeCheminant discussed indications and current generic availability within this drug class. Dr. LeCheminant 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.	Chairperson Decerbo 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. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended moving Trulicity to non-preferred.	
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Chairman Decerbo moved to move Trulicity to non-preferred and Rybelsus to preferred. Board Member Ward seconded the motion. Board Member Ward asked if the DUR Board could address criteria regarding avoidance of injectable product if it were left as non-preferred.	

Agenda Item	Record	Notes
	Dr. LeCheminant confirmed that it could be discussed with the DUR Board. Chairman Decerbo confirmed that these recommendations would apply to these products only and not for those that are utilized for weight loss only. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
g. For Possible Action: Discussion and possible adoption of Hormone and Hormone Modifiers – Antidiabetic Agents – Insulins (Vials, Pens and Inhaled).		
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. LeCheminant discussed current generic availability within this drug class. Dr. LeCheminant 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.	Chairman Decerbo moved to accept the class as clinically and therapeutically equivalent. Board Member Ward seconded the motion. A vote was held:	

Agenda Item	Record	Notes
	Yes / No / Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended moving Insulin aspart mix and insulin lispro mix to preferred.	
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Board Member Ward moved to accept the recommendation. Board Member Hautekeet seconded the motion. A vote was held: Yes / No / Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
h. For Possible Action: Discussion and possible adoption of Musculoskeletal Agents – Antigout Agents		
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened. No public comment was offered.	

Agenda Item		Record	Notes
ii.	Drug class review presentation by OptumRx.	Dr. LeCheminant discussed current generic availability within this drug class. Dr. LeCheminant 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.	Chairman Decerbo moved to accept the class as clinically and therapeutically equivalent. Board Member Khurana seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
iv.	Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended moving febuxostat to non-preferred and Uloric to preferred.	
v.	Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Board Member Ward moved to accept the recommendation. Board Member Crumby seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	

Agenda Item	Record	Notes
i. For Possible Action: Discussion and possible adoption of Neurological Agents – Antiparkinsonian Agents – Dopamine Precursors.		
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened. Comment was provided by Brian Wensel from Sunovian Pharmaceuticals regarding Kynmobi. Mr. Wensel provided information on current treatment options. He discussed the acute treatment of on/off episodes. Mr. Wensel discussed dosing, indication, tolerability, efficacy, and safety of Kynmobi. He requested that the Board review Kynmobi and add it to the PDL.	
ii. Drug class review presentation by OptumRx.	Dr. LeCheminant discussed current generic availability within this drug class. Dr. LeCheminant 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.	Chairman Decerbo moved to accept the class as clinically and therapeutically equivalent. Board Member Crumby seconded the motion. A vote was held: Yes / No / Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
iv. Presentation of recommendations for	Dr. LeCheminant recommended moving Stalevo to non-preferred and the generic, carbidopa/levodopa/entacapone to preferred.	

<table>
<tr><th>Agenda Item</th><th>Record</th><th>Notes</th></tr>
<tr><td>PDL inclusion by OptumRx.</td><td></td><td></td></tr>
<tr><td>v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.</td><td>Board Member Ward moved to accept the recommendation.

Board Member Crumby seconded the motion.

Chairman Decerbo asked if Kynmobi was placed somewhere else on the PDL. Dr. LeCheminant noted she believed it would fall under a different category and would bring back at the December meeting.

A vote was held:

<table>
<tr><th></th><th>Yes</th><th>No</th><th>Abst.</th></tr>
<tr><td>Decerbo, Mark, Pharm.D. – Chair</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Crumby, Mark, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Hautekeet, Mike, R.Ph</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Khurana, Sapandeep, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Ward, Kate, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
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</td><td></td></tr>
<tr><td>j. For Possible Action: Discussion and possible adoption of Anti-Migraine Agents – Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists.</td><td></td><td></td></tr>
<tr><td>i. Public comment.</td><td>Telephonic and web comment was called for, and the phone lines were opened.

Comment was provided by Dr. Medhi Ansarinia regarding the CGRP Receptor Antagonists. He noted that Ajovy is preferred and that in his experience as a headache specialist, he encounters less wear-off or increased headaches prior to the next dose. He asked that it remain as preferred.</td><td></td></tr>
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Agenda Item		Record	Notes
		Comment was provided by Ben Droese with Amgen Medical Affairs. He appreciated the recommendation of Aimovig as preferred and asked for any questions. Ryan Norman gave back time and opened for any questions.	
ii.	Drug class review presentation by OptumRx.	Dr. LeCheminant discussed indications and those agents used for acute and preventative treatment. She noted Emgality is the only agent indicated for cluster headache treatment. Dr. LeCheminant 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.	Chairman Decerbo 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. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
iv.	Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended moving Aimovig to preferred and Ubrelvy to non-preferred.	
v.	Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Board Member Ward moved to accept the recommendation. Chairman Decerbo and Board Member Ward agreed that abortive options were still available on preferred. Board Member Crumby seconded the motion.	

Agenda Item	Record	Notes
	A vote was held: Decerbo, Mark, Pharm.D. – Chair ☒ Yes ☐ No ☐ Abst. Crumby, Mark, Pharm.D. ☒ Yes ☐ No ☐ Abst. Hautekeet, Mike, R.Ph ☒ Yes ☐ No ☐ Abst. Khurana, Sapandeep, MD ☒ Yes ☐ No ☐ Abst. Ward, Kate, Pharm.D. ☒ Yes ☐ No ☐ Abst.	
k. For Possible Action: Discussion and possible adoption of Anti-Migraine Agents – Serotonin-Receptor 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. LeCheminant noted generic agents available in this class. Dr. LeCheminant 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.	Chairman Decerbo moved to accept the class as clinically and therapeutically equivalent. Board Member Hautekeet seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair ☒ Yes ☐ No ☐ Abst. Crumby, Mark, Pharm.D. ☒ Yes ☐ No ☐ Abst. Hautekeet, Mike, R.Ph ☒ Yes ☐ No ☐ Abst.	

Agenda Item	Record				Notes
	Khurana, Sapandeep, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended moving Frova, Relpax, and zolmitriptan nasal spray to preferred and Zomig nasal spray to non-preferred.				
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Chairman Decerbo moved to accept the recommendation. Board Member Ward seconded the motion. A vote was held:				
		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
l. For Possible Action: Discussion and possible adoption of Ophthalmic Agents – Ophthalmic Antihistamines					
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. LeCheminant noted generic agents available in this class. Dr. LeCheminant recommended the Board consider the class clinically and therapeutically equivalent.				
iii. Discussion by Board and action by Board to	Chairman Decerbo moved to accept the class as clinically and therapeutically equivalent.				

Agenda Item	Record	Notes
approve 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. Crumby, Mark, Pharm.D. ☒ Yes ☐ No ☐ Abst. Hautekeet, Mike, R.Ph ☒ Yes ☐ No ☐ Abst. Khurana, Sapandeep, MD ☒ Yes ☐ No ☐ Abst. Ward, Kate, Pharm.D. ☒ Yes ☐ No ☐ Abst.	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended moving azelastine, Lastacaft, and olopatadine to preferred and Pazeo to non-preferred.	
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Board Member Ward moved to accept the recommendation. Board Member Crumby seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair ☒ Yes ☐ No ☐ Abst. Crumby, Mark, Pharm.D. ☒ Yes ☐ No ☐ Abst. Hautekeet, Mike, R.Ph ☒ Yes ☐ No ☐ Abst. Khurana, Sapandeep, MD ☒ Yes ☐ No ☐ Abst. Ward, Kate, Pharm.D. ☒ Yes ☐ No ☐ Abst.	
m. For Possible Action: Discussion and possible adoption of Respiratory Agents – Long-Acting/Maintenance Therapy.		

Agenda Item	Record	Notes
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened. Public comment was provided by Dr. Tayo Fakunle for Alvesco. She provided indications, dosing, and clinical trial information regarding safety and efficacy for Alvesco. In addition, Dr. Fakunle provided tolerability and side effect information along with the mechanism of action. She asked that Alvesco be added to the PDL.	
ii. Drug class review presentation by OptumRx.	Dr. LeCheminant noted generic agents available in this class. Dr. LeCheminant 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.	Chairman Decerbo moved to accept the class as clinically and therapeutically equivalent. Board Member Ward seconded the motion. A vote was held: Yes / No / Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended moving Asmanex and Bevespi to non-preferred.	
v. Discussion by Board and action by Board for approval of drugs	Board Member Ward asked for the rationale for maintaining Tudorza as preferred on the PDL as a single agent when the combination agents were moved to non-preferred. Dr. LeCheminant mentioned that while she does not have cost information in front of her now, she did recall a financial	

Agenda Item	Record	Notes
for inclusion on the PDL.	reason for leaving as preferred and maintaining as many agents as preferred as possible for additional options. Chairman Decerbo moved to accept the recommendation. Board Member Hautekeet seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
7. Drug Classes without Proposed Changes		
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened. Comment was provided by Emily Smith from Zealand Pharma regarding glucagon products. She noted her appreciation for the opportunity to provide testimony in December for these agents. Melissa Sommers with Novartis provided public comment regarding Entresto. She noted updates to the label regarding reducing CV death and hospitalizations in patients with heart failure. She requested that Entresto be added as preferred and provided supporting clinical literature. Dr. LeCheminant noted that these criteria would be reviewed at the next DUR Board meeting. Mr. Whittington noted that Entresto is not currently a drug on the PDL and asked Gabriel Lither if it would be best to wait until December. Mr. Lither noted that it could be addressed today but would	

	likely be best to wait until December. Dr. LeCheminant commented that she would bring these in December. Robert Rollins, a pediatric cardiologist, provided public comment regarding Hemangeol. He noted better compliance, no alcohol present, and a better flavoring for babies. He requested it to be added to preferred. Chairman Decerbo noted that pricing data for this product was previously reviewed. Board Member Ward asked if there were any established PA criteria for Hemangeol. Dr. LeCheminant confirmed there are no PA criteria. Chairman Decerbo commented that unless the Board felt differently, he was comfortable not making any changes at this time.	
ii. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Chairman Decerbo moved to accept the remaining drug classes with no changes being accepted. Board Member Ward seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
8. OptumRx Reports: New Drugs to Market and New Line Extensions	Dr. LeCheminant reviewed daridorexant, a new drug indicated for the treatment of narcolepsy that is expected to be approved in January. Dr. LeCheminant mentioned two drugs with new formulations, dextroamphetamine transdermal, and buprenorphine subcutaneous injection. She noted that generic Cayston is likely to be available in December.	
9. Closing Discussion		
a. Public comments on any subject.	Telephonic and web comment was called for, and the phone lines were opened.	

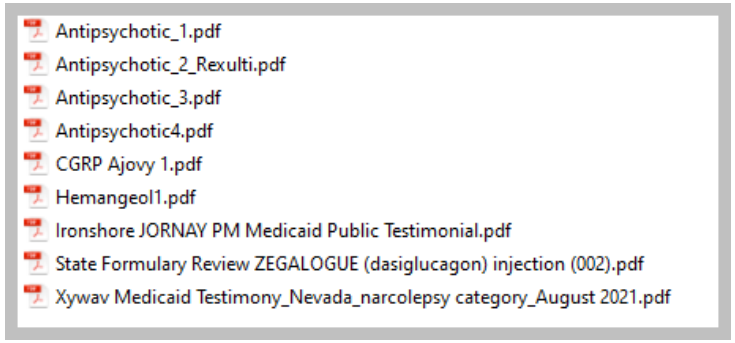
	No public comment was offered.	
b. Date and location of the next meeting.	Chairman Decerbo confirmed the next meeting is scheduled for December 9, 2021, and will be a hybrid meeting.	
c. Adjournment.	Chairman Decerbo adjourned the meeting at 4:54 PM.	

Attachment A – Members of the Public in Attendance

Abbott, Susan, Covis Pharma
Alegria, Veronica, DHCFP
Ansarinia, Dr. Mehdi
Appolonia, Patrick
Ashton, Elisa, Johnson & Johnson
Asokan, Vimal, Wellpoint
Bailey, Alan, UCB
Bala, Kaysen
Barnes, Justin, Ironshore Pharma
Basset, Dylan, Pierre-Fabre
Bayo, KayOnda, Bristol Myers Squibb
Belz, Jeanette, Nbelz & Case
Bitton, Ryan, HPN
Bogard, Lisa, WellPoint
Booth, Robert
Calecc, Justin
Cameron, Stormy, Artia Solutions
Camille, Kerr
Chan, Betty, Gilead
Chow, Ellen
Colabianchi, Jeana, Sunovion
Cooper, Christa
Cruz, Ashley, Carra NV
De Rosa, Regina, WellPoint
Droese, Ben, Amgen
Duke, Michelle
Dynak, Dawn, Gilead
Eldridge, Edward, Gilead
Fakunle, Tayo, Covis Pharma
Ferroli, Joseph, Takeda
Fox, Linda, DHHS
Gaon, Dominic, WellPoint
Germain, Joe, Biogen
Gorzynski, Andy
Groppenbacher, Shannon, Johnson & Johnson
Hawkins, Tina, Magellan
Hill, Laura, AbbVie
Howard, Kathleen, Scilex Pharma
Kam, Calvin, WellPoint
Kniffin, Jason
Large, David
Legg, Jody, Mirum Pharma
Lim, Luke, WellPoint
Lovan, Charlie, AbbVie
Morgan, Derek, Ironshore Pharma
Nguyen, Bao, Janus
Norman, Ryan
Oliver, Carmen, Biohaven Pharma
Ou, Karen, Gilead
Parsa, Pirooz, Bristol Myers Squibb
Patadia, Hiten, Otsuka
Patel, Kalpana, Scilex Pharma
Pearce, Robert
Pericci, Michele, Scilex Pharma
Phillips, Katherine, Jazz Pharma
Profant, Deb, Jazz Pharma
Quon, Warner, Idorsia
Reemts, Robert, UCB
Ritter, Jean
Roehr, Steven, Magellan
Rollins, Robert
Roy, Melissa
Santarone, Christopher, Bristol Myers Squibb
Schillo, John, Lundbeck
Schlatter, David, Covis Pharma
Sebastian, Paul, Optum
Shurtleff, Madeline, Otsuka
Smith, Emily, Zealand Pharma
Smith, Jason, Gilead
Sommers, Melissa, Novartis
Springs, Tami, Pierre-Fabre
Stepien, Scott , Ispen
Walter, Lindsey, Novartis
Wensel, Brian, Sunovion
Yamashita, Kelvin
Young, Sara, UCB
Yun, Sophia, Janus
Zarob, Michael, Alkermes
Zimmerman, David, Novo Nordisk

Attendees with no last name available:
Christa
Dewan
Jasi
Kenneth
Mike

Attachment B – Submitted Written Comment



OPTUMRx®

Proposed New Classes

INTRODUCTION

- Approximately 6 million Americans aged ≥ 20 years have heart failure (HF). In 2018, 83,616 people died from HF in the United States (US) (*Virani et al 2021*). The total percentage of the population with HF is projected to rise from 2.4% in 2012 to 3.0% in 2030.
- Pediatric cardiomyopathies, which are the most common cause of pediatric HF, are rare diseases with an annual incidence of 1.13 cases per 100,000 among children < 18 years of age. Dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM) are the most common forms observed in this patient population (*Lee et al 2017, Virani et al 2021*).
- Many conditions or comorbidities are associated with an increased risk for developing HF. Hypertension is the most important modifiable risk factor in the US. Other important risk factors for the development of HF include obesity, diabetes, metabolic syndrome, and atherosclerotic disease (*Yancy et al 2013*). In children, cardiomyopathy may be caused by coronary artery abnormalities, tachyarrhythmias, exposure to infection or toxins, or are secondary to other underlying disorders (*Lee et al 2017*).
- There are 2 forms of heart failure:
  - Heart failure with reduced ejection fraction (HFrEF): Ejection fraction (EF) ≤ 40%; also referred to as systolic heart failure
  - Heart failure with preserved ejection fraction (HFpEF): EF ≥ 50%; also referred to as diastolic heart failure (*Yancy et al 2013*).
- The following table outlines the American College of Cardiology Foundation/American Heart Association (ACCF/AHA) and the New York Heart Association (NYHA) Functional classes for systolic heart failure (*Yancy et al 2013*):

Table 1. ACCF/AHA Heart Failure Stages and NYHA Classes for Systolic Heart Failure

ACCF/AHA Stages	NYHA Class
• **A:** At high risk for HF but without structural heart disease or symptoms of HF • **B:** Structural heart disease but without signs or symptoms of HF • **C:** Structural heart disease with prior or current symptoms of HF • **D:** Refractory HF requiring specialized treatment	• **I:** No limitation of physical activity. Ordinary physical activity does not cause symptoms of HF. • **II:** Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in symptoms of HF. • **III:** Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes symptoms of HF. • **IV:** Unable to carry on any physical activity without symptoms of HF, or symptoms of HF at rest.

Abbrv: ACCF/AHA = American College of Cardiology Foundation/American Heart Association, NYHA = New York Heart Association, HF = heart failure.

- The cardinal symptoms of HF are dyspnea and fatigue. HF leads to exercise intolerance, fluid retention, pulmonary congestion, and peripheral edema often resulting in hospitalizations (*Yancy et al 2013*).
- The Atherosclerosis Risk in Communities (ARIC) study identified that African Americans have the highest risk for HF with a greater 5-year fatality rate than Caucasians ($p < 0.05$) (*Lloyd-Jones et al 2002, Virani et al 2021*).
- In order to predict one's risk of HF, a number of risk score models may be used including the Framingham Heart Failure Risk Score, Candesartan in Heart failure-Assessment of Reduction in Mortality and morbidity (CHARM) risk score, Seattle Heart Failure Model, Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) risk score, and Heart Failure risk score (*National Heart, Lung, and Blood Institute [NHLBI] and Boston University 2015, Yancy et al 2013*).
- Corlanor (ivabradine) reduces spontaneous pacemaker activity at the cardiac sinus node by blocking the hyperpolarization-activated cyclic nucleotide-gated (HCN) channel to selectively inhibit the funny-current (I_f), thus reducing the heart rate. Ventricular repolarization and myocardial contractility are not affected.

- Verquvo (vericiguat) stimulates soluble guanylate cyclase (sGC), an important enzyme in the nitric oxide signaling pathway. By directly stimulating sGC, independently of and synergistically with nitric oxide, vericiguat augments levels of intracellular cyclic guanosine monophosphate (cGMP), leading to smooth muscle relaxation and vasodilation (*Verquvo prescribing information 2021*).
- HF guidelines state that ivabradine is an alternative (not first-choice) addition to the treatment regimen of selected patients who are not adequately controlled by their current therapy (*Ponikowski et al 2016, Yancy et al 2013, Yancy et al 2016, Yancy et al 2017*). HF guidelines do not currently contain recommendations for vericiguat. Of note, for most of the agents used in the management of pediatric patients with HF, the evidence supporting efficacy comes largely from adult studies (*Singh 2019*).
- Angina is a symptom of coronary artery or heart disease (CAD/CHD), also referred to as ischemic heart disease (IHD). (*Centers for Disease Control and Prevention [CDC] 2019*). According to the AHA, CHD is the leading cause of cardiovascular (CV) death in the US (*Virani et al 2021*). In 2018, CHD mortality across all ages in the US included 365,744 individuals.
- Stable angina (SA) occurs upon physical exertion or during mental or emotional stress and typically resolves upon rest (*CDC 2019*). Coronary artery stenosis results in reduced blood flow that manifests as chest pain/discomfort when myocardial oxygen demand is increased upon exertion (*Kones 2010[a]*).
- Factors that increase risk of CHD include smoking, dyslipidemia, hypertension, diabetes, and a family history of these risk factors (*Dobesh et al 2020*). Therefore, one aspect of management involves lifestyle and pharmacologic interventions of these factors to slow progression of CHD. The other aspect of treatment involves reducing the number of angina episodes and increasing the duration of exercise before angina occurs.
- Ranexa (ranolazine ER) is an antianginal agent that does not impact heart rate or blood pressure (*Kones 2010[b], Ranexa prescribing information 2019*). Although its exact mechanism on reducing anginal symptoms is unknown, it is postulated that inhibition of the late phase of the inward sodium channel in cardiac myocytes reduces intracellular calcium. This, in turn, may reduce myocardial oxygen consumption and ventricular tension resulting in myocardial relaxation and reduction in anginal symptoms.
- Ranolazine ER is an alternative for initial therapy in relieving anginal symptoms when other treatments cannot be used or are contraindicated. In fact, ranolazine ER is considered a third line agent (after either a calcium channel blocker or long-acting nitrate) for patients who cannot take a β-blocker due to a contraindication or intolerance (*Fihn et al 2012, Dobesh et al 2020*). Ranolazine ER can also be considered for combination therapy with β-blockers when symptoms are not controlled with initial β-blocker treatment.
- This review includes miscellaneous drugs, which modify the CV system. The current review includes the sinus node inhibitor, Corlanor (ivabradine), the sGC stimulator, Verquvo (vericiguat), and Ranexa (ranolazine ER), an antianginal inhibitor.
- Medispan class: Cardiovascular Agents – Misc; Sinus Node Inhibitors; Ivabradine; Antianginals-Other; Ranolazine

Table 2. Medications Included Within Class Review

Drug	Generic Availability
Corlanor (ivabradine)	-
Ranexa (ranolazine ER)	✔
Verquvo (vericiguat)	-

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

INDICATIONS

Table 3. Food and Drug Administration Approved Indications

Indication	Corlanor (ivabradine)	Ranexa (ranolazine ER)	Verquvo (vericiguat)
To reduce the risk of hospitalization for worsening HF in adult patients with stable, symptomatic chronic HF with left ventricular ejection fraction (LVEF) ≤ 35%, who are in sinus rhythm with resting heart rate	✔		

Indication	Corlanor (ivabradine)	Ranexa (ranolazine ER)	Verquvo (vericiguat)
≥ 70 beats per minute (bpm) and either are on maximally tolerated doses of β-blockers or have a contraindication to β-blocker use			
Treatment of stable symptomatic heart failure due to DCM in pediatric patients ≥ 6 months of age, who are in sinus rhythm with an elevated heart rate	✔		
Treatment of chronic angina		✔	
To reduce the risk of cardiovascular death and HF hospitalization following a hospitalization for HF or need for outpatient IV diuretics, in adults with symptomatic chronic HF and EF < 45%			✔

(*Prescribing information: Corlanor 2019, Ranexa 2019, Verquvo 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

Ivabradine

- The Systolic Heart failure treatment with the I_f inhibitor ivabradine Trial (SHIFT) enrolled 6588 patients in NYHA Functional Class II to IV, sinus rhythm with a rate of ≥ 70 bpm, and an EF ≤ 35%. Patients were also required to have had a HF hospitalization in the previous 12 months and no sustained atrial fibrillation or flutter. Patients were randomized to ivabradine (titrated to a maximal dosage of 7.5 mg twice daily) or placebo with standard therapy. Standard therapy included placebo added to a diuretic (in 84%), digoxin (22%), an angiotensin-converting enzyme inhibitor (ACE-I) (79%), an angiotensin receptor blocker (ARB) (14%), a β-blocker (90%), and a mineralocorticoid receptor antagonist (60%). Only 26% of patients were, however, on an optimized β-blocker dose. The median follow-up was approximately 23 months. The primary composite outcome of CV-related death or HF hospitalization was observed in 24% of ivabradine-treated patients and 29% of placebo-treated patients with an absolute risk reduction (ARR) of 4.24% ($p < 0.0001$). However, the reduction in CV death (or all-cause death) was not significant, but the ARR for HF hospitalization was 4.73%, equating to a number needed to treat (NNT) of 21 (*Swedberg et al 2010*).
  - Although inclusion criteria for the SHIFT trial included patients with a heart rate of ≥ 70 bpm, a pre-specified subgroup analysis of the primary endpoint demonstrated significantly more patients with a baseline heart rate of ≥ 77 bpm benefited from ivabradine-treatment compared to < 77 bpm ($p = 0.03$).
  - In terms of safety, ivabradine treatment was associated with more bradycardia (difference, 7.9%), phosphenes (difference, 2%), atrial fibrillation (difference, 1%), and blurred vision (difference, < 1%); of which, only bradycardia led to higher rates of discontinuation with ivabradine treatment (difference, 1.18%; $p < 0.002$).
- One post-hoc analysis of the SHIFT trial examined the correlation between different co-morbidity loads and key endpoints with each treatment group. Those co-morbidities analyzed (from the largest to smallest proportions) included hypertension, myocardial infarction (MI), diabetes, estimated glomerular filtration rate (eGFR) < 60 mL, chronic obstructive pulmonary disease (COPD), anemia, stroke, and peripheral artery disease (PAD). Based on the HF population from SHIFT, cardiac and non-cardiac co-morbidities significantly affected CV outcomes. The primary endpoint, the composite of CV death or HF hospitalization rate, increased with the co-morbidity load ($p < 0.0001$) with most events in patients with ≥ 4 comorbidities for both ivabradine and placebo (*Böhm et al 2015*).
- Another post-hoc analysis of the SHIFT trial assessed the impact of ivabradine on early readmissions in patients hospitalized for HF. A total of 1186 patients were identified with ≥ 1 HF hospitalization; of these, 334 patients were readmitted within 3 months for any reason. Ivabradine significantly reduced the risk of early recurrent hospitalizations following a first HF hospitalization. This reduction of risk was significant from the first month onwards (30% relative risk reduction; incidence rate ratio [IRR], 0.70; $p < 0.05$) and ranged from a relative risk reduction of 21 to 25% within 2 and 3 months following a HF hospitalization. However, mortality rates were similar to placebo within the first 3 months following a HF hospitalization. It is important to note, SHIFT was not designed or powered to determine the effect of treatment in patients hospitalized for HF; therefore, the role of ivabradine before and after hospitalization cannot be fully concluded and further studies are needed (*Komajda et al 2016*).

- Additional safety evidence for ivabradine comes from the MorBidity-mortality EvAlUaTion of the I_f inhibitor ivabradine in patients with coronary disease and left ventricULar dysfunction (BEAUTIFUL) trial, a randomized controlled trial (RCT) in which 10,917 patients with CHD and an EF < 40% were assigned to treatment with ivabradine 7.5 mg twice daily or placebo (with standard therapy) and followed for a median of 19 months. Ivabradine did not reduce the primary outcome of CV-related death, MI, or HF hospitalization. In a pre-specified subgroup of patients with a heart rate of ≥ 70 bpm (total population, N = 5392; ivabradine, n = 2699), ivabradine did significantly reduce the incidence of hospitalization due to fatal and nonfatal MI, MI or unstable angina, and coronary revascularization, after a median of 19 months (*Fox et al 2008*).
  - There was no significant difference in the incidences of serious adverse events (23% for both; p = 0.7); however, more psychiatric disorders were observed with ivabradine treatment compared to placebo (0.3 vs 0.1%, respectively; p = 0.01).
- Ivabradine has also been studied in the Ivabradine in Stable Coronary Artery Disease without Clinical Heart Failure study (SIGNIFY). This study included patients who had stable coronary artery disease without clinical HF (N = 19,102) and with a heart rate of ≥ 70 bpm. The addition of ivabradine 10 mg twice daily to standard therapy did not reduce the risk of death from CV causes or nonfatal MI after a median of 27.8 months (*Fox et al 2014*).
  - The incidence of bradycardia was significantly greater with ivabradine (at the higher 10 mg twice daily dosing) compared to placebo (18 vs 2.3%, respectively; p < 0.001). Other adverse events that occurred significantly more often with ivabradine included atrial fibrillation (5.3 vs 3.8%, respectively) and phosphenes (5.4% vs 0.5%, respectively) (p < 0.001 for both).
  - Significantly more serious adverse events were observed with ivabradine (p = 0.001). Those serious adverse events included cardiac disorders (19 vs 16.7%; p < 0.001) and eye disorders (1.8 vs 1.4%; p = 0.02).
- The approval of ivabradine's pediatric DCM indication was based on a double-blind (DB) clinical trial of 116 patients aged 6 months to < 18 years with DCM in sinus rhythm, NYHA/Ross class II to IV HF, and LVEF ≤ 45%. Patients were randomized to receive ivabradine or placebo. The majority of patients were treated concomitantly with ACE-Is (94%). Doses of study medication were titrated over a 2- to 8-week period to achieve a 20% heart rate reduction without inducing bradycardia (*Bonnet et al 2017*).
  - The target heart rate reduction was obtained at the end of the titration period in a significantly higher proportion of patients treated with ivabradine vs placebo (70% vs 12% respectively; odds ratio = 17.24; 95% confidence interval (CI), 5.91 to 50.30; p < 0.0001).
  - A statistically significant reduction in heart rate was observed with ivabradine vs placebo at the end of the titration period (-21.2 ± 13.3 bpm vs -1.4 ± 11.5 bpm, respectively).
- A Cochrane review evaluated the effectiveness and safety of ivabradine in patients with chronic HF via an analysis of data from 19 RCTs involving a total of 19,628 individuals (*Benstoem et al 2020*). Two meta-analyses, focusing on patients with HFrEF and long-term ivabradine treatment, were performed. Results from these analyses revealed no difference between ivabradine and placebo/usual care/no treatment for mortality from cardiovascular causes (relative risk [RR] 0.99; 95% CI, 0.88 to 1.11 [n=3 studies; moderate certainty evidence]) and no difference in the rate of serious adverse events (RR 0.96; 95% CI, 0.92 to 1.00 [n=2 studies; moderate certainty evidence]). Overall, few studies contributed data to the meta-analyses due to inconsistency in trial design and outcome reporting and measurement. Additionally, the risk of bias among studies varied from low to high, with several studies containing insufficient detail to inform a judgment.

Ranolazine ER

- The Combination Assessment of Ranolazine in Stable Angina (CARISA) study was a randomized, DB trial that compared exercise duration in 823 patients with chronic SA who received either ranolazine ER (750 mg twice daily [n = 272] or 1000 mg twice daily [n = 261]) or placebo (n = 258). Time to angina during exercise, weekly angina frequency, and weekly nitroglycerin use were secondary outcomes. Patients continued on either atenolol 50 mg, amlodipine 5 mg, or diltiazem CD 180 mg daily (*Chaitman et al 2004*).
  - The mean differences from placebo in modified Bruce treadmill exercise duration at trough ranolazine ER levels (12 hours after dosing) were 23.7 seconds with ranolazine ER 750 mg and 24 seconds with ranolazine ER 1000 mg (p = 0.03).
  - The time to angina was also found to be statistically significant between each ranolazine ER dose and placebo.
  - The mean number of angina attacks per week was 3.3, 2.5, and 2.1 for placebo, ranolazine ER 750 mg (p = 0.006 vs placebo), and ranolazine ER 1000 mg (p < 0.001 vs placebo), respectively.

- Similarly, a significant reduction in mean nitroglycerin doses per week was observed with 3.1 for placebo, 2.1 for ranolazine ER 750 mg (p = 0.016), and 1.8 for ranolazine ER 1000 mg (p < 0.001).
- In the Efficacy of Ranolazine in Chronic Angina (ERICA) trial, the efficacy of ranolazine ER was evaluated in 565 patients with chronic SA with symptoms despite treatment with a maximum dose of amlodipine. Patients were randomized to receive either ranolazine ER 1000 mg twice daily (n = 281) or placebo (n = 284) for 6 weeks. All patients received amlodipine 10 mg daily and 45% of patients also took long-acting nitrates (*Stone et al 2006*).
  - The mean number of angina attacks per week was 4.3 with placebo and 3.3 with ranolazine ER (p = 0.028).
  - The mean number of nitroglycerin doses per week was significantly less with ranolazine ER compared to placebo (2.7 vs 3.6, p = 0.014).
- A systematic review of 7 RCTs evaluated ranolazine ER efficacy in 3,317 patients with chronic SA due to CAD compared to placebo or conventional treatment. Outcomes included exercise stress test duration, time to onset of angina or ST-segment depression, weekly nitroglycerin use, weekly anginal attacks, and quality of life. Generally, these outcomes were shown to be improved with use of ranolazine ER at higher doses (at least 750 mg twice daily) compared to placebo. One study that compared ranolazine ER 400 mg 3 times daily to atenolol demonstrated a small benefit in exercise outcomes when evaluated at peak time (1 hour after ranolazine ER dosing). Improvements in exercise duration were generally between 25 and 30 seconds and the difference in the decrease in weekly anginal attacks or nitroglycerin use between ranolazine ER and placebo was ≤ 1 (*Banon et al 2014*).

Vericiguat

- In the Vericiguat Global Study in Subjects with Heart Failure with Reduced Ejection Fraction (VICTORIA) Phase 3, multinational trial, 5,050 patients with NYHA class II to IV chronic HF and an EF < 45% were randomly assigned to a target dose of vericiguat 10 mg once daily (n = 2,526) or placebo (n = 2,524), in addition to guideline-based medical therapy. Enrolled patients also had to have evidence of worsening HF. The primary outcome was a composite of death from CV causes or first hospitalization for HF, which occurred in 897 patients (35.5%) in the vericiguat group vs 972 patients (38.5%) in the placebo group (hazard ratio [HR], 0.90; 95% CI, 0.82 to 0.98; p = 0.02) at a median of 10.8 months. However, death from CV causes (16.4% vericiguat vs 17.5% placebo; HR, 0.93; 95% CI, 0.81 to 1.06) and hospitalization for HF (27.4% vs 29.6%; HR, 0.90; 95% CI, 0.81 to 1.00) were not significantly different between groups. Total hospitalizations for HF (initial and recurrent) were significantly reduced with vericiguat (1,223 vs 1,336; p = 0.02) as was the composite of death from any cause or first HF hospitalization (37.9% vericiguat vs 40.9% placebo; HR, 0.90; 95% CI, 0.83 to 0.98; p = 0.02). Serious adverse events occurred in 32.8% of patients in the vericiguat group vs 34.8% of patients in the placebo group. Symptomatic hypotension (9.1% vs 7.9%) and syncope (4% vs 3.5%) were observed more frequently in the vericiguat group (*Armstrong et al 2020a*).

- Of note, ivabradine and vericiguat have been studied separately in patients with HFpEF via the EDIFY and VITALITY-HFpEF trials, respectively. Both trials were placebo-controlled, multicenter trials. EDIFY included 179 HF patients in sinus rhythm with a heart rate of ≥ 70 bpm, N-terminal pro–B-type natriuretic peptide (NT-proBNP) ≥ 220 pg/mL, and LVEF ≥ 45%. Patients were randomly assigned to ivabradine 7.5 mg twice daily or placebo and followed up for 8 months. At trial conclusion, reductions in heart rate with ivabradine did not improve outcomes (*Komajda et al 2017*). Additionally, VITALITY included 789 chronic HF patients with a LVEF ≥ 45% and NYHA class II to III symptoms. Patients were randomly assigned to vericiguat up-titrated to 15 mg once daily (n = 264), 10 mg once daily (n = 263), or placebo (n = 262). Results revealed that vericiguat 15 or 10 mg once daily did not improve the Kansas City Cardiomyopathy Questionnaire (KCCQ) physical limitation score (PLS) compared to placebo after 24 weeks (*Armstrong et al 2020b*).

CLINICAL GUIDELINES

Heart Failure

- The 2016 and 2017 focused updates of the American College of Cardiology/American Heart Association/Heart Failure Society of America (ACC/AHA/HFSA) HF guidelines recommend the following medications in patients with HFrEF (Stage C and D; NYHA Class I to IV): (*Yancy et al 2013, Yancy et al 2016, Yancy et al 2017*).
  - First line treatments include an ACE-I or ARB in conjunction with an evidence-based β-blocker and diuretics, as needed.
    - Entresto (sacubitril/valsartan) has been approved for patients with symptomatic HFrEF and is intended to be substituted for ACE-Is or ARBs. Angiotensin receptor neprilysin inhibitors (ARNIs) may be considered first line; however, recommendations are made with a lower level of evidence than those associated with ACE-Is or ARBs

and recommendations are made only if a patient can tolerate an ACE-I or ARB. For those patients for whom an ARNI is not appropriate, continued use of an ACE-I, followed by an ARB, for all classes of HFrEF remains strongly advised.
  - Add-on treatments vary according to the patient specific factors, but may include an aldosterone antagonist, hydralazine-nitrates, an ARNI, ivabradine, digoxin, and device therapy (ie, implantable cardioverter-defibrillator [ICD] or cardiac resynchronization therapy [CRT]).
  - Ivabradine can be beneficial in patients who have stable, symptomatic (NYHA Class II or III) chronic HFrEF, are in normal sinus rhythm, have a heart rate of ≥ 70 bpm at rest, and are on the maximally tolerated dose of β-blockers
- Based on the 2016 European Society of Cardiology/Heart Failure Association (ESC/HFA) HF guidelines, ivabradine is recommended to be prescribed after treatment failure with maximally tolerated doses of ACE-I/ARB/ARNIs, β-blockers, mineralocorticoid receptor antagonists, and in patients still symptomatic with a LVEF ≤ 35%, in sinus rhythm, and with a heart rate ≥ 70 bpm. If patients still have resistant symptoms, then clinicians may consider adding digoxin, hydralazine plus isosorbide dinitrate, or propose a left ventricular assist device (LVAD) or heart transplant (*Ponikowski et al 2016).*
  - Diuretics and ACE-Is/ARBs are considered first-line therapies, whereas β-blockers and devices for electric therapy are used less often in children than in adults. In end-stage disease, heart transplantation is the best choice of treatment, while a left ventricular assist device can be used as a bridge to transplantation (due to the difficulties in finding organ donors), recovery (in the case of myocarditis), or destination therapy (for patients with systemic disease).
- In 2014, the European Medicine's Agency (EMA) published updated guidance for ivabradine in the treatment of angina. Updated guidance states that ivabradine should only be used to alleviate angina symptoms, but should be stopped if no to limited benefit is observed after 3 months of treatment. Additionally, increased incidences of atrial fibrillation and bradycardia were observed in trials; although study doses were higher than EMA-approved doses (*EMA 2014, Fox et al 2014*).
- Due to vericiguat's recent approval, official recommendations regarding its use are not incorporated in current HF practice guidelines.

Ischemic heart disease/chronic stable angina
- Guidelines for treatment of chronic stable angina, including AHA and ACCF, on the diagnosis and management of stable IHD include the following recommendations (*Fihn et al 2012*):

  Class I recommendations (all have level of evidence B)
  - β-blockers for initial therapy for relief of anginal symptoms.
  - Calcium channel blockers or long-acting nitrates for initial therapy for relief of anginal symptoms for patients in whom β-blockers are contraindicated or not tolerated.
  - Calcium channel blockers or long-acting nitrates in combination with a β-blocker for patients in whom β-blockers do not provide adequate control of symptoms.
  - Short-acting nitroglycerin (sublingual or spray) is recommended for immediate relief of angina.

  Class IIa recommendations (all level of evidence B unless indicated otherwise)
  - Long-acting, non-dihyrodpyridine calcium channel blockers can be used instead of β-blockers for initial therapy.
  - Ranolazine ER can be useful as a substitute for β-blockers for relief of symptoms for patients who cannot tolerate, who have a contraindication to, or in whom β-blockers are not successful.
  - Ranolazine ER can be used in combination with a β-blocker for relief of symptoms for patients in whom initial treatment with a β-blocker alone is not adequate (Level of evidence: A)

SAFETY SUMMARY
- Ivabradine is contraindicated in patients with acute decompensated heart failure, clinically significant hypotension or bradycardia, severe hepatic impairment, pacemaker dependence (heart rate maintained exclusively by the pacemaker), concomitant use of strong cytochrome P450 3A4 (CYP3A4) inhibitors, and sick sinus syndrome, sinoatrial block or third degree atrioventricular (AV) block, unless a functioning demand pacemaker is present.
- Key warnings and precautions include the following:
  - Fetal toxicity: Embryo-fetal toxicity and cardiac teratogenic effects were observed in animal models. Females should use effective contraception when taking ivabradine.

- Atrial fibrillation: Ivabradine increases the risk of atrial fibrillation (ivabradine 5% vs placebo 3.9% per patient per year). Cardiac rhythm should be regularly monitored and ivabradine should be discontinued if atrial fibrillation develops.
- Bradycardia and conduction disturbances: Bradycardia may increase the risk of QT prolongation leading to severe arrhythmias, especially in patients with risk factors such as use of QT prolonging medications. Bradycardia, sinus arrest, and heart block were observed in trials with ivabradine. Concomitant use of verapamil or diltiazem should be avoided, as they can lower heart rate. Ivabradine should be avoided in patients with second degree AV block, unless a functioning demand pacemaker is present.

- The most common adverse effects for ivabradine (incidence ≥ 1%) are bradycardia, hypertension, atrial fibrillation, and luminous phenomena (phosphenes).
- Ranolazine ER is contraindicated in patients with liver cirrhosis, concomitant use of strong CYP3A4 inhibitors (ie, ketoconazole, clarithromycin, nelfinavir) and concomitant use of CYP3A inducers (ie, rifampin, phenobarbital, St. John's wort).
- Key warnings and precautions include the following:
  - QT interval prolongation: Clinical experience in an acute coronary syndrome population did not show an increased risk of proarrhythmia or sudden death. There is little experience with use of ranolazine ER at doses higher than 1000 mg twice daily, with other QT-prolonging drugs, in patients with a family history of long QT syndrome, or with known acquired QT interval prolongation.
  - Renal failure: Ranolazine ER has caused acute renal failure in patients with a creatinine clearance (CrCL) < 30 mL/min. Renal function should be assessed at baseline and periodically in patients with moderate to severe renal impairment (CrCL < 60 mL/min). Ranolazine ER should be discontinued if marked increases in serum creatinine and blood urea nitrogen are observed.
- The most common adverse effects for ranolazine (incidence > 4% and more common than placebo) are dizziness, headache, constipation, and nausea. Adverse effects that led to discontinuation in controlled studies included dizziness, nausea, asthenia, constipation, and headache.
- In a long-term, open-label study evaluating the safety of ranolazine ER use for 2 years, 23.3% of approximately 750 patients discontinued treatment (*Koren et al 2007*). Slightly over 40% of the discontinuations were due to adverse events of which the most common were dizziness and constipation.
- Vericiguat is contraindicated in patients with concomitant use of other sGC stimulators and in pregnancy.
- Key warning and precaution with vericiguat include the risk for embryo-fetal toxicities. Women of childbearing potential should obtain a pregnancy test before treatment initiation and should use effective contraception during treatment and for at least 1 month after the final dose.
- The most common adverse effects for vericiguat (incidence ≥ 5%) are hypotension and anemia.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Corlanor (ivabradine)	Tablets, oral solution	Oral	Twice daily	For adults, the dose should be assessed and adjusted to a resting heart rate of 50 to 60 bpm after 2 weeks. For pediatric patients, the dose should be assessed and adjusted to target a heart rate reduction of ≥ 20% (based on tolerability) after 2 weeks. Should be taken with meals. Oral solution can also be used for adults who are unable to swallow tablets.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ranexa (ranolazine ER)	Extended-release tablets	Oral	Twice daily	Can be titrated to a maximum dose of 1000 mg twice daily based on symptoms. Dose greater than 500 mg twice daily should not be used in patients taking moderate CYP3A4 inhibitors such as diltiazem, verapamil, fluconazole, erythromycin, and grapefruit juice. Monitor clinical response and adverse effects closely in patients taking P-glycoprotein inhibitors such as cyclosporine as ranolazine ER concentrations may be increased.* Can be taken with or without meals. Tablets should not be crushed, chewed, or broken.
Verquvo (vericiguat)	Tablets	Oral	Once daily	Double the dose approximately every 2 weeks to reach the target maintenance dose of 10 mg once daily, as tolerated by the patient. Should be taken with meals. May be crushed and mixed with water immediately before administration for patients who are unable to swallow whole tablets.

See the current prescribing information for full details; *Dose adjustment of other agents used concomitantly with ranolazine ER may be required; refer to prescribing information for ranolazine ER and concomitant medications for details.

CONCLUSION

- Ivabradine has a novel mechanism action for the treatment of adult and pediatric patients with HF and specific cardiac abnormalities.
- Ivabradine 10 mg twice daily has demonstrated no clinical benefit in patients with stable coronary heart disease without clinical HF based on results from the SIGNIFY trial (*Fox et al 2014*).
- In 2014, the EMA published updated guidance for ivabradine in the treatment of angina. Updated guidance states that ivabradine should only be used to alleviate angina symptoms, but should be stopped if no to limited benefit is observed after 3 months of treatment. Additionally, increased incidences of atrial fibrillation and bradycardia were observed in trials; although study doses were higher than EMA-approved doses (*EMA 2014, Fox et al 2014*).
- In the BEAUTIFUL and SHIFT trials, HF patients with ≥ 70 bpm had clinical benefit, specifically for reducing the rate of hospitalizations (*Fox et al 2014, Swedberg et al 2010*).
- The SHIFT trial measured effects of ivabradine in a very niche HF population, most whom were not dose optimized on β-blockers. Compared to placebo plus standard care, ivabradine plus standard care significantly reduced the composite endpoint of CV-related deaths and HF hospitalizations; however, this was primarily driven by rates of HF hospitalization as the rates of CV-related deaths were no different from placebo.

- In all trials, ivabradine has demonstrated increased incidences of bradycardia, eye disturbances (e.g., blurred vision or phosphenes), and atrial fibrillation (*Fox et al 2008, Fox et al 2014, Swedberg et al 2010*).
- Based on HF guidelines, ivabradine can be beneficial in patients who have stable, symptomatic (NYHA Class II or III) chronic HFrEF, are in normal sinus rhythm, have a heart rate of ≥ 70 bpm at rest, and are on maximally tolerated doses of β-blockers (*Ponikowski et al 2016, Yancy et al 2013, Yancy et al 2016, Yancy et al 2017*).
- Ranolazine ER is an antianginal agent that does not impact hemodynamic parameters such as heart rate or blood pressure. Although its exact mechanism of action is unknown, it is postulated that its action reduces intracellular calcium in cardiac myocytes leading to myocardial relaxation.
- Clinical trials have demonstrated statistical improvement in exercise duration, weekly anginal attacks, and weekly nitroglycerin use compared to placebo in patients with SA receiving background standard of care treatment (*Chaitman et al 2004, Stone et al 2006, Banon et al 2014*). Well-designed trials comparing ranolazine ER to standard of care treatments such as β-blockers or calcium channel blockers are lacking.
- According to guidelines, including the ACCF and AHA, ranolazine ER is an alternative treatment option for the relief of anginal symptoms in patients with stable IHD (*Fihn et al 2012*). Ranolazine ER can be considered as a third line agent (after either a calcium channel blocker or long-acting nitrate) for patients who cannot take a β-blocker due to a contraindication or intolerance. For patients who have persistent symptoms despite β-blocker therapy, ranolazine ER can be used in combination with a β-blocker However, the use of either a calcium channel blocker or long-acting nitrate in combination with a β-blocker should be considered first.
- The mechanism of action of vericiguat (sGC stimulation) is also unique for the treatment of adults with symptomatic chronic HF and an EF <45%.
- In the VICTORIA trial, vericiguat was associated with significantly less occurrences of the composite of death from CV causes or first hospitalization for HF as compared to placebo at a median of 10.8 months. However, death from CV causes and hospitalization for HF were not significantly different between groups. Serious adverse events in VICTORIA occurred in 32.8% of patients in the vericiguat group vs. 34.8% of patients in the placebo group.
- Due to vericiguat's recent approval, official recommendations regarding its use are not incorporated in current HF practice guidelines.

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INTRODUCTION

Phosphate Binders

- Hyperphosphatemia, an important and inevitable clinical consequence of advanced stages of chronic kidney disease (CKD), requires appropriate management due to the risk for secondary hyperparathyroidism and cardiovascular disease. Persistent or chronic hyperphosphatemia, along with an elevated calcium times phosphorus (Ca x P) product, is associated with an increased risk of vascular, valvular, and other soft-tissue calcification in patients with CKD. Elevated phosphorus levels may also directly influence several components of CKD-mineral and bone disorder (CKD-MBD) such as secondary hyperparathyroidism, bone abnormalities, calcitriol deficiency, and extraskeletal calcification. In addition, there is evidence consistently demonstrating that hyperphosphatemia is a predictor of mortality in CKD stage 5 patients who are receiving dialysis. Because of these reasons, control of serum phosphorus levels in patients with CKD is an important component of care (*Kidney Disease Improving Global Outcomes [KDIGO] 2009, KDIGO 2017, National Kidney Foundation [NKF] 2003, Kestenbaum et al 2005, Voormolen et al 2007*).
- The 2 principal modalities used to control serum phosphorus levels in patients with CKD include restricting dietary phosphorus intake and administering phosphate binders. When dietary phosphorus restriction is inadequate in controlling serum phosphorus levels, the administration of phosphate binders is recommended. The phosphate binder class can be divided into 2 subcategories: calcium- and non-calcium-containing products. Calcium-based phosphate binders include calcium carbonate and calcium acetate; calcium-free binders include aluminum hydroxide, lanthanum carbonate, magnesium carbonate, sevelamer hydrochloride, sevelamer carbonate, ferric citrate, and sucroferric oxyhydroxide. The use of calcium carbonate (available over-the-counter) as a phosphorus binder is off-label and therefore is not detailed in this review.
- The 2017 KDIGO guideline for the diagnosis, evaluation, prevention, and treatment of CKD-MBD does not specifically recommend one type of phosphate-binder as first-line therapy, but suggests restricting the dose of calcium-based phosphate binders in adult patients with CKD stage 3a to 5 (with or without dialysis) receiving phosphate-lowering treatment. In children, it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels *(KDIGO 2017).*
- The sevelamer hydrochloride salt was the initial sevelamer formulation developed; however, because of the incidence of metabolic acidosis associated with its use, a buffered formulation was created. The sevelamer carbonate formulation has advantages compared to sevelamer hydrochloride because it does not lower a patient's bicarbonate level and does not result in the development of metabolic acidosis *(Perry and Plosker 2014)*. An advantage to the use of lanthanum carbonate is a decrease in the pill burden compared to other products (*Prescribing information: Fosrenol 2020, Renagel 2020, Renvela 2020*). Two iron-based, calcium-free phosphate binders are Velphoro (sucroferric oxyhydroxide) and Auryxia (ferric citrate). Velphoro may reduce the pill burden for those patients who require higher doses of sevelamer as demonstrated in trials (*Prescribing information: Auryxia 2021, Velphoro 2020; Wuthrich et al 2013*).
- Available evidence supports the efficacy of all of the phosphorus binders in controlling serum phosphorus levels. It is generally accepted that no one product is effective and acceptable to every patient. Although treatment guidelines recommend serum phosphorus levels to be maintained within or slightly above the normal range (depending on CKD stage), there is currently no evidence to demonstrate that lowering phosphorus to a specific target range results in improved clinical outcomes in patients with CKD. Despite this lack of evidence, it is still reasonable to use phosphorus binders to lower phosphorus levels in CKD patients with hyperphosphatemia to prevent the development of secondary hyperparathyroidism and cardiovascular disease.
- The main considerations for selection of phosphate binders include absorbability, adequate gastrointestinal (GI) tolerability, and cost or cost-effectiveness (*Frazão et al 2012*).
- Medispan Therapeutic Class: Phosphate Binder Agents

Table 1. Medications Included Within Class Review – Phosphate Binders

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

* Fosrenol chewable tablets are available generically; however, the Fosrenol oral powder packet is not generically available.
† Calcium acetate 667 mg tablets are also available over-the-counter (Calphron).

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

Potassium Removing Agents

- Hyperkalemia is a common clinical problem that is most often a result of impaired urinary potassium excretion due to acute or chronic kidney disease and/or disorders or drugs that inhibit the renin-angiotensin-aldosterone system (RAAS). The most serious manifestations of hyperkalemia are muscle weakness or paralysis, cardiac conduction abnormalities, and cardiac arrhythmias, including sinus bradycardia, sinus arrest, slow idioventricular rhythms, ventricular tachycardia, ventricular fibrillation, and asystole. These manifestations usually occur when the serum potassium concentration is ≥ 7 mEq/L with chronic hyperkalemia or possibly at lower levels with an acute rise in serum potassium or in patients with an underlying cardiac conduction disorder (*Mount 2020*).
- There are no clear guidelines regarding the appropriate setting for the treatment of hyperkalemia. The decision for hospital admission for continuous electrocardiogram (ECG) monitoring is a matter of clinical judgment in each case. Patients believed to have a rapid rise in potassium commonly need inpatient care, whereas patients whose hyperkalemia has developed over a period of weeks can often be managed in an outpatient setting with close follow-up (*Hollander-Rodriquez and Calvert 2006, NKF 2016, Rafique et al 2017*).
  - Urgent treatment of hyperkalemia includes 3 main phases: 1) antagonizing cardiac effects of potassium (using intravenous [IV] calcium gluconate); 2) redistributing potassium into cells (using insulin with dextrose, beta-2-adrenergic agonists, or sodium bicarbonate); and 3) removing excess potassium from the body (ie, using hemodialysis, loop diuretics, or cation exchange resins) (*Hollander-Rodriquez and Calvert 2006, Mount 2020, Raebel 2012*).
  - In patients who do not require urgent treatment, lowering total body potassium may be the only step necessary (*Hollander-Rodriquez and Calvert 2006, NKF 2016, Rafique et al 2017*).
- Long-term treatment or prevention of hyperkalemia should be tailored to correcting the underlying cause of hyperkalemia (*Hollander-Rodriquez and Calvert 2006*).
- Cation exchange resins are used in clinical practice for removing excess potassium from the body. Prior to 2015, Kayexalate (sodium polystyrene sulfonate) was the only potassium binding agent approved in the United States for the treatment of hyperkalemia; however, the use of sodium polystyrene sulfonate has been limited by tolerability and safety concerns (ie, colonic necrosis and sodium absorption leading to volume overload) and questions about efficacy (*Veltassa Food and Drug Administration [FDA] Summary Review 2015*).
- In October 2015, the FDA approved Veltassa (patiromer), a non-absorbed, cation exchange polymer that contains a calcium-sorbitol counterion, for the treatment of hyperkalemia.
- In May 2018, the FDA approved Lokelma (sodium zirconium cyclosilicate), a non-absorbed zirconium silicate, for the treatment of hyperkalemia in adults.
- Medispan Therapeutic Class: Potassium Removing Agents

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

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

*Sodium polystyrene sulfonate is generically available; brand Kayexalate is no longer available; SPS is a branded generic.

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

INDICATIONS

Table 3. FDA-Approved Indications for Phosphate Binders

Generic name	Reduce serum phosphate in end stage renal disease	Adjunct to reduction in dietary intake of phosphate and dialysis to reduce serum phosphorus in patients with kidney failure on dialysis	Control serum phosphorus in patients with CKD on dialysis	Iron deficiency anemia in CKD in patients not on dialysis
calcium acetate	✔ (PhosLo)	✔ (Phoslyra)		
ferric citrate			✔	✔
lanthanum carbonate	✔			
sevelamer carbonate			✔ *	
sevelamer hydrochloride			✔ †	
sucroferric oxyhydroxide			✔	

* in adults and children 6 years of age and older †Safety and efficacy in CKD patients who are not on dialysis have not been studied.

(Prescribing information: Auryxia 2021, Fosrenol 2020, PhosLo 2013, Phoslyra 2020, Renagel 2020, Renvela 2020, Velphoro 2020)

Table 4. FDA-Approved Indications for Potassium Removing Agents

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

*Should not be used as an emergency treatment for life-threatening hyperkalemia

(Prescribing information: Lokelma 2020, sodium polystyrene sulfonate powder for suspension 2020, sodium polystyrene sulfonate suspension 2017, Veltassa 2018)

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

SUMMARY

Phosphate Binders

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

Shigematsu et al 2008, Shigematsu et al 2010, Sprague et al 2009, St. Peter et al 2008, Suki et al 2007, Wilson et al 2009).

- In general, the true benefits of phosphorus lowering with respect to hard clinical outcomes have not been established, and most clinical trials have evaluated surrogate endpoints. A systematic review of 18 studies evaluated the rate of all-cause mortality among those treated with non-calcium-based phosphate binders compared to calcium-based phosphate binders in patients with CKD (*Jamal et al 2013*). The non-calcium based group which included sevelamer and lanthanum had a statistically significant reduction of 22% in all-cause mortality compared to calcium-based phosphate binders (risk ratio 0.78, 95% confidence interval [CI]: 0.61 to 0.98, $I^2 = 43\%$; 11 randomized clinical trials, N = 4622). Note that 2 observational studies and 1 cross-sectional study were included. No significant reduction in cardiovascular events was observed.
- Clinical trials have consistently demonstrated that sevelamer hydrochloride is effective at lowering phosphorus levels and maintaining phosphate control comparable to calcium acetate and calcium carbonate therapy (*Bleyer et al 1999, Evenepoel et al 2009, Hervas et al 2003, Pieper et al 2006, Qunibi et al 2004).* A 2018 systematic review concluded that sevelamer may lower death from all causes and significantly decrease the risk of hypercalcemia compared with calcium-based agents (*Ruospo et al 2018*). A 2016 meta-analysis of 25 studies with 88% of patients on hemodialysis found lower all-cause mortality with sevelamer (risk ratio 0.54, 95% CI: 0.32 to 0.93) compared to calcium-based binders, but no statistical difference for cardiovascular mortality was observed (*Patel et al 2016*).
- Clinical trials demonstrate that lanthanum carbonate and sevelamer show comparable efficacy in lowering phosphorous although limited studies have compared the 2 therapies for efficacy (*Kasai et al 2012*). Findings from a meta-analysis showed that, compared with calcium-based agents, lanthanum significantly decreased the risk for hypercalcemia but had similar effects on phosphate levels (*Ruospo et al 2018*). A randomized controlled trial also found similar effects on phosphorus levels with lanthanum compared to calcium acetate at the 1 year mark (*Kovesdy et al 2018*).
- The efficacy and safety of sucroferric oxyhydroxide were evaluated in 3 trials: a fixed dose study, a dose titration study, and a dose titration extension study. Sucroferric oxyhydroxide demonstrated efficacy by significantly reducing serum phosphorus in hemodialysis and peritoneal dialysis patients from 6 to 52 weeks (*Velphoro prescribing information 2020, Wuthrich et al 2013*).
  - In the fixed dose study, all sucroferric oxyhydroxide dose groups showed a significant decrease in serum phosphorus ($p \leq 0.02$), except the 250 mg/day group. The proportion of sucroferric oxyhydroxide-treated patients achieving goal phosphorus levels after 6 weeks of treatment ranged from 35 to 60% for 1000 to 2500 mg/day, and 42.1% in the sevelamer control arm. The median time to reach first controlled serum phosphorus levels was not different for sucroferric oxyhydroxide (1 week) vs the sevelamer (2 weeks) control arm ($p > 0.16$) (*Wuthrich et al 2013*).
  - In the dose titration study, sucroferric oxyhydroxide 1000 to 3000 mg/day was statistically superior to the sucroferric oxyhydroxide low dose (250 mg) control in maintaining the phosphorus-lowering effect in hemodialysis patients at week 27 ($p < 0.001$) (*Floege et al 2014*). In the extension trial, sucroferric oxyhydroxide demonstrated a greater change from baseline in serum phosphorus when compared to sevelamer carbonate from weeks 32 to 40. However, from weeks 44 to 52, changes in serum phosphorus between sevelamer carbonate and sucroferric oxyhydroxide were similar (*Floege et al 2015*). The greatest changes from baseline for serum phosphorus occurred up to week 12 for sevelamer carbonate and up to week 20 for sucroferric oxyhydroxide (*Velphoro prescribing information 2020*).
  - The most frequent adverse events were hypophosphatemia and discolored feces for the sucroferric oxyhydroxide groups. Sucroferric oxyhydroxide patients experienced more discolored feces, hypophosphatemia, muscle spasms, and constipation compared to sevelamer HCl in the active comparator trial (*Wuthrich et al 2013*).
- Ferric citrate is an iron-based, calcium-free phosphate binder that has been studied in several published trials. Ferric citrate is similarly safe and effective to 2 current first-line phosphate binders, calcium acetate and sevelamer (*Lewis et al 2015*). Ferric citrate offers a reduced pill burden vs sevelamer carbonate but not vs calcium acetate. In addition to reducing serum phosphorus, ferric citrate raises iron stores (evidenced by increased hemoglobin, serum ferritin, and serum transferrin saturation) and decreases IV iron and erythropoietin stimulating agent usage (*Auryxia Prescribing Information 2021, Block et al 2015, Lewis et al 2015, Umanath et al 2015, Choi 2020*).

Potassium Removing Agents

- The FDA first approved sodium polystyrene sulfonate in 1958, 4 years before passage of the Kefauver-Harris Drug Amendment, which requires drug manufacturers to prove the effectiveness of their products before marketing (*Sterns et al 2010*).

- In 1961, Scherr et al reported the largest clinical experience with sodium polystyrene sulfonate suspended in water in an uncontrolled study of hyperkalemic patients with acute and chronic renal failure, using the newly approved sodium polystyrene sulfonate. In 23 of 30 cases, the plasma potassium fell by at least 0.4 mEq/L in the first 24 hours. Two patients with pre-treatment potassium levels of 6.1 and 7.4 mEq/L developed hypokalemia (3.3 and 2.3 mEq/L) while receiving 40 g/day of oral resin for 2 and 6 days. On the strength of this study and several smaller case series, the FDA's Drug Efficacy Study Implementation (DESI) Program, charged with reviewing pre-1962 drugs that were already on the market, ruled sodium polystyrene sulfonate powder "effective" (*Sterns et al 2010*).

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

mEq/L [95% CI: 4.3 to 4.5] for 5 g, 10 g, and 15 g; 5.1 mEq/L [95% CI: 5.0 to 5.2] for placebo; p < 0.001 for all comparisons).
    - Patients who completed the 28-day randomized withdrawal phase had the option to continue treatment with sodium zirconium cyclosilicate, in an open-label extension phase for up to 11 months (n = 123). The treatment effect on serum potassium was maintained during continued therapy *(Lokelma Prescribing Information 2020, Roger et al 2019)*.
    - The same study protocol was performed in Japan, Russia, South Korea, and Taiwan (HARMONIZE-Global). Maintenance of normokalemia was higher in the 5 g group (58.6%) and 10 g group (77.3%) compared to placebo (24%) (p < 0.001 for all comparisons) (*Zannad et al 2020).*
  - Sodium zirconium cyclosilicate was also evaluated in an open-label 12-month study in 751 hyperkalemic patients. The mean baseline potassium level in this study was 5.6 mEq/L. Following the acute phase treatment of sodium zirconium cyclosilicate 10 g 3 times a day, patients who achieved normokalemia (3.5 to 5.0 mEq/L) within 72 hours (n = 746; 99%) entered the maintenance phase. For maintenance treatment, the initial dosage was 5 g once daily and was adjusted to a minimum of 5 g every other day up to maximum of 15 g once daily, based on serum potassium level. The treatment effect on serum potassium was maintained during continued therapy, regardless of whether glomerular filtration rate was < 30 or ≥ 30 mL/min/1.73m^2 *(Lokelma Prescribing Information 2020, Spinowitz et al 2019, Roger et al 2021)*.
  - The safety and efficacy of sodium zirconium cyclosilicate were evaluated in patients with end stage renal disease (ESRD) receiving hemodialysis through a double-blind, placebo-controlled, Phase 3b randomized clinical trial. A total of 196 patients with pre-dialysis hyperkalemia were randomized to receive either placebo or sodium zirconium cyclosilicate 5 g daily on non-dialysis days, with the option of titrating to 15 g daily. A total of 41.2% of patients receiving sodium zirconium cyclosilicate achieved a pre-dialysis potassium serum level between 4.0 and 5.0 mmol/L following 4 weeks of therapy compared to 1.0% in the placebo group (p < 0.001) *(Fishbane et al 2019)*.
- A 2020 Cochrane review of 15 randomized controlled trials (RCTs) evaluated the evidence on the effectiveness and tolerability of potassium binders in patients with CKD and chronic hyperkalemia (n = 1849). Twelve of the 15 studies included patients with CKD not on dialysis and 3 studies were in patients receiving dialysis. Calcium polystyrene sulfonate, sodium polystyrene sulfonate, patiromer, and sodium zirconium cyclosilicate were the potassium binders studied in the included trials. Ten studies compared a potassium binder to placebo. Little to no effect on mortality was observed with patiromer or sodium zirconium cyclosilicate vs placebo. Impact on mortality was not evaluated with the older agents, calcium or sodium polystyrene sulfonate. There was no apparent impact of these agents on GI-related symptoms (nausea, diarrhea, constipation, vomiting) or quality of life. No studies evaluated the impact on cardiac arrhythmias or major GI events. The authors concluded that the current evidence comparing different potassium binders vs placebo on outcomes of cardiac arrhythmias or major GI events is lacking (*Natale et al 2020*).

CLINICAL GUIDELINES

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

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

- **Kidney Disease Outcomes Quality Initiative (KDOQI) – US Commentary on the 2017 KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of CKD-MBD** *(Isakova 2017)*

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

- **NKF - Best practices in managing hyperkalemia in CKD** (*NKF 2016*)
  - Although not a guideline, NKF's best practices provides a general guide to clinicians on management of acute and chronic hyperkalemia in patients with CKD.
  - Chronic hyperkalemia requires ongoing pharmacologic and non-pharmacologic interventions.
  - In addition to monitoring dietary potassium, pharmacologic options include fludrocortisone acetate for patients with aldosterone deficiency, cation exchange resins such as sodium polystyrene sulfonate, and patiromer. Sodium zirconium cyclosilicate is not listed as this agent became available after the best practices document was published.

SAFETY SUMMARY

Phosphate Binders

- Sevelamer carbonate and sevelamer hydrochloride are contraindicated in patients with bowel obstruction. Cases of dysphagia, bowel obstruction and perforation, and esophageal tablet retention have been reported in association with use of the tablet formulation of sevelamer, some requiring hospitalization and intervention. Inflammatory disorders may resolve upon sevelamer discontinuation. The sevelamer suspension formulation should be considered in patients with a history of swallowing disorders. Adverse effects possibly related to sevelamer included nausea, vomiting, dyspepsia, diarrhea, flatulence, abdominal pain, and constipation. Ciprofloxacin should be taken at least 2 hours before or 6 hours after sevelamer, and mycophenolate mofetil should be taken at least 2 hours before sevelamer.
- Calcium acetate is contraindicated in patients with hypercalcemia. Calcium supplements should be used with caution in patients with CKD due to the increased risk of developing hypercalcemia. The most common adverse effects include hypercalcemia, nausea, and vomiting. Diarrhea has been reported with calcium acetate oral solution and may be more pronounced when administered with nutritional supplements containing maltitol. The administration of calcium acetate may decrease the bioavailability of tetracyclines, fluoroquinolones or levothyroxine (Phoslyra).
- Ferric citrate is contraindicated in patients with iron overload. Ferric citrate should be kept out of the reach of children to lower the risk of accidental overdose of iron. Adverse events reported in > 5% of patients treated with ferric citrate in clinical trials included diarrhea, nausea, constipation, vomiting, discolored feces, abdominal pain, hyperkalemia, and cough. Doxycycline should be taken at least 1 hour before ferric citrate. Ciprofloxacin should be taken at least 2 hours before or after ferric citrate.
- Bowel obstruction, ileus, and fecal impaction are contraindications to lanthanum carbonate therapy. Serious adverse events consisting of GI obstruction, ileus, subileus, GI perforation, and/or fecal impaction have been reported with this medication, and some of these events required surgery or hospitalization. Adverse events that were more commonly associated with lanthanum carbonate therapy included nausea, vomiting, and abdominal pain. Compounds that bind aluminum-, magnesium-, or calcium-based cationic antacids and thyroid hormone replacement therapy should be separated by at least 2 hours from lanthanum carbonate. Fluoroquinolones should be taken at least 1 hour before or 4 hours after lanthanum. Patients should be advised to chew lanthanum carbonate tablets completely and to not swallow them whole. Serious GI complications have been associated with unchewed or incompletely chewed tablets.
- Sucroferric oxyhydroxide does not have any contraindications. Due to the potential for drug interactions, levothyroxine should be taken at least 4 hours before sucroferric oxyhydroxide. Doxycycline, acetylsalicylic acid, and cephalexin must be taken at least 1 hour before sucroferric oxyhydroxide. Common adverse events include dark/discolored feces, nausea, and diarrhea.

Potassium Removing Agents

- Patiromer is contraindicated in patients with known hypersensitivity to patiromer or any of its components. Warnings and precautions of patiromer include worsening of GI motility and hypomagnesemia. The most common adverse effects (≥ 2%) with patiromer use were constipation, hypomagnesemia, diarrhea, nausea, abdominal discomfort, and flatulence.
- Sodium polystyrene sulfonate powder for suspension is contraindicated in patients with obstructive bowel disease and neonates with reduced gut motility. Sodium polystyrene sulfonate suspension is contraindicated in patients with hypokalemia, obstructive bowel disease, as oral administration in neonates, and in neonates with reduced gut motility.

Warnings and precautions for sodium polystyrene sulfonate include intestinal necrosis; development of hypokalemia or other electrolyte disturbances; fluid overload in patients sensitive to high sodium intake; and risk of aspiration.
  - Sodium polystyrene sulfonate may cause some degree of gastric irritation. Anorexia, nausea, vomiting, and constipation may occur especially if high doses are given. Occasionally diarrhea develops.
- Sodium zirconium cyclosilicate does not have any contraindications. Warnings and precautions for sodium zirconium cyclosilicate include GI adverse events in patients with motility disorders, edema, and hypokalemia in hemodialysis patients. The most common adverse effect was mild to moderate edema.

DOSING AND ADMINISTRATION

Table 5. Dosing and Administration of Phosphate Binders

Generic name	Available Formulations	Route	Usual Recommended Frequency	Comments
calcium acetate	Capsule, tablet, solution	Oral	Administered with each meal	--
ferric citrate	Tablet	Oral	Three times daily with meals	• Do not crush or chew because it may cause discoloration of teeth and mouth.
lanthanum carbonate	Chewable tablet, powder	Oral	Administered with meals or immediately after meals	• Use is not recommended in children. In animal studies, lanthanum was deposited into developing bone including the growth plate. Consequences of lanthanum bone deposition are unknown. • Powder can be considered in patients with poor dentition or difficulty swallowing tablets.
sevelamer carbonate	Powder for oral suspension, tablet	Oral	Three times daily with meals	• Dose in adults is based on serum phosphorus levels. • Dose in pediatric patients should be based on body surface area.
sevelamer hydrochloride	Tablet	Oral	Three times daily with meals	--
sucroferric oxyhydroxide	Chewable tablet	Oral	Three times daily with meals	• Tablets should be chewed or crushed and not swallowed whole.

See the current prescribing information for full details

Table 6. Dosing and Administration of Potassium Removing Agents

Generic name	Available Formulations	Route	Usual Recommended Frequency	Comments
patiromer	Powder for suspension	Oral	Once daily with or without food	• Administer at least 3 hours before or 3 hours after other oral medications. • Do not administer in its dry form.
sodium polystyrene sulfonate	Powder for suspension; suspension	Oral; rectal (enema)	Oral: 1 to 4 times daily Rectal: Every 6 hours	• Administer at least 3 hours before or 3 hours after other oral medications. • Patients with gastroparesis may require a 6-hour separation. • The enema should be retained as long as possible and followed by a cleansing enema.
sodium zirconium cyclosilicate	Powder for suspension	Oral	Starting dose is 10 g administered 3 times daily for up to 48	• Other oral medications should be administered at least 2 hours before or 2

Generic name	Available Formulations	Route	Usual Recommended Frequency	Comments
			hours; for maintenance, recommended dose is 10 g once daily or 5 g once daily on non-dialysis days for hemodialysis patients	hours after sodium zirconium cyclosilicate.

CONCLUSION

Phosphate Binders

- The phosphate binders (or phosphate depleters) class is an important aspect of the medical management of patients with CKD; these agents are used to lower a patient's phosphorus level. If phosphorus levels remain elevated in this population, the patient is at a greater risk for the development of secondary hyperparathyroidism or cardiovascular disease. In addition, there is available evidence to demonstrate that hyperphosphatemia is a predictor of mortality in CKD stage 5 patients who are receiving dialysis. In patients with CKD stage 3 to stage 5 (with or without dialysis), decisions about phosphate-lowering treatment should be based on progressively or persistently elevated serum phosphate. The broader term "phosphate-lowering" treatment is used instead of phosphate binding agents since all possible approaches (ie, binders, diet, or dialysis) can be effective (*NKF 2003, KDIGO 2009, KDIGO 2017*).
- The 2 subgroups of phosphate binders currently available include the calcium and non-calcium containing products. Available evidence supports the efficacy of all of the phosphate binders in controlling serum phosphorus levels. It is important to note that although the true benefits of these agents, with respect to hard clinical outcomes, have not been established, it is still reasonable to prescribe these products in patients with CKD who have elevated phosphorus levels to prevent the development of secondary hyperparathyroidism and cardiovascular disease.
- In adult patients with CKD stage 3a to 5 (with or without dialysis) receiving phosphate-lowering treatment, KDIGO suggests restricting the dose of calcium-based phosphate binder. In children, it is reasonable to base the choice of phosphate-lowering treatment on serum calcium levels *(KDIGO 2017).*
- Sevelamer, a non-calcium-containing phosphate binder, is available in 2 salt formulations: hydrochloride (Renagel) and carbonate (Renvela). The hydrochloride formulation was developed first, but due to the incidence of metabolic acidosis associated with its use, a buffered sevelamer formulation was later developed. The sevelamer carbonate product will most likely be preferred in this patient population due to a decrease in the incidence of metabolic acidosis associated with its use. Additionally, sevelamer carbonate is the only phosphate binder that is FDA-approved for use in children (6 years of age and older).
- Lanthanum carbonate (Fosrenol) is another non-calcium-containing phosphate binder. An advantage to this agent, in addition to not causing an increase in serum calcium levels, appears to be its decreased pill burden compared to the other products (*NKF 2003, KDIGO 2009*).
- Two iron-based, calcium-free phosphate binders are now available.
  - Sucroferric oxyhydroxide provides long-term control of hyperphosphatemia, as demonstrated by the 52-week extension trial (*Floege et al 2015*). Sucroferric oxyhydroxide may reduce the pill burden for those patients that require higher doses of sevelamer as demonstrated in trials (*Wuthrich et al 2013*).
  - Ferric citrate has been shown to provide significant reductions in serum phosphate levels in 3 studies (*Block et al 2015, Dwyer et al 2013, Lewis et al 2015*). Based on secondary study endpoints, ferric citrate raises iron stores (evidenced by increased serum ferritin and serum transferrin saturation) and decreases IV iron and erythropoietin stimulating agent usage (*Lewis et al 2015, Umanath et al 2015*). Ferric citrate's effects may make it an attractive option for dialysis patients who require concomitant use of a phosphate binder and anemia treatments.
- The main considerations for selection of phosphate binders include absorbability, adequate GI tolerability, and cost or cost-effectiveness (*Frazão et al 2012*).

Potassium Removing Agents

- Hyperkalemia is a common clinical problem that is most often a result of impaired urinary potassium excretion due to acute or chronic kidney disease and/or disorders or drugs that inhibit the RAAS *(Mount 2020).*

- Acute or urgent treatment of hyperkalemia includes 3 main phases: 1) antagonizing cardiac effects of potassium by using IV calcium gluconate; 2) redistributing potassium into cells using insulin with dextrose, beta-2-adrenergic agonists, or sodium bicarbonate; and 3) removing excess potassium from the body using hemodialysis, loop diuretics, or cation exchange resins (ie, sodium polystyrene sulfonate) (*Hollander-Rodriquez et al 2006, Mount 2020, Raebel 2012*).
  - In patients who do not require urgent treatment, lowering total body potassium may be the only step necessary (*Hollander-Rodriquez et al 2006*).
- In October 2015, the FDA approved Veltassa (patiromer), a non-absorbed, cation exchange polymer that contains a calcium-sorbitol counterion, for the treatment of hyperkalemia. Patiromer should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action.
- In a randomized withdrawal study, patiromer has been shown to be effective in lowering serum potassium levels in patients with CKD receiving RAAS inhibitor therapy. Patiromer has also been shown to provide sustained reductions of serum potassium for up to 1 year.
  - Compared with sodium polystyrene sulfonate, patiromer has more robust prospective long-term data and may have a more favorable adverse event profile (sodium polystyrene sulfonate is associated with intestinal necrosis and sodium retention), although the pivotal trials for patiromer did not address its relative efficacy and safety vs sodium polystyrene sulfonate.
  - In addition, the role of patiromer for the outpatient treatment of hyperkalemia is unknown, as chronic management of hyperkalemia is generally accomplished through dietary modifications, discontinuation or dose lowering of hyperkalemia-exacerbating agents, or the use of diuretics.
- In May 2018, the FDA approved Lokelma (sodium zirconium cyclosilicate), a non-absorbed zirconium silicate that acts as a highly-selective potassium-removing agent, for the treatment of hyperkalemia. Similar to patiromer, sodium zirconium cyclosilicate should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action. The safety and efficacy of sodium zirconium cyclosilicate were based on data from 2 double-blind, placebo-controlled studies and 2 open-label studies in adult patients with hyperkalemia.
  - The placebo-controlled studies demonstrated that patients treated with sodium zirconium cyclosilicate had significant reductions in serum potassium levels vs placebo-treated patients. The 2 open-label studies showed that the treatment effect of sodium zirconium cyclosilicate on serum potassium was maintained during continued therapy.

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Therapeutic Class Overview
Movement Disorder Agents

INTRODUCTION

- Huntington disease (HD) is a progressive neurodegenerative disorder characterized by motor dysfunction, cognitive decline, and neuropsychiatric disturbances (*Coppen and Roos 2017*).
  - Motor dysfunction in HD may include involuntary movements (eg, chorea, dystonia, and tics) and voluntary movements (eg, bradykinesia, apraxia, and motor impersistence) (*Austedo dossier 2017, Coppen and Roos 2017*).
    - Choreic movements are rapid and unpredictable contractions of the facial muscles, trunk, and extremities which vary in frequency, intensity, and amplitude (*Austedo dossier 2017, Suchowersky 2018a*).
    - Dystonia is characterized by sustained or intermittent muscle contractions which lead to abnormal posture of the trunk and extremities. It is more commonly observed in advanced disease stages (*Coppen and Roos 2017*).
    - Motor function slowly deteriorates as HD progresses, and chorea may eventually be replaced by bradykinesia and parkinsonism in advanced stages of the disease (*Suchowersky 2018a, Suchowersky 2018b*).
- HD affects an estimated 1 in 7300 individuals (approximately 43,000 people) in the United States. It is a rare and fatal autosomal dominant genetic disorder associated with onset in early adulthood and death within 20 years of symptom onset (*Austedo dossier 2017, Austedo Food and Drug Administration [FDA] Summary Review 2017*).
- Tardive dyskinesia (TD) is an iatrogenic condition that results from the long-term use of dopamine receptor blocking agents (DRBAs), predominantly antipsychotics/neuroleptics (first generation antipsychotics [FGAs], also known as typical antipsychotics, as well as second-generation antipsychotics [SGAs], which are also known as atypical antipsychotics) and metoclopramide (*Rana et al 2013*).
  - While the pathophysiology of TD is not well-understood, the most prominent theory suggests chronic exposure to neuroleptics results in dopamine-2 (D2) receptor up-regulation with postsynaptic dopamine receptor supersensitivity (*Waln and Jankovic 2013*).
  - Prospective studies of patients treated with FGAs suggest that the annual incidence of TD is between 3 to 8%. With SGAs, the mean annual incidence is estimated at 2.1 to 4.2%. Although TD prevalence has been less studied with metoclopramide, the published data indicate a prevalence ranging from 1 to 10% (*Waln and Jankovic 2013*).
- TD is characterized by rapid, repetitive, stereotypic movements mostly involving the oral, buccal, and lingual area (*Muller et al 2015*). Movements may include tongue thrusting, lip smacking or pursing, grimacing and chewing movements, piano-playing finger movements, trunk and pelvic thrusting, flexion/extension of the ankles or toes, irregular respirations, and various vocalizations (*Rana et al 2013*).
- According to the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV), TD develops during exposure to a DRBA for ≥ 3 months (or 1 month in patients ≥ 60 years of age) or within 4 weeks of withdrawal from an oral medication (or within 8 weeks of withdrawal from a depot medication). The disorder should persist for ≥ 1 month after discontinuation of an offending drug to qualify as TD (*Waln and Jankovic 2013*).
- The first step in the treatment of TD is to discontinue the offending agent via slow taper. Sudden withdrawal of the offending drug should be avoided, as symptoms of TD could worsen. In patients with psychiatric conditions which require continued use of a neuroleptic, switching from an FGA to an SGA should be considered. Quetiapine and clozapine are the preferred SGAs due to their low receptor occupancy and fast dissociation from D2 receptors (*Vijayakumar and Jankovic 2016*).
- Ingrezza (valbenazine), the first vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of TD, was FDA-approved on April 7, 2018. Prior to valbenazine's approval, Xenazine (tetrabenazine) and Austedo (deutetrabenazine) were FDA-approved for the treatment of Huntington's chorea in August 2008 and April 2017, respectively. Subsequently, deutetrabenazine received FDA approval for the treatment of TD in August 2017.
  - Deutetrabenazine is a chemically modified form of tetrabenazine with deuterium substituted for hydrogen at specific positions. Compared to tetrabenazine, deutetrabenazine reaches comparable systemic exposure with smaller doses, longer treatment intervals, and lower peak concentrations (*Austedo dossier 2017*, *Coppen and Roos 2017*).
    - While deutetrabenazine has been designated a new molecular entity and an orphan drug, it was approved through the 505(b)(2) pathway with tetrabenazine as the Reference Listed Drug (RLD) (*Austedo FDA Summary Review 2017*).

- Differences between valbenazine and deutetrabenazine include once-daily dosing (vs twice-daily dosing) and the absence of a boxed warning for depression and suicidality in patients with HD. Of note, valbenazine has not been studied in patients with HD.

- Medispan class: Psychotherapeutic and Neurological Agents – Misc.; Movement Disorder

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Austedo (deutetrabenazine)	-
Ingrezza (valbenazine)	-
Xenazine (tetrabenazine)	✔

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

INDICATIONS

Table 2. FDA Approved Indications

Indication	Austedo (deutetrabenazine)	Ingrezza (valbenazine)	Xenazine (tetrabenazine)
Chorea associated with HD	✔		✔
Treatment of adults with TD	✔	✔	

(*Prescribing information: Austedo 2017, Ingrezza 2018, Xenazine 2017)*

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

CLINICAL EFFICACY SUMMARY

Huntington Disease (HD)

- The approval of deutetrabenazine was supported by the First-Time Use of Austedo in HD (First-HD) study conducted by the Huntington Study Group (HSG). The Phase 3, double-blind (DB), multicenter (MC), randomized controlled trial (RCT) compared deutetrabenazine with placebo for 12 weeks, followed by a 1-week washout in 90 adults with HD (*HSG 2016*).
  - The study included patients with a Unified Huntington's Disease Rating Scale (UHDRS) total maximal chorea (TMC) score ≥ 8 at baseline and a UHDRS total functional capacity score ≥ 5 at screening (TMC score ranges from 0 to 28, with higher scores indicating more severe chorea) (*Coppen and Roos 2017, Geschwind and Paras 2016*).
  - The primary endpoint was the change from baseline in UHDRS-TMC score.
    - The placebo-adjusted mean change from baseline in TMC with deutetrabenazine was -2.5 points (95% confidence interval [CI], -3.7 to -1.3; $p < 0.001$).
    - In the deutetrabenazine group, the mean TMC scores improved by -4.4 points from 12.1 (95% CI, 11.2 to 12.9) to 7.7 (95% CI, 6.5 to 8.9) over 12 weeks. In the placebo group, mean TMC scores improved by -1.9 points from 13.2 (95% CI, 12.2 to 14.3) to 11.3 (95% CI, 10.0 to 12.5).
  - Four secondary endpoints were assessed hierarchically in the following order: Patient Global Impression of Change (PGIC), Clinical Global Impression of Change (CGIC), 36-Item Short Form (SF-36) physical functioning subscale score, and Berg Balance Test (BBT). For the PGIC and CGIC, treatment success was defined as an answer of "much" or "very much" improved overall HD symptoms at week 12.
    - The proportion of patients who reported treatment success on the PGIC was 31.1% greater with deutetrabenazine than placebo ($p = 0.002$).
    - The proportion of clinicians who reported treatment success on the CGIC was 28.9% greater with deutetrabenazine than placebo ($p = 0.002$).
    - The placebo-adjusted improvement in the SF-36 physical functioning subscale was 4.34 points with deutetrabenazine ($p = 0.03$).
    - BBT improvement observed with deutetrabenazine did not achieve statistical significance over placebo ($p = 0.14$).
  - In the First-HD study, the incidence of overall, psychiatric, and nervous system adverse events (AEs) was similar between the deutetrabenazine and placebo groups.

  - While generally mild to moderate, AEs resulted in dose reductions for 3 patients (6.7%) in each group. Serious AEs resulted in drug suspension for 1 patient (2.2%) in each group.
  - Somnolence and diarrhea were reported more frequently with deutetrabenazine than with placebo.
- The Phase 3, open-label (OL), MC, long-term Alternatives for Reducing Chorea in HD (ARC-HD) study evaluated the safety and efficacy of deutetrabenazine in 112 patients in 2 cohorts (*Austedo dossier 2017, Frank et al 2017*).
  - The rollover cohort included 75 patients from the First-HD study who underwent washout of deutetrabenazine or placebo. The switch cohort included 37 patients previously on tetrabenazine who were switched overnight to deutetrabenazine at approximately half their previous tetrabenazine dose.
  - Patients in the switch cohort demonstrated improved TMC from baseline with deutetrabenazine 8 weeks following conversion (-2.0 points, $p < 0.001$). Improvements in TMC from baseline were also observed in the rollover cohort at week 2 (-1.9; $p < 0.0001$; n = 58) and maintained through week 28 (-4.4; $p = 0.0055$; n = 14). Common AEs included somnolence, falls, depression, and insomnia.
- A DB, RCT was conducted in 84 ambulatory patients with HD who received tetrabenazine at a maximum dose of 100 mg daily (n = 54) or placebo (n = 30) for 12 weeks. Tetrabenazine treatment resulted in a statistically significant reduction in chorea severity, measured as a change in the chorea score of the UHDRS, compared with placebo (5 unit reduction [tetrabenazine group] vs 1.5 unit reduction [placebo]; adjusted mean effect size -3.5; 95% CI, -5.2 to -1.9; $p < 0.0001$). This change represented a clinically meaningful 24% reduction in chorea from baseline severity. There were 5 study withdrawals and 5 serious AEs in 4 patients (suicide, complicated fall, restlessness/suicidal ideation, and breast cancer) in the tetrabenazine group, compared to 1 withdrawal and no serious AEs in the placebo group (*HSG 2006*).

Tardive Dyskinesia (TD)

- The safety and efficacy of deutetrabenazine was established in the ARM-TD and AIM-TD trials, which were 12-week DB, placebo-controlled (PC), MC, RCTs. Both studies evaluated the change from baseline in items 1 to 7 of the Abnormal Involuntary Movement Scale (AIMS) score as the primary efficacy endpoint. The AIMS total score ranges from 0 to 28, and a decreased score indicates improvement (*Anderson et al 2017, Fernandez et al 2017*).
  - The Phase 2/3 ARM-TD study randomized 117 adults with moderate to severe TD to receive deutetrabenazine titrated to an optimal dose or placebo. The mean dose of deutetrabenazine at the end of titration was 38.8 mg/day. Significant reductions in AIMS scores were observed in patients who received deutetrabenazine compared to placebo (*Fernandez et al 2017*).
    - The least squares mean AIMS score improved by -3.0 points in the deutetrabenazine group vs -1.6 points in the placebo group (treatment difference -1.4; 95% CI, -2.6 to -0.2; $p = 0.019$).
    - Secondary endpoints included proportion of patients who experienced treatment success at week 12 on the CGIC and PGIC. Although CGIC and PGIC results were numerically higher for the deutetrabenazine group, the difference was not statistically significant.
    - The rates of AEs were similar between the deutetrabenazine and placebo groups, including depression and suicidal ideation.
  - The Phase 3 AIM-TD study randomized 298 adults with TD to receive 1 of 3 fixed doses of deutetrabenazine (12, 24, or 36 mg/day) or placebo. Significant reductions in AIMS scores were observed in patients who received 24 or 36 mg of deutetrabenazine per day (*Anderson et al 2017*).
    - The least squares mean AIMS score improved by -3.3, -3.2, -2.1, and -1.4 points in the deutetrabenazine 36 mg/day, 24 mg/day, 12 mg/day, and placebo groups, respectively. The treatment difference was -1.9 points (95% CI, -3.09 to -0.79; $p = 0.001$) with deutetrabenazine 36 mg/day, -1.8 points (95% CI, -3.00 to -0.63; $p = 0.003$) with deutetrabenazine 24 mg/day, and -0.7 points (95% CI, -1.84 to 0.42; $p = 0.217$) with deutetrabenazine 12 mg/day.
    - The overall rate of AEs was similar between groups (51%, 44%, 49%, and 47% for deutetrabenazine 36 mg/day, 24 mg/day, 12 mg/day, and placebo, respectively).
    - Rates of depression, depressed mood, and suicidal ideation were low in all treatment arms; no dose-response relationship was detected.
- The FDA approval of valbenazine was based on the results from the KINECT 3 trial, a 6-week, phase 3, DB, PC, MC, RCT with 224 patients with moderate to severe TD. Patients received valbenazine 40 mg once daily, valbenazine 80 mg once daily, or placebo (*Hauser et al 2017, FDA Ingrezza Medical Review*).
  - In this trial, 85.5% received concomitant antipsychotics (16.7% on FGAs and 76.7% on SGAs). The mean baseline AIMS dyskinesia score was 10.0 (range 0 to 20) between the treatment groups.

- The primary endpoint, which was a modified version of the AIMS score, included 7 items rating involuntary movements in the orofacial region, extremities, and trunk on a scale from 0 (no dyskinesia) to 4 (severe dyskinesia).
  - At week 6, the AIMS dyskinesia score was reduced by 3.2 in the valbenazine 80 mg group compared to 0.1 in the placebo group ($p < 0.001$). In the valbenazine 40 mg group, the AIMS dyskinesia score decreased by 1.9 compared to 0.1 in the placebo group ($p = 0.002$).
- The percentage of patients who achieved an AIMS response (defined in the trial as a reduction of ≥ 50% from baseline score) was 40.0% in the 80 mg group ($p < 0.001$) and 23.8% in the 40 mg group ($p = 0.02$), compared to 8.7% in the placebo group.
- The key secondary endpoint of mean Clinical Global Impression of Change - Tardive Dyskinesia (CGI-TD) score, which investigators used to rate the overall change in TD at week 6, did not reach statistical significance for either valbenazine dosage group when compared to placebo ($p = 0.056$ and $p = 0.074$ for valbenazine 80 mg and 40 mg, respectively).
- The mean PGIC score, which characterized the patient's perception of improvement in their TD symptoms, was slightly worse in both valbenazine treatment groups compared to placebo at week 6; however, the differences did not reach nominal statistical significance.
- The most common AEs observed with valbenazine (both dosage groups combined) vs placebo were somnolence (5.3% vs 3.9%), akathisia (3.3% vs 1.3%), and dry mouth (3.3% vs 1.3%). Suicidal ideation was the most common AE in the placebo group (5.3% vs 2.6% in both valbenazine groups combined).

- A meta-analysis was conducted using two 12-week DB, PC, RCTs with deutetrabenazine (12 to 48 mg/day) (n = 413) and four 4 to 6 week DB, RCTs with valbenazine (12.5 to 100 mg/day) (n = 488). With respect to AIMS scores, both deutetrabenazine (standardized mean difference [SMD] -0.40; 95% CI, -0.19 to -0.62; $p < 0.001$; weighted mean difference [WMD] -1.44; 95% CI, -0.67 to -2.19; $p < 0.001$) and valbenazine (SMD -0.58; 95% CI, -0.26 to -0.91; $p < 0.001$; WMD -2.07; 95% CI, -1.08 to -3.05; $p < 0.001$) demonstrated statistically significant improvement over placebo. Results were confirmed regarding responder rates (≥ 50% AIMS total score reduction for deutetrabenazine: risk ratio [RR] 2.13; 95% CI, 1.10 to 4.12; $p = 0.024$; number-needed-to-treat [NNT], 7; 95% CI, 3 to 333; $p = 0.046$; valbenazine: RR 3.05; 95% CI = 1.81 to 5.11; $p < 0.001$; NNT, 4; 95% CI, 3 to 6; $p < 0.001$). Inconsistent improvements were noted in PGIC ($p = 0.15$) and CGIC scores for deutetrabenazine ($p = 0.088$), and for CGIC scores for valbenazine ($p = 0.67$). In a 54-week, OL extension study of deutetrabenazine and a dose-blinded valbenazine study (48 weeks), responder rates increased over time. No increase in cumulative or specific AEs vs placebo was observed (*Solmi et al 2018*).

CLINICAL GUIDELINES

Huntington Disease (HD)

- **American Academy of Neurology (AAN):** Pharmacologic treatment of chorea in HD (*Armstrong and Miyasaki 2012*)
  - Whether chorea requires treatment should be an individualized decision for providers and their patients with HD.
    - While some studies reported that improving chorea decreases disability or increases quality of life, other studies failed to show an association between chorea and functional decline in HD.
    - The impact of chorea on quality of life should be weighed against other issues, including mood disturbance, cognitive decline, AEs, and polypharmacy risks.
  - For HD chorea which requires pharmacological management, tetrabenazine (up to 100 mg/day), amantadine (300 to 400 mg/day), or riluzole (200 mg/day) are recommended.
    - Tetrabenazine likely provides very important antichoreic benefits, and riluzole 200 mg/day likely provides moderate benefits. The degree of benefit is unknown for amantadine.
    - Patients on tetrabenazine should be monitored for parkinsonism and depression/suicidality while patients on riluzole should be monitored for elevated liver enzymes.
  - Nabilone may be used for modest decreases in HD chorea, but there is insufficient evidence to recommend long-term use, particularly given concerns for abuse potential.
  - While neuroleptic agents (eg, clozapine) may be reasonable options with a historical suggestion of antichoreic benefit, formal recommendations are not provided due to a lack of studies with sufficient sample sizes and validated outcome measures.
  - The guideline has not been updated since the FDA approval of deutetrabenazine.

Tardive dyskinesia (TD)

- As a follow-up to the 2013 AAN evidence-based treatment guidelines for tardive syndromes (TS) (*Bhidayasiri et al 2013*), Bhidayasiri published a treatment algorithm based on a systematic review of the literature for TS in 2018. Published studies were evaluated for effectiveness of pharmacologic and surgical treatments for TS from 2012 to 2017, using the same rating system ranging from A (highest level of evidence for effectiveness) to U (insufficient evidence) (*Bhidayasiri et al 2018*).
  - While the 2013 guidelines did not make any Level A recommendations, the 2018 update recommends the new generation VMAT2 inhibitors, valbenazine and deutetrabenazine, as Level A treatment options. Tetrabenazine may be used only if new VMAT2 inhibitors are unavailable.
  - If TS remains troublesome, treatment with a Level B (recommendation should be done based on benefit/risk profile) recommendation, such as gingko biloba extract or clonazepam, should be utilized.
  - If TS continues to be troublesome, short-term amantadine, tetrabenazine, deep brain stimulation, or globus pallidus interna may be tried (Level C; recommendation may or might be done; lowest recommendation level considered useful within the scope of practice).
  - There continues to be insufficient evidence to support or refute TS treatment by withdrawing causative agents or switching from typical to atypical DRBAs (Level U).

SAFETY SUMMARY

- **Contraindications**
  - Deutetrabenazine and tetrabenazine are contraindicated in the following populations:
    - Patients with HD who are actively suicidal, or have untreated or inadequately treated depression
    - Patients with hepatic impairment
    - Patients concurrently on monoamine oxidase inhibitors (MAOIs) or who have discontinued MAOI therapy within 14 days
    - Patients concurrently on another VMAT2 inhibitor
  - Valbenazine has no contraindications.
- **Warnings/precautions**
  - **Boxed warning** for deutetrabenazine and tetrabenazine**:** Depression and suicidality in patients with HD
    - Patients with HD have a greater risk of depression and suicidality. Treatment with deutetrabenazine may further increase this risk in patients with HD. Patients on deutetrabenazine should be closely monitored for worsening depression, suicidal thoughts, or unusual changes in behavior.
  - Additional key warnings and precautions for deutetrabenazine and tetrabenazine include:
    - Clinical worsening (eg, decline in mood, cognition, rigidity, and functional capacity) and AEs (eg, sedation, depression, parkinsonism, akathisia, restlessness, cognitive decline) in patients with HD
    - Neuroleptic malignant syndrome (NMS) in patients with HD and TD
      - NMS is a potentially fatal syndrome associated with hyperpyrexia, muscle rigidity, altered mental status, and autonomic instability. While NMS has not been observed with deutetrabenazine, it has been observed with its RLD, tetrabenazine. Deutetrabenazine should be discontinued immediately if NMS occurs.
    - Akathisia, agitation, and restlessness in patients with HD and TD
      - In the First-HD study, akathisia, agitation, or restlessness was reported by 4% of patients treated with deutetrabenazine and 2% of patients on placebo. In patients with TD, 2% of patients treated with deutetrabenazine and 1% of patients on placebo experienced these events.
    - Parkinsonism in patients with HD
      - Patients with HD often develop rigidity as part of their underlying disease progression. Drug-induced parkinsonism may cause more functional impairment than untreated chorea. Patients who develop parkinsonism during treatment with deutetrabenazine should reduce their dosage.
    - Sedation and somnolence (also a warning for valbenazine)
      - Sedation is a common dose-limiting AE with deutetrabenazine. In the First-HD study, 11% of patients treated with deutetrabenazine reported somnolence compared with 4% of patients on placebo.
    - QTc prolongation (also a warning for valbenazine)
- **Adverse effects**

- The most common AEs (incidence > 8% and greater than placebo) with deutetrabenazine in the First-HD study included somnolence, diarrhea, dry mouth, and fatigue. In the TD studies, the most common AEs (incidence > 3% and greater than placebo) with deutetrabenazine included nasopharyngitis and insomnia.
- The most common AEs (incidence > 10% and at least 5% greater than placebo) with tetrabenazine included sedation/somnolence, fatigue, insomnia, depression, akathisia, anxiety, and nausea.
- The most common AEs (incidence ≥ 2%) with valbenazine included somnolence, anticholinergic AEs (dry mouth, constipation, blurred vision, urinary retention), balance disorders/falls, headache, akathisia, vomiting, nausea, and arthralgia.

- **Drug Interactions**
  - Deutetrabenazine and tetrabenazine
    - These agents are contraindicated in patients taking MAOIs, reserpine, or other VMAT2 inhibitors.
    - Strong cytochrome P450 (CYP) 2D6 inhibitors increase the systemic exposure to the metabolites of these agents.
    - Concurrent use with neuroleptic drugs (ie, dopamine antagonists, antipsychotics) may increase risk for parkinsonism, NMS, and akathisia.
    - Concomitant use with other drugs that are known to cause QT prolongation should be avoided.
  - Valbenazine
    - Concomitant use of an MAOI is not recommended.
    - Concomitant use with strong CYP3A4 inducers is also not recommended, as this could lead to reduced levels of valbenazine.
    - Valbenazine dose may need to be decreased when given concomitantly with strong CYP3A4 and CYP2D6 inhibitors.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Austedo (deutetrabenazine)	Tablets	Oral	Twice daily	Initial daily dose: 6 mg (HD) or 12 mg (TD); maximum daily dose = 48 mg; dose should be titrated at weekly intervals; administer with food
Ingrezza (valbenazine)	Capsules	Oral	Daily	A lower dose should be administered in patients with moderate to severe hepatic failure
Xenazine (tetrabenazine)	Tablets	Oral	1 to 3 times daily (depending on dose)	Dose should be titrated slowly at weekly intervals and individualized; titration should be stopped or slowed down if patient experiences AEs; patients who require > 50 mg/day should first be tested to determine if they are poor or extensive metabolizers

See the current prescribing information for full details

CONCLUSION

- Deutetrabenazine represents an additional oral therapeutic option for patients with TD or chorea associated with HD.
  - For HD chorea, deutetrabenazine is comparable in safety and efficacy to its RLD, tetrabenazine. The use of both products in HD is limited by dose-related AEs (eg, somnolence, parkinsonism) and a boxed warning for depression and suicidality in a population that is already at a significantly increased risk.

- The first step in the treatment of TD is to discontinue the offending agent by slow taper. The patient can switch to quetiapine and clozapine (SGA of choice) if needed.
- The First-HD study, which compared deutetrabenazine with placebo for 12 weeks demonstrated a statistically significant improvement in the TMC score in the deutetrabenazine group compared to placebo. Secondary endpoints such as PGIC and CGIC also showed improvement.
- The KINECT 3 trial demonstrated a significant reduction in AIMS dyskinesia score of -3.2 in the valbenazine 80 mg/day group and -1.9 in the valbenazine 40 mg/day group, however, there were no significant improvements in the CGI-TD score or patient-perceived improvement in function or quality of life.
  - The extension trial continued to demonstrate reductions in AIMS dyskinesia score from baseline to week 48 in both dosage groups.
- The ARM-TD and AIM-TD trials demonstrated significant reductions in AIMS score in patients who received deutetrabenazine compared to placebo.
- For TD, valbenazine is an alternative with the same mechanism of action and a once-daily dosing schedule compared to twice-daily deutetrabenazine.
- The AAN 2012 guideline for the treatment of chorea associated with HD recommends treatment with tetrabenazine, amantadine, or riluzole (Level B; recommendation should be done based on benefit/risk profile). Nabilone may also be used for modest decreases in HD chorea (Level C; recommendation may or might be done; lowest recommendation level considered useful within the scope of practice), but information is insufficient to recommend long-term use, particularly given abuse potential concerns (Level U; insufficient evidence). Data are insufficient to make recommendations regarding the use of neuroleptics or donepezil for HD chorea treatment (Level U).
- A treatment algorithm for TS was published in 2018, as a follow-up to the 2013 AAN evidence-based treatment guideline for TS. The most important change in recommendations was related to the addition of the new generation VMAT2 inhibitors, valbenazine and deutetrabenazine, as Level A (highest level of evidence for effectiveness) treatment options. Tetrabenazine is recommended as an alternative if new VMAT2 inhibitors are unavailable. Gingko biloba and clonazepam continued to be recommended in the Level B category as well as amantadine and tetrabenazine in the Level C category.

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

Therapeutic Class Overview
Urinary antispasmodics

INTRODUCTION

- Overactive bladder (OAB) is defined as urinary urgency, with or without urge incontinence, usually with frequency and nocturia, in the absence of a causative infection or pathological conditions. Urinary incontinence has been shown to greatly reduce quality of life in areas such as mental and general health in addition to physical and social functioning (*Gormley 2019, Coyne et al 2008, Haab 2014, International Continence Society 2015).*
  - OAB affects approximately 1 in 7 (14%) adults, both men and women, in the United States (U.S.). OAB symptom prevalence and severity tend to increase with age, and affects ~33% of people ≥ 75 years of age. Urge urinary incontinence (UUI) is consistently more common in women than in men (*FDA Gemtesa clinical review 2020, Gormley et al 2019*).
- Neurogenic detrusor overactivity (NDO) is a subtype of OAB, defined by the International Children's Continence Society (ICCS) as detrusor overactivity (ie, occurrence of involuntary detrusor contractions that are spontaneous or provoked during the filling phase) due to a relevant neurological cause (*Austin et al 2016, Food and Drug Administration [FDA] Vesicare LS clinical review 2020, Franco et al 2020*).
  - In NDO, involuntary detrusor contractions simultaneously coincide with sphincter dyssynergia and result in high bladder pressure and eventual renal damage (*FDA Vesicare LS clinical review 2020, Franco et al 2020, Wu et al 2019*).
  - NDO can develop as a result of a lesion at any level in the nervous system; the most prevalent cause of NDO in children is due to various subtypes of spina bifida resulting from neural tube closure defects during fetal development (*FDA Vesicare LS clinical review 2020, Franco et al 2020, Nepple and Cooper 2019*).
  - NDO prevalence is not easily quantifiable and epidemiology data in the pediatric population are limited. In 2009, prevalence of patients who were diagnosed with NDO in the European Union was estimated at 1.8 per 10,000 children (*FDA Vesicare LS clinical review 2020, Franco et al 2020*).
- In OAB, behavioral therapies (eg, bladder training, bladder control strategies, pelvic floor muscle training and fluid management) are considered first-line treatment in all patients with OAB. Urinary antispasmodics, including anticholinergics and the beta-3 adrenergic agonist, mirabegron, are recommended as first-line pharmacological therapy in OAB (*Gormley et al 2019, Gravas et al 2021, Harding et al 2021, Nambiar et al 2018*).
- In children with NDO, first-line therapy for the majority of patients is medical treatment with an oral anticholinergic coupled with clean intermittent catheterization (CIC) 4 to 5 times a day (*Blok et al 2020, FDA Vesicare LS clinical review 2020, Franco et al 2020, Rawashdeh et al 2012, Stein et al 2020*).
- Urinary antispasmodics belong to 2 classes of drugs, which include anticholinergic compounds known as muscarinic receptor antagonists, and beta-3 adrenergic agonists. All urinary antispasmodics, with the exception of flavoxate, are Food and Drug Administration (FDA)-approved for the treatment of OAB.
  - The anticholinergic agents act as antagonists of acetylcholine at muscarinic cholinergic receptors, thereby relaxing smooth muscle in the bladder and decreasing bladder contractions.
    - Oral immediate-release (IR) and extended-release (ER) formulations (LA, XL, and XR) are available for oxybutynin (Ditropan), tolterodine (Detrol), and trospium, while darifenacin (Enablex), fesoterodine (Toviaz), and solifenacin (Vesicare, Vesicare LS) are available as oral ER formulations.
    - Oxybutynin is also formulated as a topical gel (Gelnique) and transdermal patch (Oxytrol, Oxytrol for Women). Oxytrol for Women is an over-the-counter (OTC) product previously available as a prescription; it is specifically indicated for women ≥ 18 years of age, while Oxytrol is FDA-approved for use in men *(Oxytrol for Women Drug Facts 2016).*
    - Ditropan XL (oxybutynin) has an additional indication for pediatric patients with NDO, while IR oxybutynin tablets and syrup and solifenacin suspension are specifically FDA-approved for pediatric patients with NDO.
    - Flavoxate tablets are FDA-approved for the relief of symptoms of cystitis, prostatitis, urethritis, or urethrocystitis/ urethrotrigonitis.
  - Mirabegron (Myrbetriq, Myrbetriq Granules) and vibegron (Gemtesa) are adrenergic agonists of the human beta-3 adrenergic receptor. They relax the detrusor smooth muscle during the storage phase of the urinary bladder fill-void cycle by activation of beta-3 adrenergic receptor, which increases bladder capacity.

  - Mirabegron tablets and vibegron are indicated for treatment of OAB. Mirabegron tablets have an additional indication for pediatric patients with NDO, while mirabegron granules are specifically FDA-approved for pediatric patients with NDO.
- The anticholinergic urinary antispasmodics have demonstrated a similar safety and efficacy profile compared to one another; however, they primarily differ in their receptor selectivity and tolerability profiles. The M2 and M3 muscarinic receptor subtypes are highly concentrated in the bladder and are responsible for detrusor contraction, while M1, M4, and M5 are located throughout the body (*Brown et al 2018, Rawashdeh et al 2012*).
  - Preclinical studies have suggested that solifenacin and darifenacin may be "uroselective" for the M3 receptor in the bladder; however, the clinical implications of this suggestion have not been established *(Brown et al 2018).*
  - The development of ER formulations with more predictable pharmacokinetics has led to a lower incidence of anticholinergic adverse events (AEs). Oxybutynin undergoes first-pass metabolism to an active metabolite with a high incidence of dry mouth; however, transdermal oxybutynin formulations bypass this metabolism, maintaining the efficacy of oxybutynin with a lower incidence of AEs *(Dmochowski et al 2005).*
- Botox injection (onabotulinumtoxinA) is also indicated in OAB and NDO in patients who have an inadequate response to or are intolerant of an anticholinergic medication. In adults, Botox is indicated for the treatment of OAB with symptoms of UUI, urgency, and frequency, and also for the treatment of urinary incontinence due to detrusor overactivity associated with a neurologic condition (eg, spinal cord injury [SCI], multiple sclerosis [MS]). In children, Botox is indicated for the treatment of NDO in pediatrics ≥ 5 years of age and older (*Botox prescribing information 2021).* Botox is not included in this review.
- The agents included in this review are listed in Table 1 by brand name. Since there are some branded agents that contain the same generic component, the remaining tables in the review are organized by generic name. This review focuses on the use of the urinary antispasmodics for OAB.
- Medispan class: Urinary Antispasmodics

Table 1. Medications Included Within Class Review

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

*OTC product
†The FDA has approved a generic fesoterodine tablet AB rated to Toviaz, but it is not currently commercially available.

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	darifenacin (Enablex)	fesoterodine (Toviaz)	flavoxate	mirabegron (Myrbetriq)	mirabegron (Myrbetriq Granules)	oxybutynin (Ditropan XL)	oxybutynin (Gelnique, Oxytrol)	oxybutynin tablets, syrup	solifenacin (Vesicare)	solifenacin (Vesicare LS)	tolterodine (Detrol, Detrol LA)	trospium, trospium ER	vibegron (Gemtesa)
Treatment of OAB with symptoms of UUI, urgency, and urinary frequency	✔	✔		✔ *		✔	✔ †		✔		✔	✔	✔
Treatment of pediatric patients with symptoms of detrusor overactivity associated with a neurological condition (eg, spina bifida)						✔ ‡							
Treatment of NDO in pediatric patients		✔ ‡		✔ ‡	✔ ‡					✔ ‡			
Treatment of bladder instability in patients with uninhibited neurogenic or reflex neurogenic bladder								✔ ‡					
Symptomatic relief of cystitis, prostatitis, urethritis, or urethrocystitis/ urethrotrigonitis			✔										

* Either alone or in combination with the muscarinic antagonist solifenacin succinate.
† Oxytrol for Women is available OTC and is approved for women ≥ 18 years of age with ≥ 2 of the following symptoms for at least 3 months: urinary frequency, urinary urgency, and urge incontinence; Oxytrol is approved for OAB in men.
‡ Toviaz is indicated in patients ≥ 6 years of age with a body weight > 25 kg; Ditropan XL is indicated in patients ≥ 6 years of age; Myrbetriq Granules is indicated in patients ≥ 3 years of age, Myrbetriq tablets are indicated in patients ≥ 3 years of age with a body weight ≥ 35 kg; Vesicare LS is indicated in patients ≥ 2 years of age; the safety and efficacy of oxybutynin tablets and syrup have been demonstrated for pediatric patients ≥ 5 years of age.

(Oxytrol for Women Drug Facts 2016; Prescribing information: Detrol 2016, Detrol LA 2018, Ditropan XL 2021, Enablex 2016, flavoxate 2018, Gelnique 2019, Gemtesa 2020, Myrbetriq/Myrbetriq Granules 2021, oxybutynin tablets 2020, oxybutynin syrup 2020, Oxytrol 2017, Toviaz 2021, trospium tablets 2020, trospium extended-release capsules 2021, Vesicare 2020, Vesicare LS 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

- A 2018 Agency for Healthcare Research and Quality (AHRQ) systematic review update of nonsurgical treatments for urinary incontinence in women concluded that behavioral therapy, alone or in combination with other interventions, is generally more effective than other first- or second-line interventions (including pharmacologic interventions) alone for both stress and urgency urinary incontinence (*Balk et al 2018*). For women with urgency urinary incontinence, anticholinergics were significantly more likely to result in "cure" (odds ratio [OR], 1.80; 95% confidence interval [CI], 1.29 to 2.52) or improvement (OR, 1.79; 95% CI, 1.18 to 2.7) as compared to placebo. Additionally, anticholinergics overall were found to improve quality of life compared with no treatment, but there was inconsistency both within and across studies regarding the comparative effect of these medications on various aspects of quality of life.

- Although used for urinary incontinence, flavoxate is no more effective than other drugs used for urge incontinence or related disorders *(Micromedex 2021).* No recent clinical trials have been published with flavoxate.
- The results from clinical studies have demonstrated each of the urinary antispasmodics to be more effective vs placebo with regard to improvements in micturition frequency, urgency and urge incontinence episodes *(Chapple et al 2004, Chapple et al 2007, Dmochowski et al 2003, Dmochowski et al 2008, Dmochowski et al 2010, Herschorn et al 2010(b), Kaplan et al 2011, Kay et al 2006, Khullar et al 2011, MacDiarmid et al 2011, Mattiasson et al 2010, Nitti et al 2007, Nitti et al 2013, Salinas-Casado et al 2015, Sand et al 2011, Staskin et al 2007, Staskin et al 2009, Wagg et al 2013, Zinner et al 2005).*
- Head-to-head studies with the urinary antispasmodics have not consistently found one agent to be superior to other agents within the class *(Anderson et al 1999, Anderson et al 2006, Appell et al 2001, Barkin et al 2004, Batista et al 2015, Chapple et al 2005, Chapple et al 2007, Davila et al 2001, Diokno et al 2003, Dmochowski et al 2003, Dmochowski et al 2010, Ercan et al 2015, Halaska et al 2003, Harvey et al 2001, Herschorn et al 2010(a), Herschorn et al 2010(b), Hsiao et al 2011, Kaplan et al 2011, Kay et al 2006, Kilic et al 2006, Kinjo et al 2018, Kobayashi et al 2018, Sand et al 2004, Versi et al 2000, Zellner et al 2009).*
- The evidence to support the efficacy and safety of the oxybutynin transdermal patch (Oxytrol for Women) as an OTC product was based on the completed studies with the prescription product *(Dmochowski et al 2002, Dmochowski et al 2003, FDA Oxytrol for Women Medical Review 2013*). The Oxytrol for Women transdermal patch is the same formulation and dose as the prescription Oxytrol transdermal patch.
- A 2012 Cochrane review reported that IR formulations of oxybutynin, tolterodine, and trospium have similar efficacy, but oxybutynin was associated with more AEs. In addition, solifenacin improved symptoms of OAB more than tolterodine IR, while it was more effective than tolterodine ER *(Madhuvrata et al 2012).*
- Another review demonstrated that all anticholinergics for OAB showed similar small benefits. For urgency urinary incontinence, the drugs showed 20% or less difference from placebo in the rate of achieving urinary continence or improvement in urinary continence. The number needed to treat (NNT) to achieve continence in 1 woman were similar across drugs (range for NNT, 6 to 12). Dose-related efficacy effects were evident for fesoterodine, solifenacin, and oxybutynin. Small differences were apparent in the AEs among the anticholinergics. Dry mouth and constipation were the most common AEs. Treatment discontinuation due to AEs was greater than with placebo for all drugs except darifenacin and tolterodine (*Shamliyan et al 2012*).
- A network meta-analysis of 5 randomized controlled trials ranked the antispasmodics for treatment of OAB in women in the following order from highest to lowest efficacy: solifenacin 10 mg once daily, oxybutynin 3 mg 3 times daily, solifenacin 5 mg once daily, darifenacin 15 mg once daily, fesoterodine 8 mg once daily, darifenacin 7.5 mg once daily, and tolterodine 4 mg once daily. However, solifenacin 10 mg had the most AEs while darifenacin 7.5 mg once daily caused the least AEs. The authors concluded that solifenacin 5 mg once daily was preferred for OAB followed by oxybutynin 3 mg 3 times daily based on efficacy, AEs, and cost (*Nalliah et al 2017*).
- A network meta-analysis that compared solifenacin 5 mg/day to other antimuscarinic agents found that solifenacin was more effective than tolterodine 4 mg/day for incontinence and urgency. In addition, solifenacin had a lower risk of dry mouth compared to other antimuscarinics (*Nazir et al 2018*).
- A 2019 network meta-analysis of 128 studies of anticholinergics concluded that all the anticholinergic medications were better than placebo for patients with OAB; however, there was no clear best treatment for cure or improvement. In this analysis, transdermal oxybutynin was shown to cause less dry mouth than the other treatments (*Herbison et al 2019*).
- Three 12-week, randomized, placebo-controlled clinical trials evaluated the efficacy and safety of mirabegron 25 mg, 50 mg, or 100 mg once daily vs placebo. Mirabegron significantly reduced the mean number of incontinence episodes and the mean number of micturitions per 24 hours compared to placebo *(Nitti et al 2013).*
- Mirabegron compared with either tolterodine IR or tolterodine LA demonstrated comparable efficacy in 2 trials. However, tolterodine IR patients had more AEs *(Kuo et al 2015, Yamaguchi et al 2014).* A 2-period, 8-week crossover trial comparing mirabegron and tolterodine ER found greater tolerability with mirabegron; however, patient treatment preference and symptoms were similar between treatments (*Staskin et al* 2018). An indirect treatment comparison meta-analysis concluded that mirabegron had similar efficacy to most other antispasmodics; however, solifenacin demonstrated improved symptom control compared to mirabegron *(Obloza 2017).* Another systematic review and meta-analysis concluded that mirabegron demonstrated similar efficacy to tolterodine and solifenacin with regard to improvement in micturitions, incontinence, and nocturia with a lower incidence of dry mouth and no higher risk of hypertension (*Chen et al 2018*).
- A systematic review compared treatment with mirabegron 50 mg to several different active treatments (including darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium) in regard to micturitions, incontinence, and

dry rate (*Kelleher et al 2018*). Mirabegron had similar efficacy to other active treatments with a few exceptions: solifenacin 10 mg monotherapy and solifenacin 5 mg plus mirabegron 50 mg were found to be more efficacious at reducing micturition frequency than mirabegron 50 mg; solifenacin 5 mg plus mirabegron 25/50 mg and fesoterodine 8 mg were found to be more efficacious at reducing urgency urinary incontinence than mirabegron 50 mg; and solifenacin 5 mg plus mirabegron 25/50 mg, trospium 60 mg, solifenacin 10 mg, and fesoterodine 8 mg were associated with an improved dry rate when compared to mirabegron 50 mg. In general, mirabegron was associated with a significantly lower frequency of AEs compared to other active treatments.

- Studies examining combination therapy of mirabegron and solifenacin have demonstrated decreased frequency of incontinence, urgency episodes, and/or micturition frequency with a similar AE profile to monotherapy *(Drake et al 2016, Herschorn et al 2017, Kosilov et al 2015, Yamaguchi et al 2015).* A 12-month long-term trial of mirabegron and solifenacin also found the combination to be well tolerated with greater improvement in OAB symptoms as compared to monotherapy with either agent (*Gratzke et al 2018*). Similarly, the combination of low-dose trospium and solifenacin has also resulted in decreased frequency of incontinence in elderly patients with moderate symptoms *(Kosilov et al 2014).*
- Vibegron was studied in a Phase 3, 12-week, placebo-controlled, multi-center, randomized controlled EMPOWUR trial in 1518 adult patients with OAB (*Staskin et al 2020*). Patients were randomized to vibegron 75 mg daily, tolterodine ER 4 mg, or placebo. Micturitions decreased an average of 1.8 episodes per day with vibegron vs 1.3 with placebo ($p < 0.001$) and 1.6 for tolterodine. UUI episodes also decreased by 2 per day with vibegron vs 1.4 for placebo ($p < 0.0001$) and 1.8 with tolterodine). Efficacy was maintained up to 40 weeks without additional safety concerns (*Staskin et al 2021*).
- The efficacy of mirabegron for the treatment of NDO was evaluated in a Phase 3, 52-week, open-label, baseline-controlled, multicenter, dose titration study in 86 pediatric patients 3 to 17 years of ages with NDO on CIC (*Myrbetriq/Myrbetriq Granules prescribing information 2021*). All patients initially received a weight-based starting dose equivalent to a 25 mg daily dose followed by dose titration to a 50 mg equivalent; 94% of patients were treated at the maximum dose. A total of 68 patients had valid urodynamic measurements for evaluation of efficacy. The mean change from baseline in MCC in patients 3 to < 12 years (n = 43) was 72 mL (95% C, 45 to 99), and 113 mL (95% CI, 79 to 147) in patients 12 years to 17 years of age (n = 25).
- The efficacy and safety of solifenacin suspension for the treatment of pediatric patients (6 months to < 18 years of age of age) with NDO were evaluated in 2 open-label, baseline-controlled, Phase 3 studies. Patients were treated with sequential doses of solifenacin 2.5 to 10 mg for 12 weeks to determine an optimal dose, followed by a fixed dose for ≥ 40 weeks. The primary outcome was the change in maximum cystometric capacity from baseline to 24 weeks. Results revealed that maximum cystometric capacity significantly improved after 24 weeks of treatment (37 mL for children 6 months to < 5 years of age; $p < 0.001$ and 57.2 mL for children 5 to < 18 years of age; $p < 0.001$). Improvement continued through 52 weeks of treatment. Results for all secondary endpoints were also significant at week 24. Treatment-emergent AEs were mostly mild or moderate in nature (*Franco et al 2020*).
- In an unpublished manufacturer-sponsored, randomized, open-label trial, 124 pediatric patients between 6 and 17 years of age with NDO were randomized to receive either fesoterodine 4 mg, 8 mg or oxybutynin. The primary outcome of maximum bladder capacity improved from baseline to week 12 in all 3 treatment groups. Between group comparisons did not demonstrate significant differences in the primary outcome (*Toviaz prescribing information 2021, Clinicaltrials.gov 2021)*

CLINICAL GUIDELINES

OAB

- The 2019 American Urological Association (AUA) guideline on non-neurogenic overactive bladder, the 2021 European Association of Urology (EAU) guideline on non-neurogenic female LUTS, and the 2021 EAU guideline on the management of non-neurogenic male LUTS recommend behavioral therapies (eg, bladder training, bladder control strategies, pelvic floor muscle training, fluid management) as first-line management for OAB (*Gormley et al 2019, Gravas et al 2021, Harding et al 2021, Nambiar et al 2018*).
- Pharmacologic therapy with an oral anticholinergic or beta-3 adrenergic agonist (ie, mirabegron) is recommended as second-line therapy, with agents from both therapeutic classes at the same grade of recommendation (*Gormley et al 2019, Gravas et al 2021, Harding et al 2021, Nambiar et al 2018*).
  - If a patient experiences inadequate symptom control and/or unacceptable AEs with 1 anticholinergic, then a dose modification, a different anticholinergic, an alternative anticholinergic formulation, or a beta-3 adrenoceptor agonist may be tried (*Gormley et al 2019, Gravas et al 2021, Harding et al 2021, Nambiar et al 2018*).

- ER formulations of anticholinergics should be considered whenever possible and preferentially be prescribed over IR formulations, due to lower rates of dry mouth and AEs (*Gormley et al 2019, Gravas et al 2021, Harding et al 2021, Nambiar et al 2018*).
- Combination therapy with an antimuscarinic and beta-3 adrenoceptor agonist may be appropriate for patients who are refractory to monotherapy (*Gormley et al 2019*).
- Anticholinergics cause relatively high rates of dry mouth and constitutional effects (fatigue, constipation, gastrointestinal AEs) and should be avoided in older adults due to increased risks of cognitive impairment (*Gormley et al 2019, Gravas et al 2021, Harding et al 2021, Nambiar et al 2018, Staskin et al 2020*).
- Vibegron is the most recent beta-3 adrenergic agonist approved by the FDA for the treatment of OAB and is not included in any current OAB guidelines (*Gormley et al 2019, Gravas et al 2021, Harding et al 2021, Nambiar et al 2018*).

- The 2019 American Geriatrics Society (AGS) Beers criteria strongly recommend that anticholinergic agents (including antimuscarinic agents for urinary incontinence: darifenacin, fesoterodine, flavoxate, oxybutynin, solifenacin, tolterodine, and trospium) be avoided in older adults with or at high risk for delirium or dementia, and concomitant use of anticholinergics be avoided in older adults due to increased risk of cognitive decline (*AGS 2019*).

NDO

- The 2012 International Children's Continence Society's (ICCS) recommendations for congenital neuropathic bladder in children state that first-line therapy for the majority of children with NDO is clean intermittent catheterization (CIC) 4 to 5 times a day, coupled with or without medical treatment with an oral antimuscarinic (*Rawashdeh et al 2012*).
  - The antimuscarinic agent oxybutynin has been the standard of care medical therapy for NDO; it was the only FDA- There is excellent evidence (Level 1) to support the efficacy of anticholinergics to reduce bladder storage pressure and detrusor overactivity and intravesical storage.
    - The antimuscarinic agent oxybutynin has been the standard of care for NDO; at the time the ICCS recommendations were published, oxybutynin was the only FDA-approved medication for treatment of NDO in patients ≥ 5 years of age.
  - Non-surgical interventions should be promoted before undertaking major surgery, and include pharmacologic agents (ie, antimuscarinics, botulinum-A toxin, and antibiotics), medical devices (ie, CIC), and neuromodulation.
  - Indications for non-surgical treatments depend on issues related to intravesical pressures, upper urinary status, UTI prevalence, and degree of incontinence.
- The 2020 EAU guideline on the management of neurogenic bladder in children and adolescents recommends the use of oxybutynin in patients with detrusor overactivity with the caveat of dose-limiting side effects. The guideline cites studies that report the safe use of tolterodine, solifenacin, and trospium; however, it highlights that their use in neonates and young children is considered off-label. Due to evidence limited to case reports, the guideline makes no recommendation on use of mirabegron in this patient population (*Stein et al 2020*).

SAFETY SUMMARY

Anti-muscarinic (anticholinergic) agents

- The anticholinergic urinary antispasmodics are contraindicated with uncontrolled narrow angle glaucoma, gastric retention, and urinary retention.
- Warnings and precautions for most of the anticholinergic agents include the risk of angioedema, decreased gastrointestinal motility, urinary retention, and central nervous system effects such as dizziness, somnolence, confusion, and hallucinations. Anticholinergic agents should be used with caution in patients with myasthenia gravis or ulcerative colitis. Ditropan XL should be used with caution in patients with Parkinson's disease or in patients with pre-existing dementia treated with cholinesterase inhibitors. Solifenacin is not recommended for use in patients at high risk for QT prolongation and cautious use of tolterodine is suggested in these patients.
- Anticholinergic-related AEs are commonly associated with these agents due to their anticholinergic mechanism of action. The most common AEs include dry mouth and constipation.

Beta-3 adrenergic agonists

- A key warning and precaution with vibegron is the risk of urinary retention, especially in patients with bladder outlet obstruction and in those taking muscarinic antagonist medications for OAB. Key warnings and precautions with mirabegron include increases in blood pressure, urinary retention in patients with bladder outlet obstruction and in those taking anticholinergics for OAB, and angioedema.

- Common AEs for the beta-3 adrenergic agonists include nasopharyngitis, urinary tract infection, and headache. Additional commonly reported AEs of hypertension and tachycardia have been reported for mirabegron.
- Concomitant use of either vibegron or mirabegron with digoxin increases digoxin maximal concentrations. Mirabegron is a cytochrome P450 (CYP)2D6 inhibitor and may interact with drugs metabolized by CYP2D6.

Direct muscle relaxant

- Flavoxate is contraindicated in patients with achalasia, pyloric or duodenal obstruction, obstructive intestinal lesions or ileus, gastrointestinal hemorrhage, and obstructive uropathy.
- Flavoxate has a warning for patients with suspected glaucoma and a precaution that drowsiness and blurred vision may occur.
- AEs include nausea, vomiting, dry mouth, vertigo, headache, mental confusion (especially in the elderly), drowsiness, tachycardia, palpitation, blurred vision, and dysuria.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Darifenacin	Tablet (ER)	Oral	Once daily	• Dose should not exceed 7.5 mg/day with moderate hepatic impairment (Child-Pugh B) or when co-administered with potent CYP3A4 inhibitors; not recommended for use in severe hepatic impairment (Child-Pugh C).
Fesoterodine	Tablet (ER)	Oral	Once daily	• Not recommended for use in severe hepatic impairment (Child-Pugh C). • Dose should not exceed 4 mg/day in: ○ Adults with severe renal impairment (eGFR < 30 mL/min/1.73m^2). ○ Pediatric patients weighing > 35 kg with eGFR between 15 and 29 mL/min/1.73 m^2. ○ When co-administered with potent CYP3A4 inhibitors for adults and pediatric patients weighing > 35 kg. • Initial dose, titration, and adjustments for pediatric patients is based on weight. The use of fesoterodine is not recommended for: ○ Pediatric patients weighing between 26 and 35 kg with eGFR < 30 mL/min/1.73 m^2. ○ Pediatric patients weighing > 35 kg with eGFR < 15 mL/min/1.73 m^2 or requiring dialysis. ○ Pediatric patients weighing between 26 and 35 kg taking strong CYP3A4 inhibitors.
Flavoxate	Tablet	Oral	3 to 4 times daily	• With improvement of symptoms, the dose may be reduced.
Mirabegron	Tablet (ER), granules	Oral	Once daily	• Not recommended for use in ESRD (eGFR < 15 mL/min/1.73 m^2 or requiring dialysis) or severe hepatic impairment (Child-Pugh C). • Dose limitations are recommended in patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m^2) or moderate hepatic impairment (Child-Pugh Class B)

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				• The choice of mirabegron tablets or granules should be based on the indication and patient's weight. ○ In pediatric patients weighing < 35 kg, mirabegron granules are recommended with a weight-based starting dose. After 4 to 8 weeks of treatment, the dose may be increased to the lowest effective dose without exceeding the maximum recommended dose. ○ In pediatric patients weighing ≥ 35 kg, mirabegron tablets or granules may be administered. ○ A recommended dosage for mirabegron granules for adults has not been determined. • Mirabegron tablets and granules are 2 different products and are not substitutable on a mg-per-mg basis. • Mirabegron tablets should be swallowed whole with water and not chewed, divided, or crushed, and may be administered with or without food. • Mirabegron granules should be reconstituted with 100 mL of water and prepared as an ER oral suspension. The suspension should be administered with food to reduce potential exposure-related risks.
Oxybutynin	Tablet (IR), tablet (ER), syrup, gel, transdermal patch	Oral, transdermal	Tablet (IR), Syrup: twice to 3 times daily Tablet (ER): once daily Gel: once daily Patch: once every 3 to 4 days (Oxytrol); once every 4 days (Oxytrol for Women)	• FDA-approved for use in children ≥ 5 years of age (IR) and ≥ 6 years of age (ER) • Dose adjustment of tablets (IR) is recommended in the frail elderly due to prolonged elimination half-life.
Solifenacin	Tablet, suspension	Oral	Once daily	Tablet: • Dose should not exceed 5 mg/day in patients with severe renal impairment (CrCl < 30 mL/min), when co-administered with potent CYP3A4 inhibitors, and in moderate hepatic impairment (Child-Pugh B). • Not recommended for use in severe hepatic impairment (Child-Pugh C). Suspension: • Recommended daily dose is based on patient weight. • Administration of dose should be followed with liquid (eg, water or milk). • The recommended starting dose should not be exceeded in patients with severe renal impairment (CrCl < 30 mL/min), when coadministered with

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				potent CYP3A4 inhibitors, and in moderate hepatic impairment (Child-Pugh B). • Not recommended for use in severe hepatic impairment (Child-Pugh C).
Tolterodine	Capsule (ER), tablet	Oral	Capsule (ER): once daily Tablet: twice daily	• Dose adjustment is required for the capsule (ER) in patients with severe renal impairment, mild to moderate hepatic impairment, and those co-administered potent CYP3A4 inhibitors (2 mg once daily); not recommended for use in severe hepatic impairment (Child-Pugh C). • Capsule (ER) is not recommended in patients with CrCl < 10 mL/min. • Dose adjustment is required for the tablet in patients with significantly reduced hepatic or renal function or those currently taking potent CYP3A4 inhibitors (1 mg twice daily).
Trospium	Capsule (ER), tablet	Oral	Capsule (ER): once daily Tablet: twice daily	• Should be administered at least 1 hour before meals or on an empty stomach. • Dose adjustment is recommended in severe renal impairment for the tablet (20 mg once daily); capsule (ER) not recommended for use in severe renal impairment (CrCl < 30 mL/min). • Should be used with caution in patients with moderate to severe hepatic dysfunction.
Vibegron	Tablet	Oral	Once daily	• Tablet should be swallowed whole with water (with or without food); may be crushed and mixed with applesauce in adults. • Not recommended in ESRD or severe hepatic impairment.

Abbreviations: CrCl = creatinine clearance, eGFR = glomerular filtration rate, ER = extended-release, ESRD = end-stage renal disease, IR = immediate-release

See the current prescribing information for full details.

CONCLUSION

- The urinary antispasmodics (with the exception of flavoxate) are FDA-approved for the management of OAB, defined as urinary urgency, with or without urge incontinence, usually with frequency and nocturia.
  - In the absence of treatment, urinary incontinence has been shown to greatly reduce quality of life in areas such as physical and social functioning, as well as mental and general health.
  - Ditropan XL (oxybutynin), Toviaz (fesoterodine), and mirabegron tablets have an additional indication for pediatric patients with NDO, while IR oxybutynin tablets and syrup, solifenacin suspension, and mirabegron granules are specifically FDA-approved in pediatric patients with NDO.
- The urinary antispasmodics include 2 classes of medications: muscarinic receptor antagonists including darifenacin (Enablex), fesoterodine (Toviaz), flavoxate, oxybutynin, solifenacin (Vesicare, Vesicare LS), tolterodine (Detrol), and trospium; and the beta-3 adrenergic agonists, mirabegron (Myrbetriq, Myrbetriq Granules) and vibegron (Gemtesa). The anticholinergic agents antagonize the effects of acetylcholine at muscarinic cholinergic receptors, thereby relaxing smooth muscle tissue in the bladder and consequently decreasing bladder contractions.

- To reduce dosing frequency and anticholinergic AEs, ER (LA, XL, and XR) formulations are available for oxybutynin (Ditropan XL), tolterodine (Detrol LA), and trospium.
- Oxybutynin is the only agent that is also available in a topical gel (Gelnique) and transdermal patch (Oxytrol). Oxytrol for Women is an OTC transdermal patch indicated in women ≥ 18 years of age.
- Mirabegron and vibegron have a different mechanism of action and AE profile compared with the anticholinergic agents.

- The results from clinical studies have demonstrated each of the urinary antispasmodics to be more effective compared to placebo in regard to improvements in micturition frequency, urgency, urge incontinence episodes, and cystometric capacity (solifenacin suspension). Head-to-head studies with the urinary antispasmodics have not consistently found one agent to be superior to other agents within the class.
  - A 2012 Cochrane review reported that IR formulations of oxybutynin, tolterodine, and trospium have similar efficacy, but oxybutynin was associated with more AEs. In addition, solifenacin improved symptoms of OAB more so than tolterodine IR, while fesoterodine was more effective than tolterodine ER.
  - A 2018 AHRQ systematic review update of nonsurgical treatments for urinary incontinence in women concluded that behavioral therapy, alone or in combination with other interventions, is generally more effective than other first- or second-line interventions (including pharmacologic interventions) alone for both stress and urgency urinary incontinence (*Balk et al* 2018). For women with urgency urinary incontinence, anticholinergics were significantly more likely to result in “cure” (OR, 1.80; 95% CI, 1.29 to 2.52) or improvement (OR, 1.79; 95% CI, 1.18 to 2.7) as compared to placebo.
- Behavioral therapy is recommended first-line for OAB. Second-line pharmacologic therapies include the urinary antispasmodics: anticholinergic agents for urinary incontinence (darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium) and the beta-3 adrenergic receptor agonist, mirabegron.
- For NDO, first-line therapy for the majority of children with NDO is CIC 4 to 5 times a day, coupled with or without medical treatment with an oral antimuscarinic; oral oxybutynin has been the standard of care medical therapy for NDO.
- 2019 AGS Beers criteria strongly recommend that anticholinergic agents be avoided in older adults with or at high risk for delirium or dementia, and concomitant use of anticholinergics be avoided in older adults due to increased risk of cognitive decline.

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Therapeutic Class Overview
Glucagon Agents

INTRODUCTION

- Hypoglycemia in patients with diabetes can be defined as episodes of abnormally low plasma glucose concentration that expose the individual to potential harm. According to the American Diabetes Association (ADA), clinically important hypoglycemia is defined as blood glucose < 70 mg/dL. Level 1 hypoglycemia presents as blood glucose readings ranging from 54 to 69 mg/dL, level 2 hypoglycemia as blood glucose < 54 mg/dL, and level 3 hypoglycemia as a severe event marked by altered mental and/or physical functioning. Blood glucose < 54 mg/dL requires immediate action to resolve hypoglycemia (*ADA 2021*, *Cryer 2021*).
- Hypoglycemia frequently affects patients with type 1 diabetes (T1DM), in whom the risk of severe hypoglycemia (episodes requiring the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions) increases with intensive therapy. Patients with T1DM report an average of up to 3 episodes of severe hypoglycemia per year. Severe hypoglycemia affects patients with type 2 diabetes (T2DM) less commonly; those who are treated with a sulfonylurea, a meglitinide, or insulin are generally at higher risk (*Cryer 2021*).
  - In 2016, the Centers for Disease Control and Prevention (CDC) reported 235,000 episodes of hypoglycemia resulted in emergency department visits (incidence ratio of 10.2 per 1000 patients with diabetes) (*CDC 2020*).
- Hypoglycemia causes symptoms such as tremor, anxiety, tachycardia, sweating, hunger, dizziness, weakness, drowsiness, confusion, and possibly, seizure and coma at lower plasma glucose concentrations. Although extreme, prolonged hypoglycemia can cause brain death, the majority of episodes are reversed after the glucose level is raised. Rare fatal episodes are generally thought to be due to other mechanisms such as ventricular arrhythmia (*Cryer 2021*).
- The goal of treatment of hypoglycemia is to normalize the plasma glucose concentration by administering carbohydrates (dietary or parenteral according to the level of consciousness), or in cases of severe hypoglycemia, by administering glucagon (*Cryer 2021*).
  - Patients with symptomatic hypoglycemia should ingest glucose in the form of tablets, sweetened fruit juice, or hard candy; glucose tablets have more consistent effectiveness.
  - Patients with severe hypoglycemia can usually be treated quickly by giving intravenous (IV) dextrose or glucagon, depending on the status of IV access.
  - In a person with impaired consciousness and no established IV access, administration of glucagon (subcutaneously [SC], intramuscularly [IM], or intranasally [IN]) by a second party will usually lead to recovery of consciousness within approximately 15 minutes, although it may be followed by marked nausea or even vomiting.
    - The response to IV glucose and glucagon is transient; therefore, treatment of hypoglycemia often needs to be followed by a continuous infusion of glucose or by intake of food if the patient is able to eat.
- Injectable glucagon has been approved for use in the United States (US) for several decades. A few injectable products (eg, GlucaGen and Glucagon Emergency Kits [GEKs] by Eli Lilly [GEK-L] and Fresenius Kabi [GEK-F]) have been approved for SC or IM administration that require the caregiver to reconstitute the glucagon powder with the diluent prior to injection. Gvoke (glucagon injection) is available as an auto-injector or prefilled syringe for SC administration and does not require reconstitution. Baqsimi (glucagon nasal powder) was the first IN administered glucagon to be approved; it can be delivered by placing the tip of the device in one nostril and depressing a small plunger that discharges the powder into the nostril without need for inhalation from the patient. Zegalogue (dasiglucagon), a glucagon analog, was approved in March 2021; it is available as an auto-injector or prefilled syringe for SC administration that does not require reconstitution (*Cryer 2021*).
- Medispan Class: Antidiabetics; Diabetic Other; Glucagon

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Baqsimi (glucagon)	-
GlucaGen HypoKit (glucagon)	-
Glucagon emergency kit or solution (glucagon)*	✔
Gvoke (glucagon)	-

Drug	Generic Availability
Zegalogue (dasiglucagon)	-

* Products from Eli Lilly and Fresenius Kabi; a generic of the Eli Lilly product is available

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Baqsimi (glucagon)	GEK-F*/GEK-L*	GlucaGen HypoKit* (glucagon)	Gvoke (glucagon)	Zegalogue (dasiglucagon)
Severe hypoglycemia in patients with diabetes	✔ (≥ 4 years of age)	✔ (all ages)	✔ (all ages)	✔ (≥ 2 years of age)	✔ (≥ 6 years of age)

*Note: GlucaGen and the GEKs are indicated for use as a diagnostic aid during radiologic examinations to temporarily inhibit the movement of the gastrointestinal tract. This indication is not addressed in this review.

(*Prescribing information: Baqsimi 2021, GlucaGen HypoKit 2021, GEK-F 2019, GEK-L 2021, Gvoke 2021, Zegalogue 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

- Two randomized, open-label (OL), 2-period, crossover (XO), noninferiority studies compared the efficacy of a single 3 mg dose of Baqsimi to a single 1 mg dose of IM glucagon injection (GlucaGen) for treatment of insulin-induced hypoglycemia in adults with diabetes. One of the studies included 70 adult patients with T1DM, while the other study included 83 adult patients with T1DM or T2DM. The primary outcome measure was the proportion of patients achieving treatment success, defined as either an increase in blood glucose to ≥ 70 mg/dL or an increase of ≥ 20 mg/dL from glucose nadir within 30 minutes after receiving study glucagon (*Baqsimi prescribing information 2021*, *Rickels et al 2016, Suico et al 2020*).
  - In both studies, Baqsimi demonstrated noninferiority to IM glucagon in reversing insulin-induced hypoglycemia (98.8 to 100% for Baqsimi vs 100% for IM glucagon). In one study, the mean time to treatment success was 11.6 minutes for the Baqsimi group vs 9.9 minutes for the IM glucagon group while in the other study, the mean time to treatment success was 15.9 minutes for Baqsimi group vs 12.1 minutes for the IM glucagon group.
- In a pediatric study of 48 patients aged ≥ 4 years with T1DM, similar results for Baqsimi 3 mg vs weight-based (0.5 mg or 1 mg) IM glucagon were observed. The primary endpoint was the percentage of patients with a glucose increase of ≥ 20 mg/dL from glucose nadir within 30 minutes of glucagon administration (*Baqsimi prescribing information 2021*, *Sherr et al 2016*).
  - Across all age groups, all (100%) patients in both treatment arms achieved an increase in glucose ≥ 20 mg/dL from glucose nadir within 20 minutes of glucagon administration. The mean time to reach a glucose increase ≥ 20 mg/dL ranged from 10.8 to 14.2 minutes for Baqsimi and 10.8 to 12.5 minutes for IM glucagon.
- In a comparative usability study (N = 31) evaluating the use of Baqsimi and IM glucagon by individuals in a simulated emergency event, participants were significantly more likely to successfully administer a full dose with Baqsimi (94% of attempts) than with injectable glucagon (13% of attempts) (*Yale et al 2017*).
- In 2 OL, real-world usability studies involving caregivers of adults with T1DM (N = 69) and caregivers of children with T1DM (N = 15), Baqsimi was successful in treating episodes of moderate and severe hypoglycemia in 95.7% of adults and 100% of children. Of note, the trials had serious quality limitations and additional data are needed to validate the results (*Deeb et al 2018, Seaquist et al 2018)*.
- A study (N = 65) compared the success rates of administering IN glucagon vs injectable glucagon by trained and untrained patients with diabetes. Of all patients (trained and untrained), 90.6% successfully administered IN glucagon and 7.9% successfully administered injectable glucagon (*Settles et al 2020*).

- A meta-analysis (MA) of 8 studies (N = 269) compared the effectiveness of IN glucagon with IM/SC glucagon in patients with T1DM and hypoglycemia. The response outcomes were similar between IN glucagon and IM/SC glucagon (odds ratio [OR], 0.80; 95% confidence interval [CI], 0.28 to 2.32) (*Pontiroli et al 2020*).
- Two randomized, 2-way, XO, noninferiority studies (N = 181) compared the efficacy of Gvoke 1 mg SC to GEK-L 1 mg SC for treatment of insulin-induced hypoglycemia in adults with T1DM. The primary efficacy endpoint was the proportion of patients achieving treatment success, defined as either an increase in plasma glucose from a mean value at the time of glucagon administration to an absolute value ≥ 70 mg/dL or a relative increase of ≥ 20 mg/dL at 30 minutes after receiving study glucagon (*Gvoke prescribing information 2021, Christensen et al 2019 [poster]*).
  - In a pooled analysis of both studies, the proportion of patients who achieved treatment success was 99% in the Gvoke group and 100% in the GEK-L group, and the comparison between groups met the prespecified non-inferiority margin. The mean time to treatment success was 13.8 minutes in the Gvoke group and 10 minutes in the GEK-L group.
- An OL study of 31 patients aged ≥ 2 years with T1DM evaluated 2 doses of Gvoke for treatment of insulin-induced hypoglycemia. Patients aged 2 to < 6 years and 6 to < 12 years received Gvoke 0.5 mg SC while patients aged ≥ 12 years received either Gvoke 0.5 mg or 1 mg SC (*Gvoke prescribing information 2021*, *Buckingham et al 2018 [poster]*).
  - All evaluable patients achieved a target dose of at least 25 mg/dL.
- Two human factors studies evaluated whether the Gvoke prefilled syringe could be effectively administered (*Newswanger et al 2019*). In a formative study (N = 11), there was a 100% success rate while in the validation study (N = 75), 99% of patients successfully administered the full dose. Similarly, 2 human factors studies evaluated whether the Gvoke auto-injector could be effectively administered (*Valentine et al 2019*). In the simulated-use comparative usability study (N = 16), 88% of participants were able to successfully administer a rescue injection using Gvoke compared with 31% with the GEKs. In the validation study (N = 75), 98.7% of patients successfully administered the rescue injection using the Gvoke auto-injector.
- Dasiglucagon was evaluated in 3 Phase 3, double-blind, multi-center, randomized, placebo-controlled trials in patients with T1DM. Two trials were conducted in adult patients (trials A and B) and 1 trial was conducted in pediatric patients aged 6 to 17 years (Trial C). Patients were randomized to dasiglucagon 0.6 mg SC, placebo, or (in Trials A and C only) glucagon 1.0 mg SC (GlucaGen) following a controlled induction of hypoglycemia using IV insulin. The primary efficacy endpoint for all 3 trials was time to plasma glucose recovery (treatment success), defined as an increase in blood glucose of ≥ 20 mg/dL from time of administration, without additional intervention within 45 minutes. The primary hypothesis test was superiority of dasiglucagon vs placebo; there was no formal hypothesis test of dasiglucagon vs glucagon injection *(Battelino et al 2021, Pieber et al 2021, Zegalogue Prescribing Information 2021).*
  - In trial A (N = 170), the median time to plasma glucose recovery was significantly shorter for dasiglucagon vs placebo (10 minutes vs 40 minutes, respectively; p < 0.001). The median time to plasma glucose recovery was numerically similar between dasiglucagon and glucagon injection (10 minutes and 12 minutes, respectively).
  - In trial B (N = 45), the median time to plasma glucose recovery was significantly shorter for dasiglucagon vs placebo (10 minutes vs 35 minutes, respectively; p < 0.0001).
  - In trial C (N = 42), the median time to plasma glucose recovery was significantly shorter for dasiglucagon vs placebo (10 minutes vs 30 minutes, respectively; p < 0.0001). The median time to plasma glucose recovery was numerically similar between dasiglucagon and glucagon injection (10 minutes and 10 minutes, respectively).

CLINICAL GUIDELINES

- ADA guidelines recommend that all patients at increased risk of hypoglycemia with blood glucose < 54 mg/dL or hypoglycemia marked by altered mental and/or physical functioning be prescribed glucagon so that it would be available if needed. Caregivers, school personnel, or family members should know where it is and when and how to administer it. Glucagon administration is not limited to health care professionals, particularly with the availability of IN and stable soluble glucagon available in auto-injector pens (*ADA 2021*).
- The American Association of Clinical Endocrinologists/American College of Endocrinology guidelines recommend that SC or IM glucagon or IV glucose be given by a trained family member or medical personnel to patients experiencing severe hypoglycemia who are unable to swallow or who are unresponsive (*Handelsman et al 2015*).

SAFETY SUMMARY

- All of the glucagon products have contraindications and/or warnings in patients with pheochromocytoma, insulinoma, and known hypersensitivity to any of the constituents of the formulation. In addition, they all carry a warning for lack of efficacy in patients with decreased hepatic glycogen. Gvoke, GlucaGen, and the GEKs also have a warning for necrolytic migratory erythema (NME) due to postmarketing reports following continuous glucagon infusion.
- The most common adverse events (AEs) with Baqsimi were nausea, vomiting, headache, upper respiratory tract irritation, watery eyes, redness of eyes, and itchy nose, throat and eyes. Common AEs with the injectable products included nausea, vomiting, and injection site reactions.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Baqsimi (glucagon)	Nasal powder	IN	One actuation of the IN device into 1 nostril; if there has been no response after 15 minutes, an additional dose from a new device may be administered while waiting for emergency assistance	The dose should be administered by inserting the tip into 1 nostril and pressing the device plunger all the way in until the green line is no longer showing. The dose does not need to be inhaled.
GEK-F (glucagon) GEK-L (glucagon) GlucaGen HypoKit (glucagon)	Injection (including a kit requiring reconstitution)	IM, IV, SC	One dose (weight-based dosing in pediatric patients); if there has been no response after 15 minutes, an additional dose from a new kit may be administered while waiting for emergency assistance	The product should be reconstituted according to instructions before administration. Common SC/IM injection sites are the upper arms, thighs or buttocks.
Gvoke (glucagon)	Injection (auto-injector, prefilled syringe)	SC	One dose (weight-based dosing in pediatric patients); if there has been no response after 15 minutes, an additional dose from a new device may be administered while waiting for emergency assistance	The injection may be given in the lower abdomen, outer thigh, or outer upper arm.
Zegalogue (dasiglucagon)	Injection (auto-injector, prefilled syringe)	SC	One dose (0.6 mg); if there has been no response after 15 minutes, an additional dose from a new device may be administered while waiting for emergency assistance	The injection may be given in the lower abdomen, buttocks, thigh, or outer upper arm.

See the current prescribing information for full details

CONCLUSION

- Severe hypoglycemia is generally defined as a hypoglycemic event that requires assistance from another person to administer carbohydrates or glucagon or take other corrective action. Immediate treatment is necessary to increase blood sugar and prevent serious complications, such as loss of consciousness, seizure, coma, or death.
- Treatment guidelines recommend that glucagon be given by a trained caregiver to patients experiencing severe hypoglycemia who are unable to swallow or who are unresponsive (*ADA 2021*, *Handelsman et al 2015).*

- Injectable glucagon in the form of kits containing a prefilled syringe of diluent and a vial of glucagon powder for reconstitution has been approved for use in the US for many years. Recently, new products have been approved that provide additional options for the treatment of severe hypoglycemia in patients with diabetes that may simplify the process of glucagon administration. Gvoke and dasiglucagon (a glucagon analog) are available in the form of an auto-injector or prefilled syringe that does not require reconstitution, while Baqsimi is the first IN formulation of glucagon.

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Therapeutic Class Overview
Calcitonin gene related peptide (CGRP) inhibitors

INTRODUCTION

- Migraine is a common, recurrent, incapacitating disorder characterized by moderate to severe headaches and disabling features, including nausea, vomiting, neurologic symptoms, photophobia, and phonophobia. Cluster headache is less prevalent than migraine and characterized by attacks of severe, unilateral pain with ipsilateral autonomic symptoms, which occur every other day to multiple times daily during a cluster period (*International Headache Society [IHS] 2018, Starling et al 2015).*
  - The 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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Therapeutic Class Overview
Ophthalmic Immunomodulators

INTRODUCTION

- Dry eye disease (DED) refers to a group of disorders of the tear film that are due to reduced tear production or excessive tear evaporation (*American Academy of Ophthalmology [AAO] 2018[a], Shtein 2021*). The condition can be associated with discomfort and/or visual symptoms and may result in disease of the ocular surface. The ocular surface and tear-secreting glands are recognized to be responsible for the maintenance of tear production and to clear tears. Therefore, disease or dysfunction results in an unstable and poorly maintained tear film that causes ocular irritation symptoms and an epithelial disease known as keratoconjunctivitis sicca (KCS). Decreased tear secretion and clearance initiates an inflammatory response on the ocular surface, which plays a role in the pathogenesis of KCS. Symptoms of KCS include, but are not limited to, dryness, discomfort, irritation/pain, foreign body sensation, and blurred vision (*AAO 2018[a]).*
  - Rare complications of severe dry eyes include ocular surface keratinization; corneal scarring, thinning, or neovascularization; microbial or sterile corneal ulceration with possible perforation; and severe visual loss.
  - Frequent instillation of ophthalmic medications (eg, natural tears) may cause dry eye symptoms by preventing the normal maintenance of the tear film. Other factors known to exacerbate symptoms of dry eye include environmental factors such as reduced humidity, air drafts, air conditioning, or heating. Associated systemic diseases include Sjögren's Syndrome, rosacea, and viral infection. Common drug-induced causes of dry eye symptoms include systemic medications such as anticholinergics, antidepressants, antihistamines, diuretics, and retinoids (*AAO 2018[a]*).
  - Eysuvis (loteprednol etabonate ophthalmic suspension) 0.25% is a corticosteroid indicated for the short-term use for up to 2 weeks for the treatment of the signs and symptoms of DED (*Eysuvis prescribing information 2020*). This product is reviewed with the ophthalmic corticosteroids with the other formulations of loteprednol etabonate.
- Ocular allergy includes 5 subtypes such as seasonal and perennial allergic conjunctivitis, vernal keratoconjunctivitis (VKC), atopic keratoconjunctivitis, and giant papillary conjunctivitis. VKC is a chronic, bilateral, severe form of inflammation on the ocular surface that can result in corneal scarring and vision loss if not treated properly (*Hamrah and Dana 2021*).
  - VKC typically affects those living in warm, dry, subtropical climates. The prevalence in these areas is approximately 0.03% of the population. Males are more commonly affected than females (ratio, 3.2:1) as are patients < 20 years of age. The most common concomitant atopic diseases are asthma and allergic rhinitis.
  - Pruritus is the primary symptom, but patients may also experience photophobia, thick mucus discharge, tearing, burning, foreign body sensation, pain, and blurred vision. Symptoms tend to occur most commonly in the spring. Bilateral signs of VKC include giant cobblestone-like papillae on the conjunctiva of the upper eyelid.
  - Treatment of VKC typically consists of trigger avoidance and the use of over-the-counter ophthalmic antihistamine/mast cell stabilizer products, followed by an oral antihistamine. If VKC is not well-controlled, ophthalmic corticosteroids may be considered. Ophthalmic immunomodulators may be added for patients who have an inadequate response to ophthalmic corticosteroids.
- Medispan Therapeutic Classes: Ophthalmic Immunomodulators; Ophthalmic Integrin Antagonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Cequa (cyclosporine ophthalmic solution) 0.09%	-
Restasis, Restasis Multidose (cyclosporine ophthalmic emulsion) 0.05%	-
Verkazia (cyclosporine ophthalmic emulsion) 0.1%	-
Xiidra (lifitegrast ophthalmic solution) 5%	-

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Cequa (cyclosporine ophthalmic solution)	Restasis, Restasis Multidose (cyclosporine ophthalmic emulsion)	Verkazia (cyclosporine ophthalmic emulsion)	Xiidra (lifitegrast ophthalmic solution)
To increase tear production in patients whose tear production is presumed to be suppressed due to ocular inflammation associated with KCS*		✔		
To increase tear production in patients with KCS	✔			
Treatment of the signs and symptoms of DED				✔
Treatment of VKC in children and adults			✔	

*Increased tear production was not seen in patients currently taking topical anti-inflammatory drugs or using punctal plugs.

(*Prescribing information: Cequa 2019, Restasis 2017, Restasis Multidose 2016, Verkazia 2021, Xiidra 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

- The ophthalmic immunomodulator products have not been directly compared in clinical trials and have primarily been compared to vehicle. Indirect comparisons are very challenging since the inclusion criteria, endpoints, use of artificial tears, and vehicles differed among the trials (*Holland et al 2019, Nichols et al 2021*). In addition, signs and symptoms of DED correlate poorly.
- **DED**
  - The pivotal trials for cyclosporine ophthalmic emulsion were 2 randomized, placebo-controlled trials that included 877 patients and an open-label, extension trial that included 412 patients (*Barber et al 2005, Sall et al 2000*). All patients were diagnosed with moderate-to-severe KCS and decreased tear production based on the Schirmer tear test. The combined results of the 2 placebo-controlled trials demonstrated that cyclosporine ophthalmic emulsion 0.05% and 0.1% were associated with significant improvements from baseline in corneal staining, Schirmer tear test scores, Ocular Surface Disease Index (OSDI) scores, Subjective Facial Expression Rating Scale scores, and various dry eye related symptoms (*Sall et al 2000*). Specifically compared to placebo, at 4 months, improvements in corneal staining were significant in both cyclosporine ophthalmic emulsion groups compared to placebo ($p \leq 0.044$), and at 6 months, only the cyclosporine ophthalmic emulsion 0.05% group demonstrated significance over placebo ($p = 0.008$). Additionally, at 6 months, improvements in Schirmer tear test scores were significantly greater for both cyclosporine ophthalmic emulsion groups compared to placebo ($p \leq 0.05$ for both) and from baseline scores (p values not reported). Improvements in OSDI and Subjective Facial Expression Rating Scale scores were significant compared to baseline for all treatment groups ($p < 0.001$), but there were no significant differences among these groups (p values not reported). Improvements in blurred vision were significantly greater in the cyclosporine ophthalmic emulsion 0.05% group than placebo at all follow-up visits ($p \leq 0.014$), and significant improvements were achieved at all time points within all treatment groups when compared to baseline for relief of dry eye symptoms including dryness ($p < 0.001$), sandy/gritty feeling ($p < 0.001$), and itching ($p \leq 0.038$). A Chinese, double-blind study used similar subjective ratings for dry eye symptoms and found that cyclosporine ophthalmic emulsion 0.05% improved measures over 8 weeks (*Chen et al 2010*).
  - An open-label, extension trial was also conducted to determine the long-term safety of cyclosporine ophthalmic emulsion 0.1%. After 3 consecutive 12-month periods, results demonstrated that cyclosporine ophthalmic emulsion was safe and well tolerated. Over 3 years, adverse events were found in 65.3% (269/412) of patients with ocular burning reported most commonly (12.1%). This trial also demonstrated sustained efficacy of cyclosporine ophthalmic emulsion over an extended period of time (*Barber et al 2005*).

- A trial comparing Restasis (cyclosporine ophthalmic emulsion) 0.05% to punctal plugs or a combination of both demonstrated that both treatments improved the symptoms of dry eye, but punctal plugs achieved results more rapidly than cyclosporine ophthalmic emulsion 0.05% (*Roberts et al 2007*).
- A systematic review of 18 randomized controlled trials (RCTs) examined the efficacy and safety of topical cyclosporine 0.05% to 2% with or without artificial tears for treatment of DED. All cyclosporine formulations proved safe for the treatment of DED. Symptoms improved in 100% (9/9 RCTs), tear function improved in 72% (13/18 RCTs) and ocular surface damage was ameliorated in 53% (9/17 RCTs) (*Saccheti et al 2014*).
  - Statistical comparison of cyclosporine efficacy through a meta-analysis of data was not possible due to a lack of standardized criteria and comparable outcomes among studies.
- A systematic review and meta-analysis of 30 randomized, controlled clinical studies (N = 4009) assessed the effectiveness and safety of topical cyclosporine 0.05 % in the treatment of DED. Eighteen studies compared cyclosporine 0.05% plus artificial tears vs artificial tears alone. However, due to incomplete results data or considerable statistical heterogeneity, only a meta-analysis on mean conjunctival goblet cell density was conducted. The mean density (MD) was greater in the cyclosporine treated group (MD 22.5 cells per unit, 95% confidence interval [CI], 16.3 to 28.8). Additionally, the analysis could not demonstrate the benefit of cyclosporine for tear production and helping to reduce signs and symptoms of dry eye. The remaining 12 studies were not assessed due to inconsistent data reporting (*de Paiva et al 2019*).
- Two multicenter, randomized, controlled clinical studies evaluated the efficacy of Cequa (cyclosporine ophthalmic solution) 0.09% in 1048 patients with KCS. In both studies, there was a significantly ($p < 0.01$) higher percentage of eyes with increases of ≥ 10 mm from baseline in Schirmer wetting as compared to vehicle at day 84. This effect was seen in approximately 17% of patients treated with cyclosporine ophthalmic solution vs approximately 9% of patients treated with vehicle (*Cequa prescribing information 2018, Goldberg et al 2019, Sheppard et al 2020, Tauber et al 2018*).
- A systematic review and meta-analysis of 11 RCTs (N = 1085) evaluated the effect of cyclosporine 0.05% in diverse dosages with or without artificial tears for DED. Pooled results showed that cyclosporine had better tear-breakup time (mean difference [MD] 0.94; 95% CI, 0.08 to 1.80) when compared to artificial tears; however, high heterogeneity was noted ($I^2 = 85\%$). In a subgroup analysis, results showed significant treatment effect for cyclosporine only when treatment duration was > 3 months (*Tuan et al 2020*).
- The safety and efficacy of lifitegrast ophthalmic solution for the treatment of DED were assessed in a total of 1181 patients (1067 of which received lifitegrast 5%) in four 12-week, randomized, multicenter, double-masked, vehicle-controlled studies (*Holland et al 2017, Semba et al 2012, Sheppard et al 2014, Tauber et al 2015*). The use of artificial tears was not allowed during the studies. The clinical trials evaluated various endpoints related to signs and symptoms of DED. However, the Food and Drug Administration (FDA) approval relied on an assessment of symptoms based on change from baseline in patient reported eye dryness score (EDS; 0 to 100 visual analogue [VAS] scale) and an assessment of signs based on the inferior corneal staining score (ICSS; 0 to 4 scale).
  - A larger reduction in EDS favoring lifitegrast was observed in all studies at day 42 and day 84.
    - EDS was used as a primary symptom endpoint in 2 of the 4 studies (OPUS-2 and OPUS-3); the other 2 evaluated EDS as a secondary endpoint.
    - In OPUS-1, the primary symptom endpoint was the visual-related function subscale score of the Ocular Surface Disease Index (VR-OSDI) questionnaire. No difference between lifitegrast and placebo was seen in the mean change from baseline to day 84 ($p = 0.7894$) (*Sheppard et al 2014*).
  - At day 84, a larger reduction in ICSS favoring lifitegrast was observed in 3 of the 4 studies (no statistically significant difference between lifitegrast and placebo was found in the OPUS-2 study).
  - In a 1-year safety study (N = 331: 220 lifitegrast; 111 placebo), there were no serious ocular treatment-emergent adverse events. Overall, 53.6% of participants receiving lifitegrast experienced ≥ 1 ocular treatment-emergent AE vs 34.2% in the placebo group; most treatment-emergent adverse events were mild to moderate in severity, with burning, instillation site reaction, reduced visual acuity, dry eye, and dysgeusia reported most commonly (*Donnenfeld et al 2016*).
  - Ocular comfort of lifitegrast was also assessed in OPUS-3 (N = 711). Drop comfort scores (0 = very comfortable, 10 = very uncomfortable) were assessed immediately after instillation and at 1, 2, and 3 minutes post-instillation. The results showed that drop comfort scores with lifitegrast improved within 3 minutes of instillation with scores approaching that of placebo (*Nichols et al 2018*).
- A pooled analysis of 5 randomized trials (lifitegrast N = 1287, placebo N = 1177) evaluated the safety and tolerability of lifitegrast ophthalmic solution 5.0% for the treatment of dry eye. Overall, the majority of treatment related adverse

events reported (> 5%) were instillation site irritation, instillation site reaction and instillation site pain; the most common non-ocular adverse event reported was dysgeusia in 14.5% of patients receiving lifitegrast vs 0.3% in the placebo group. The analysis also noted that drop comfort scores in the lifitegrast treatment group improved within 3 minutes of instillation and continued to improve across visits through 1 year (*Nichols et al 2019*).

- **VKC**
  - The Vernal KeratoconjunctiTIs Study (VEKTIS) was a double-blind, multi-center, Phase 3, RCT that evaluated the safety and efficacy of Verkazia (cyclosporine ophthalmic emulsion) 0.1% in the treatment of active VKC in 169 children and adolescents aged 4 to < 18 years. Patients had severe keratitis according to the corneal fluorescein staining (CFS) score of 4 or 5 on the modified Oxford scale (range, 0 to 5 with higher scores indicating more severe disease). Patients were randomized to cyclosporine ophthalmic cationic emulsion 0.1% instilled as 1 drop 4 times daily (high-dose group), 1 drop twice daily plus vehicle twice daily (low-dose group), or vehicle 4 times daily for 4 months (*Bremond-Gignac et al 2020, Leonardi et al 2019[a]*).
    - The primary endpoint was the mean composite score of CFS score, use of rescue medication with dexamethasone 0.1% 4 times daily and corneal ulceration over 4 months. The composite scores of the high-dose and low-dose groups were significantly higher, favoring the active treatment groups vs vehicle. The mean differences from vehicle were 0.76 (95% CI, 0.26 to 1.27; p = 0.007) for the high-dose group and 0.67 (95% CI, 0.16 to 1.18; p = 0.010) for the low-dose group.
      - The secondary endpoints, mean change from baseline in CFS score and mean number of rescue medication courses, were significantly improved in the high-dose cyclosporine group. The mean numbers of corneal ulcerations were not significantly different vs vehicle (0.001 and 0.003 per month in the high-dose and low-dose cyclosporine groups, respectively). Corneal ulcers occurred in 4 (7.0%), 3 (5.6%), and 3 (5.2%) patients in the high-dose, low-dose, and vehicles groups, respectively.
      - A total of 142 patients entered the 8-month DB follow-up period in which patients remained on their allocated regimen of high-dose or low-dose cyclosporine. Patients originally randomized to vehicle who completed the 4-month treatment period (n = 49) were allocated to either the high-dose (n = 22) or low-dose (n = 26) groups which was pre-determined with the initial randomization. The mean CFS scores remained stable to month 12. The percentages of patients requiring rescue medications were stable in both groups through month 8, but higher rates of patients required rescue medication in months 10 to 12 for the high-dose and low-dose groups (18.3% and 20.0%, respectively). The changes in months 10 to 12 were primarily due to patients using cyclosporine intermittently. The most common adverse events through month 12 were instillation site pain (13.9%) and instillation site pruritus (6.9%).

CLINICAL GUIDELINES

- **DED**
  - The AAO Preferred Practice Pattern for Dry Eye Syndrome makes treatment recommendations based on disease severity (*AAO 2018[a]*).
    - For mild disease, education and environmental modifications, aqueous enhancement using artificial tears, gels or ointments, and eyelid therapy with warm compresses and eyelid scrubs are recommended.
    - For moderate disease, the AAO recommends in addition to the treatments for mild disease, anti-inflammatory agents such as topical cyclosporine, lifitegrast, and corticosteroids; punctal plugs; or spectacle side shields and moisture chambers.
      - Low-dose topical corticosteroid therapy should be used at infrequent intervals for short periods of time (ie, several weeks) to suppress ocular surface inflammation. Patients prescribed corticosteroids for dry eye should be monitored for adverse events such as increased intraocular pressure and cataract formation.
    - For severe disease, the AAO recommends in addition to all the previously mentioned treatments, systemic cholinergic agonists or anti-inflammatory agents, mucolytic agents, autologous serum tears, contact lenses, permanent punctal occlusion, or tarsorrhaphy.
  - Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) recommends a step-wise approach based on disease severity (*Jones et al 2017*).
    - Step 1: education, lid hygiene, warm compress, modification of environmental factors, omega-3 fatty acid supplementation, or ocular lubricants. Ocular lubricants are considered mainstay of treatment; however, they only offer palliative relief with no disease modifying potential.
    - Step 2 (if above inadequate):

- Non-pharmacological: punctual occlusion (most widely used tear conservation approach), pulsed light therapy, moisture goggles
- Pharmacological: topical antibiotic for blepharitis, limited duration topical corticosteroid, topical cyclosporine, topical lifitegrast.

- Step 3 (if above inadequate): oral secretagogues, allogenic serum eye drops, or therapeutic contact lenses
- Step 4 (if above inadequate): longer duration topical steroid, membrane grafts, punctual occlusion or other surgical approaches.

- **VKC**
  - The AAO Conjunctivitis Preferred Practice Patterns recommend ophthalmic and oral antihistamines/mast cell stabilizers, and environmental changes to reduce allergen or irritant exposure. For acute exacerbations, patients should be treated with ophthalmic corticosteroids to control severe symptoms and signs. Topical compounded cyclosporine 2% has demonstrated a reduction in the signs and symptoms of VKC vs placebo. Restasis (cyclosporine ophthalmic emulsion) 0.05% with more frequent dosing (ie, 4 to 6 times daily) has been shown to be effective for the treatment of severe VKC and/or atopic keratoconjunctivitis. Ophthalmic cyclosporine may allow for reduced use of ophthalmic steroids (*AAO 2018[b]*).
  - The European Academy of Allergy and Clinical Immunology (EAACI) position paper on ocular allergy aligns with the AAO guidelines for the recommendations of the step-wise approach to treatment for VKC (*Leonardi et al 2019[b]*).

SAFETY SUMMARY

- Restasis / Restasis Multidose (cyclosporine ophthalmic emulsion) 0.05%
  - Cyclosporine ophthalmic emulsion is contraindicated in patients with known or suspected hypersensitivity to any ingredient in the formulation.
  - Warnings include the risk of eye injury and contamination when administering the medication if the vial tip touches the eye or other surfaces and use with contact lenses. Cyclosporine ophthalmic emulsion should not be administered while wearing contact lenses. If contact lenses are worn, they should be removed prior to the administration of the emulsion. Lenses may be reinserted 15 minutes following administration of cyclosporine ophthalmic emulsion.
  - Ocular burning was the most frequently reported AE. Other adverse events included ocular pain, conjunctival hyperemia, discharge, foreign body sensation, pruritus, stinging, and visual disturbance (most often blurring).
- Cequa (cyclosporine ophthalmic solution) 0.09%
  - The ophthalmic solution has no contraindications for use.
  - Cyclosporine ophthalmic solution has similar warnings as the ophthalmic emulsion formulation.
  - Pain on drop instillation was the most frequently reported AE followed by conjunctival hyperemia. Other adverse events included blepharitis, eye irritation, headache, and urinary tract infection.
- Verkazia (cyclosporine ophthalmic emulsion) 0.1%
  - There are no contraindications in the labeling for Verkazia.
  - The most common adverse events with Verkazia include eye pain (12%) and eye pruritis (8%).
- Xiidra (lifitegrast ophthalmic solution) 5%
  - Lifitegrast ophthalmic solution is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation.
  - The most commonly reported adverse events reported in 5 to 25% of patients were instillation site irritation, dysgeusia, and reduced visual acuity.
  - Other adverse events reported in 1 to 5% of patients included blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus, and sinusitis.
  - Post marketing adverse events reported include rare serious cases of hypersensitivity (anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, urticaria, allergic conjunctivitis, dyspnea, angioedema, and allergic dermatitis), eye swelling, and rash.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Cequa (cyclosporine ophthalmic solution) 0.09%	Ophthalmic solution	Ophthalmic	Instill 1 drop twice daily (approximately 12 hours apart)	Cyclosporine ophthalmic solution can be used concomitantly with artificial tears; however, patients should allow for a 15-minute interval between the products. To avoid contamination, care should be taken not to touch the bottle tip to the eye or other surfaces. Discard the vial immediately after use.
Restasis, Restasis Multidose (cyclosporine ophthalmic emulsion) 0.05%	Ophthalmic emulsion	Ophthalmic	Instill 1 drop twice daily (approximately 12 hours apart)	Cyclosporine ophthalmic emulsion can be used concomitantly with artificial tears; however, patients should allow for a 15-minute interval between the products. To avoid contamination, care should be taken not to touch the bottle tip to the eye or other surfaces. Restasis (single-dose vial): Discard vial immediately after use. Restasis Multidose is packaged in a multi-dose preservative-free 10 mL bottle containing 5.5 mL.
Verkazia (cyclosporine ophthalmic emulsion) 0.1%	Ophthalmic emulsion	Ophthalmic	Instill 1 drop 4 times daily	Contact lenses should be removed prior to the administration of Verkazia and may be reinserted 15 minutes following administration. If ≥ 1 ophthalmic product is used, the eye drops should be administered ≥ 10 minutes apart to avoid diluting products. Verkazia should be administered 10 minutes prior to any eye ointment, gel or other viscous eye drops. To avoid contamination, care should be taken not to touch the bottle tip to the eye or other surfaces. Discard vial immediately after use.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Xiidra (lifitegrast ophthalmic solution)	Ophthalmic solution	Ophthalmic	Instill 1 drop twice daily (approximately 12 hours apart)	Contact lenses should be removed prior to the administration of lifitegrast and may be reinserted 15 minutes following administration. Discard the single-use container immediately after using in each eye.

See the current prescribing information for full details

CONCLUSION

- Agents in this class are indicated for the treatment of the signs and/or symptoms of DED or for the treatment of VKC.
- Direct comparative studies of the 3 cyclosporine formulations are not available. The vehicles of each of the cyclosporine products differ.
- **DED**
  - Restasis (cyclosporine ophthalmic emulsion) 0.05% was the first ophthalmic emulsion FDA-approved to increase tear production in patients with KCS. In August 2018, the FDA approved Cequa (cyclosporine ophthalmic solution) 0.09% to increase tear production in patients with KCS (*Cequa prescribing information 2018*). This is the first cyclosporine product to utilize nanomicellar technology. This formulation allows the drug molecule to overcome solubility difficulties, penetrate the eye's aqueous layer, and prevent the release of active lipophilic molecule prior to penetration.
    - In clinical trials, Restasis (cyclosporine ophthalmic emulsion) 0.05% demonstrated significant increases in tear production and decreases in dry eye symptoms compared to placebo and demonstrated safety for up to 3 years (*Barber et al 2005, Roberts et al 2007, Sall et al 2000*). For Cequa (cyclosporine ophthalmic solution) 0.09%, there was a significantly ($p < 0.01$) higher percentage of eyes with increases of ≥ 10 mm from baseline in Schirmer wetting as compared to vehicle at day 84 *(Cequa prescribing information 2018, Goldberg et al 2019, Sheppard et al 2020, Tauber et al 2018)*.
  - Xiidra (lifitegrast ophthalmic solution) is indicated for the treatment of the signs and symptoms of DED. Lifitegrast is a novel small molecule integrin antagonist that inhibits T cell-mediated inflammation by blocking the binding of 2 important cell surface proteins (lymphocyte function-associated antigen 1 [LFA-1] and intercellular adhesion molecule 1 [ICAM-1]), thus lessening overall inflammatory responses. However, the exact mechanism of action of lifitegrast in DED is unknown.
    - Lifitegrast also demonstrated significant improvements in the signs and symptoms of DED compared with placebo in clinical trials. Lifitegrast was well tolerated with no unexpected adverse events in a 1-year safety exposure study (*Donnenfeld et al 2016, Holland et al 2017, Semba et al 2012, Sheppard et al 2014, Tauber et al 2015*).
  - Ophthalmic immunomodulators improve signs of DED in patients who are inadequately treated with artificial tears and other therapies. Lifitegrast demonstrated improvement in symptoms of DED; however, cyclosporine has not consistently improved symptoms in DED compared to placebo. Direct comparative data between cyclosporine products and lifitegrast are lacking.
- **VKC**
  - VKC is a bilateral chronic form of allergic conjunctivitis that presents in childhood and is associated with allergy and atopy (*AAO 2018[b]*). Treatment options include environmental changes to minimize allergen or irritant exposure, cold compresses, eye lubricants, and ophthalmic antihistamines/mast cell stabilizers. For acute exacerbations, topical corticosteroids are administered to reduce the signs and symptoms.
    - Verkazia (cyclosporine ophthalmic emulsion) 0.1% is indicated for the treatment of VKC. Cyclosporine ophthalmic emulsion) 0.1% improved signs and symptoms of VKC over 4 months compared to vehicle and demonstrated safety over 12 months.
    - For patients with VKC who are inadequately treated, intolerant, or require tapering with ophthalmic corticosteroids, Verkazia (cyclosporine ophthalmic emulsion) 0.1% offers an additional treatment option for the patient with VKC.

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INTRODUCTION

- Antipsychotic medications have been used for over 50 years to treat schizophrenia and a variety of other psychiatric disorders (*Miyamato et al 2005*).
- Antipsychotic medications generally exert their effect in part by blocking dopamine (D)-2 receptors (*Crismon et al 2020*).
- Antipsychotics are divided into 2 distinct classes based on their affinity for D2 and other neuroreceptors: typical antipsychotics, also called first-generation antipsychotics (FGAs), and atypical antipsychotics, also called second-generation antipsychotics (SGAs) (*Miyamato et al 2005)*.
- Atypical antipsychotics do not have a uniform pharmacology or mechanism of action; these differences likely account for the different safety and tolerability profiles of these agents (*Crismon et al 2020, Jibson et al 2021*). The atypical antipsychotics differ from the early antipsychotics in that they have affinity for the serotonin 5-HT2 receptor in addition to D2.
  - Clozapine is an antagonist at all dopamine receptors (D1-5), with lower affinity for D1 and D2 receptors and high affinity for D4 receptors. Aripiprazole and brexpiprazole act as partial agonists at the D2 receptor, functioning as an agonist when synaptic dopamine levels are low and as an antagonist when they are high. Cariprazine is a partial agonist at D2 and D3. Pimavanserin does not have dopamine blocking activity and is primarily an inverse agonist at 5-HT2A receptors. The remaining atypical antipsychotics share the similarity of D2 and 5-HT2A antagonism, but differ in activity at other central nervous system (CNS) receptor classes.
- There are a number of atypical antipsychotic formulations available as both branded and generic products. Food and Drug Administration (FDA)-approved indications for the atypical antipsychotics include irritability associated with autistic disorder, bipolar disorder, Tourette's disorder, major depressive disorder (MDD), schizophrenia, schizoaffective disorder, and hallucinations and delusions associated with Parkinson's disease (PD) psychosis.
- Autism
  - Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by impairment in socialization, communication, and behavior (*Weissman et al 2019*).
  - ASD are more common in males than females and estimates of prevalence vary based on populations studied.
  - Data from the Autism and Developmental Disabilities Monitoring Network in the U.S. reported a prevalence of 18.5 per 1000 children at age 8 in 2016 (*Centers for Disease Control [CDC] 2021*).
  - The pathogenesis of ASD is not completely understood but is believed to have a genetic component, which alters brain development (*Augustyn 2020*).
  - Overall treatment goals include maximization of functioning, improvement in quality of life, and helping the patient achieve and maintain independence.
  - Specific treatment goals include improving social, communication, and adaptation skills, improving academic functioning, and decreasing nonfunctional behaviors.
  - Treatments include educational and behavioral therapies and pharmacologic interventions to treat targeted symptoms including aggression, impulsivity, hyperactivity, anxiety, sleep disturbances, and depression (*Weissman et al 2019*).
- Bipolar disorder
  - Bipolar disorder is characterized by discrete mood instability. The lifetime prevalence of bipolar disorder is reported to be between 1% and 3%, although the true prevalence is uncertain (*Stovall 2020*).
  - Genetics, in addition to environmental factors, appear to play an important role in the pathogenesis of bipolar disorder.
  - Drugs commonly used to treat acute mania or hypomanias include lithium, anticonvulsants, and antipsychotics. Benzodiazepines may be helpful when adjunctive treatment is needed for insomnia, agitation, or anxiety (*Stovall 2021*).
- Major depressive disorder (MDD)
  - MDD manifests with symptoms of depressed mood, loss of interest or pleasure in almost all activities, altered sleep, change in appetite or weight, poor energy and/or concentration, thoughts of worthlessness, and potentially thoughts of death or suicide (*Teter et al 2021*).

- For the diagnosis of MDD, patients must have ≥ 5 symptoms that have been present during the same 2-week period or represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure. The goal of treatment is full remission (*Diagnostic and Statistical Manual of Mental Disorders [DSM] V 2013*).
- Based on data from 2013 to 2016, approximately 8.1% of individuals aged ≥ 20 years in the United States (U.S.) meet the criteria for depression. Women are more likely to experience symptoms of depression in their lifetime as compared to men (10.4% vs 5.5%) (*CDC 2021*).

- Schizophrenia
  - Schizophrenia is a disorder involving chronic or recurrent psychosis and is associated with significant functional impairment. Schizophrenia is believed to be caused by an increase in the cerebral activity of dopamine in the mesolimbic and/or mesocortical regions of the brain (*Keepers et al 2021).*
  - The disease includes positive symptoms such as hallucinations, delusions, and disorganized speech, as well as negative symptoms including flat affect, cognitive impairment, and impairment in executive functioning (*DSM V 2013*, *Keepers et al 2021*).
  - For the diagnosis of schizophrenia, patients must have ≥ 2 symptoms that have been present for a significant portion of time during a 1-month period and continuous signs of the disturbance persist for at least 6 months. Symptoms must include 1 of the following: delusions, hallucinations, and disorganized speech, but may also include grossly disorganized or catatonic behavior, and negative symptoms (*DSM V 2013*).
  - The prevalence of schizophrenia is approximately 0.25% to 0.64%, and the lifetime incidence is 10.2 to 22 per 100,000 person-years (*McGrath et al 2008*, *National Institute of Mental Health, van Os et al 2009*).
  - The pathogenesis of schizophrenia is unknown, and may be related to disruption(s) in one or more neurotransmitter systems (*Fischer and Buchanan 2020[b]*).
  - Symptoms of schizophrenia fall into 3 categories: positive symptoms (eg, hallucinations, delusions, disorganized thoughts and behavior), negative symptoms (eg, flat affect, decreased expressiveness, apathy), and cognitive symptoms (eg, impaired attention, memory, and executive functioning) (*Fischer and Buchanan 2020[a]*).
- Tourette's disorder
  - Tourette's disorder ranges greatly in terms of symptom severity and is often associated with comorbidities (*Murphy et al 2013*).
  - Tourette's disorder is characterized by persistent and repetitive motor and/or vocal tics, and onset is typically observed in childhood. For diagnosis, tics need to be present for at least 1 year. The pathophysiology of chronic tic disorders is not known but believed to be due to motor issues at both cortical and subcortical levels that are not properly modulated at the cortico-striatal-thalamo-cortical circuits.
  - Other comorbidities often observed with Tourette's disorder include attention-deficit hyperactivity disorder (ADHD) and obsessive compulsive disorder (OCD).
  - The prevalence of chronic tic disorders has been estimated as 0.5% to 3%, with approximately 7% of school-age children having had tics in the previous year.
- Parkinson's disease psychosis
  - Parkinson's disease is characterized by motor symptoms, which include tremor, bradykinesia, rigidity, and postural instability *(Bozymski et al 2017).*
  - Nonmotor symptoms can also occur in PD, which include autonomic dysfunction, sensory disturbances, and neuropsychiatric manifestations such as hallucinations, delusions, cognitive impairment, sleep disturbances, depression, and anxiety.
  - Approximately 60% of patients with PD develop psychosis.
  - For the diagnosis of PD psychosis, patients must meet the following criteria: primary diagnosis of PD; present with at least delusions, hallucinations, illusions, or false sense of presence; symptoms recurrent or continuous for at least 1 month; and exclusion of dementia-related psychosis or psychotic disorders.
- The agents included in this review are listed in Table 1 by brand name. Those drugs excluded from this review include Equetro (carbamazepine ER) capsule. Since there are multiple branded agents that contain the same generic component, the remaining tables in the review are organized by generic name. This review is restricted to the atypical antipsychotic agents and their respective FDA-approved indications.
  - Aripiprazole lauroxil is the prodrug of aripiprazole, and paliperidone is the active metabolite of risperidone.
- Medispan class: Antipsychotics/Antimanic agents; Antipsychotics – Misc., Quinolinone derivatives, Dibenzo-oxepino Pyrroles, Dibenzodiazepines.

Table 1. Medications included within class review

Drug	Generic
Single Entity Agents	
Abilify (aripiprazole tablets)	✔
aripiprazole orally disintegrating tablets (ODT), oral solution	✔ *
Abilify MyCite (aripiprazole tablet with sensor)	-†
Caplyta (lumateperone capsules)	-
Clozaril (clozapine tablets)	✔
Fanapt (iloperidone tablets)	-
clozapine ODT	✔ *
Geodon (ziprasidone hydrochloride [HCl] capsules)	✔
Geodon (ziprasidone mesylate injection)	✔
Invega (paliperidone extended-release [ER] tablets)	✔
Latuda (lurasidone tablets)	-
Nuplazid (pimavanserin tablets, capsules)	-
Rexulti (brexpiprazole tablets)	-
Risperdal (risperidone tablets, oral solution)	✔
risperidone ODT	✔ *
Saphris (asenapine sublingual tablet)	✔
Secuado (asenapine transdermal system)	-
Seroquel (quetiapine tablets)	✔
Seroquel XR (quetiapine ER tablets)	✔
Versacloz (clozapine oral suspension)	-
Vraylar (cariprazine capsules)	-
Zyprexa (olanzapine tablets, injection)	✔
Zyprexa Zydis (olanzapine ODT)	✔
Long-Acting Injectable Products	
Abilify Maintena (aripiprazole ER)	-
Aristada (aripiprazole lauroxil ER)	-
Aristada Initio (aripiprazole lauroxil ER)	-
Invega Sustenna (paliperidone palmitate)	-
Invega Trinza (paliperidone palmitate)	-
Perseris (risperidone ER)	-
Risperdal Consta (risperidone microspheres)	-
Zyprexa Relprevv (olanzapine pamoate)	-
Combination Products	
Symbyax (olanzapine/fluoxetine capsules)	✔

* Brand product discontinued; generic products are available.
† Abilify MyCite is the only drug-device combination product, comprised of a tablet with an embedded sensor, a wearable sensor patch, a smartphone application, and a web-based portal.

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

INDICATIONS

- The following summarizes all FDA-approved indications:

- Autism: Aripiprazole and risperidone are the only agents indicated for the treatment of irritability associated with autistic disorder in pediatric patients (aged 6 to 17 years and 5 to 17 years, respectively).
- Bipolar disorder: All oral agents in this class review are indicated for use in bipolar disorder, except clozapine, iloperidone, lumateperone, paliperidone, brexpiprazole, and pimavanserin. Aripiprazole ER (Abilify Maintena only) and Risperdal Consta are the only long-acting injectables indicated for the treatment of bipolar disorder.
  - Oral aripiprazole, olanzapine/fluoxetine, risperidone, quetiapine, asenapine, and lurasidone are approved for use in pediatric patients ≥ 10 years of age with bipolar disorder. Oral olanzapine is approved for use in patients ≥ 13 years of age with bipolar disorder.
- Depression: Aripiprazole, brexpiprazole, and quetiapine ER are indicated as adjunctive treatment for MDD in patients already taking an antidepressant. Olanzapine/fluoxetine is indicated for treatment-resistant depression.
- Schizophrenia: All agents in this class review are indicated for use in schizophrenia with the exception of pimavanserin, and the combination agent, Symbyax (olanzapine/fluoxetine). Clozapine and paliperidone products, excluding Invega Trinza, are indicated for the treatment of schizoaffective disorder. Clozapine is the only agent in this class that is FDA-approved for treatment-resistant schizophrenia.
  - Oral aripiprazole (with the exception of tablets with sensor), lurasidone, olanzapine, quetiapine, and risperidone are approved for use in patients ≥ 13 years of age and paliperidone oral products are approved for patients ≥ 12 years of age with schizophrenia.
- Tourette's Disorder: Aripiprazole is the only agent indicated for the treatment of Tourette's disorder in pediatric patients, aged 6 to 18 years.
- Parkinson's disease psychosis: Pimavanserin is the first atypical antipsychotic FDA-approved for use in patients with PD psychosis.
- Prescribing considerations: The labeling for iloperidone and ziprasidone state that when deciding among the alternative treatments, the prescriber should consider that these drugs are associated with prolongation of the QTc interval. In addition, patients must be titrated to an effective dose of iloperidone; thus control of symptoms may be delayed during the first 1 to 2 weeks of treatment compared to other antipsychotics that do not require similar titration.

- Table 2 highlights FDA-approved indications at a high level.

Table 2. Food and Drug Administration approved indications

Agent	Autism	Bipolar disorder: manic/mixed	Bipolar disorder: depressive	Depression – treatment-resistant	MDD: adjunct	Schizoaffective disorder	Schizophrenia	Schizophrenia: treatment-resistant	Tourette's Disorder	Parkinson's disease psychosis
Single Entity Products										
aripiprazole‖	✔ *	✔ *¶	-	-	✔ ¶	-	✔ *¶	-	✔ *	-
asenapine	-	✔ *¥	-	-	-	-	✔	-	-	-
brexpiprazole	-	-	-	-	✔	-	✔	-	-	-
cariprazine	-	✔	-	-	-	-	✔	-	-	-
clozapine	-	-	-	-	-	✔	-	✔	-	-
iloperidone	-	-	-	-	-	-	✔	-	-	-
lumateperone	-	-	-	-	-	-	✔	-	-	-
lurasidone	-	-	✔ *	-	-	-	✔ *	-	-	-
olanzapine‖	-	✔ *	-	-	-	-	✔ *	-	-	-
paliperidone	-	-	-	-	-	✔	✔ *	-	-	-
pimavanserin	-	-	-	-	-	-	-	-	-	✔
quetiapine	-	✔ *	✔	-	✔ †	-	✔ *	-	-	-
risperidone	✔ *	✔ *	-	-	-	-	✔ *	-	-	-
ziprasidone HCl	-	✔	-	-	-	-	✔	-	-	-
ziprasidone mesylate	-	-	-	-	-	-	✔ §	-	-	-
Long-Acting Injectable Products										
aripiprazole ER (Abilify Maintena)	-	✔	-	-	-	-	✔	-	-	-
aripiprazole lauroxil ER (Aristada, Aristada Initio)	-	-	-	-	-	-	✔	-	-	-
paliperidone palmitate (Invega Sustenna)	-	-	-	-	-	✔	✔	-	-	-
paliperidone palmitate (Invega Trinza)	-	-	-	-	-	-	✔	-	-	-
risperidone microspheres	-	✔	-	-	-	-	✔	-	-	-

Agent	Autism	Bipolar disorder: manic/mixed	Bipolar disorder: depressive	Depression – treatment-resistant	MDD: adjunct	Schizoaffective disorder	Schizophrenia	Schizophrenia: treatment-resistant	Tourette's Disorder	Parkinson's disease psychosis
(Risperdal Consta)										
risperidone ER (Perseris)	-	-	-	-	-	-	✔	-	-	-
olanzapine pamoate ER (Zyprexa Relprevv)	-	-	-	-	-	-	✔ ‡	-	-	-
Combination Products										
olanzapine/ fluoxetine	-	-	✔ *	✔	-	-	-	-	-	-

Abbreviations: ER = extended release, IM = intramuscular, ODT = orally disintegrating tablet
*FDA-approved indications for pediatric patients.
† Indicated for the ER formulation.
‡ Patients must be observed by a health care professional for 3 hours post-dose administration with Zyprexa Relprevv.
§ IM injection indicated for acute agitation associated with schizophrenia.
‖ IM injection indicated for acute agitation associated with schizophrenia and bipolar mania.
¶ Indicated for the drug-device combination with tablet and sensor. The ability to improve patient compliance or modify aripiprazole dosage has not been established. The ability to track drug ingestion in "real-time" or during an emergency is not recommended because detection may be delayed or not occur.
¥ Saphris sublingual tablets indicated for bipolar disorder, but not Secuado patches.

(*Prescribing information: Abilify 2020, Abilify Maintena 2020, Abilify MyCite 2020, Aristada 2021, Aristada Initio 2021, Caplyta 2019, Clozaril 2021, Fanapt 2017, Geodon 2020, Invega 2021, Invega Sustenna 2021, Invega Trinza 2021, Latuda 2019, Nuplazid 2020, Perseris 2019, Rexulti 2020, Risperdal 2021, Risperdal Consta 2021, Saphris 2017, Secuado 2019, Seroquel 2020, Seroquel XR 2020, Symbyax 2021, Versacloz 2020, Vraylar 2019, Zyprexa 2020, Zyprexa Relprevv 2020, Zyprexa Zydis 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

- The goal of this review is to evaluate key published literature regarding atypical antipsychotics for FDA-approved indications in children, adolescents, and adults. Numerous studies evaluating the efficacy of antipsychotic medications have been conducted. In clinical practice, the role of the atypical antipsychotics has been clearly established for the treatment of bipolar disorder and schizophrenia. In general, clinical consensus guidelines do not differentiate one agent from another, supporting the concept that all patients will require an individualized approach to treatment selection, taking into account the agent's safety profile and patient's individual risk factors.
- Key clinical studies evaluating the roles of atypical antipsychotic agents in the treatment of FDA-approved indications are included in the review. However, in recognition of the vast number of published studies of older atypical antipsychotics in adults, only a selection of randomized controlled studies (RCTs), systematic reviews (SRs), and meta-analyses (MAs) are presented.

CHILDREN/ADOLESCENTS

- The Agency for Healthcare Research and Quality (AHRQ) conducted a SR evaluating the safety and efficacy of antipsychotics in children and adolescents. The review included 135 studies of atypical antipsychotics (aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone), conducted in patients 24 years of age or younger, and used for various psychiatric conditions including schizophrenia and related disorders, autism spectrum disorders, bipolar disorder, and tic disorder, among others. Overall, indications associated with moderate strength evidence for the use of atypical antipsychotics included schizophrenia and related psychoses, bipolar disorder, autism spectrum disorders, and ADHD. The risk of weight gain was highest for olanzapine, clozapine, and lurasidone. It was found that atypical antipsychotics probably increase short-term risk for high triglyceride levels, extrapyramidal symptoms, sedation, and somnolence vs placebo (*Pillay et al 2017*).

Autism Spectrum Disorder

- For the treatment of irritability associated with autistic disorder, risperidone has been approved in pediatric patients aged 5 to 17 years and aripiprazole has been approved in patients aged 6 to 17 years. Very few RCTs have been conducted evaluating safety and efficacy, and only 1 low-quality study has been conducted evaluating comparative effectiveness. The primary outcome measure in trials was the change from baseline to endpoint in the Aberrant Behavior Checklist-Irritability subscale of the ABC (ABC-I), which measured symptoms of irritability in autistic disorder. One risperidone trial measured the Clinical Global Impression-Change (CGI-C) scores as a co-primary outcome measure.
- The safety and efficacy of aripiprazole was evaluated in 2 placebo-controlled (PC), 8-week trials. Over 75% of these subjects were under 13 years of age. In one of these trials, children and adolescents with autistic disorder (N = 98) received daily doses of placebo or aripiprazole 2 to 15 mg/day. The mean daily dose of aripiprazole at the end of the 8-week period was 8.6 mg/day. Aripiprazole significantly improved ABC-I subscale scores, including emotional and behavioral symptoms of irritability, aggression towards others, deliberate self-injuriousness, temper tantrums, and quickly changing moods (*Owen et al 2009*). In the second of these trials in children and adolescents with autistic disorder (N = 218), 3 fixed doses of aripiprazole (5, 10, or 15 mg/day) were compared to placebo. ABC-I subscale scores were significantly decreased by 12.4 points with 5 mg/day, 13.2 with 10 mg/day, and 14.4 with 15 mg/day compared with 8.4 with placebo. Clinical Global Impressions (CGI)-Improvement scores were significantly improved: 2.6 points with 5 mg/day, 2.5 with 10 mg/day, and 2.5 with 15 mg/day compared with 3.3 with placebo. At the higher doses, ABC stereotypy, hyperactivity, CGI-S (Severity of Illness) scores, and other secondary measures were also improved (*Marcus et al 2009*).
- In one MA of 3 trials evaluating pediatric patients (N = 316) treated with aripiprazole, results demonstrated a greater increase in weight vs placebo (weight gain,1.13 kg; 95% confidence interval [CI], 0.71 to 1.54; $p < 0.00001$), and a higher relative risk (RR) for sedation (RR, 4.28; 95% CI, 1.58 to 11.6; $p = 0.004$) and tremor (RR, 10.26; 95% CI, 1.37 to 76.63; $p = 0.02$) (*Hirsch et al 2016*).
- A 2018 MA evaluated the efficacy of aripiprazole in patients with autism spectrum disorder (N = 408) and found aripiprazole significantly improved irritability, hyperactivity, and inappropriate speech but not social withdrawal compared with placebo. The RR for response rate was also improved with aripiprazole (RR, 2.08; 95% CI, 1.24 to 3.46) (*Maneeton et al 2018*).

- The safety and efficacy of risperidone was evaluated in two 8-week and one 6-week, PC pivotal trials (*McCracken et al 2002, Shea et al 2004*). Approximately 90% of these subjects were under 12 years of age. In the two 8-week trials, the efficacy and safety of risperidone were measured in patients aged 5 to 16 years (N = 101) in weight-based, twice-daily doses of 0.5 to 3.5 mg/day (the RUPP trial) and in patients aged 5 to 12 years (N = 79) who received 0.02 to 0.06 mg/kg/day given once or twice daily (*McCracken et al 2002, Shea et al 2004*). The 6-week trial measured efficacy and safety in patients using lower than FDA-approved recommended dosing, and outcomes did not demonstrate efficacy (*Risperdal prescribing information 2021*). In the RUPP trial, risperidone-treated patients exhibited a 56.9% reduction in the mean ABC-I score from baseline, compared to a 14.1% reduction observed in the placebo group ($p < 0.001$) (*McCracken et al 2002*). Risperidone was generally well tolerated, and most adverse events were mild and transient. Due to the uncertainty of a clear benefit with regard to the core symptoms of autism, the authors recommend that risperidone be reserved for the treatment of moderate-to-severe behavioral problems accompanying autism. In the second 8-week trial, risperidone patients demonstrated a 64% improvement in ABC-I subscale vs 31% improvement with placebo, which was a significant positive finding for hyperactivity (*Shea et al 2004*). Somnolence was the most frequently reported adverse event (72.5% vs 7.7%), and risperidone-treated subjects experienced statistically greater increases in weight (2.7 kg vs 1 kg), pulse rate, and systolic blood pressure.
- In an extension of the RUPP trial, 63 responders received open-label (OL) risperidone for another 16 weeks. Risperidone dose adjustments were allowed up to a maximum total daily dose of 3.5 mg/day. At the end of the 4-month extension, an intention-to-treat analysis revealed a minor, but clinically insignificant increase in ABC-I score. There was also a significant time effect on the ABC-I scale at the end of the 4-month extension phase ($p = 0.02$) (*McDougle et al 2005*).
- Additional trials have been conducted measuring effects of risperidone; however, most trials included less than 50 patients. The outcomes of these trials are more sensitive to variability within the trials due to the small effect size (*Aman et al 2008, Capone et al 2008, Gagliano et al 2004, Gencer et al 2008, Luby et al 2006, Miral et al 2008, Nagaraj et al 2006*).
- One head-to-head, prospective, 8-week trial was conducted comparing the effects of aripiprazole ≤ 10 mg/day (mean dose, 5.5 mg/day) to risperidone ≤ 3 mg/day (mean dose, 1.12 mg/day) in patients (N = 59) aged 4 to 18 years of age. Approximately 65% of patients were diagnosed with autism, and additional diagnoses included Asperger syndrome, pervasive developmental disorder, and disruptive behavior disorder. Study authors stated double-blind (DB) techniques were not enforced for all patients. At the end of the trial, the mean change from baseline in ABC-I subscale score was not statistically different ($p = 0.06$), but numerically favored risperidone. No differences were detected between groups for each adverse event or in the rate of discontinuations due to adverse events. Study authors concluded the safety and efficacy of both agents were comparable (*Ghanizadeh et al 2014*).
- A network MA evaluated 8 clinical trials (N = 878) with risperidone, aripiprazole, lurasidone, and placebo in pediatric autism spectrum disorder. Both risperidone and aripiprazole significantly reduced irritability compared with placebo with similar safety profiles. Lurasidone was not significantly different from placebo (*Fallah et al 2019*).

Bipolar Disorder

Manic/Mixed Episodes

- Aripiprazole, olanzapine, olanzapine/fluoxetine, risperidone, quetiapine and asenapine have FDA-approved indications for the treatment of pediatric patients diagnosed with bipolar disorder. All agents are approved for ages ≥ 10 years, except olanzapine which is approved in patients aged ≥ 13 years. In pediatric patients with bipolar disorder, evidence is extremely limited.
- In an AHRQ SR of 135 trials evaluating typical and atypical antipsychotics, a total of 19 trials measured efficacy and safety in adolescents with bipolar disorder. Compared with placebo, atypical antipsychotics decrease mania and depression symptoms slightly, and improve symptom severity and global functioning to a small extent. In addition, these agents probably increase response and remission rates vs placebo for manic/mixed phases (*Pillay et al 2017*).
- In a 21-day, DB, PC trial, 403 patients aged 10 to 17 years with bipolar I disorder were randomized to placebo or asenapine 2.5 mg, 5 mg, or 10 mg twice daily. The primary endpoint, change from baseline in Young Mania Rating Scale (YMRS) score, demonstrated a statistically significant and dose-dependent mean difference in YMRS scores at 21 days for all asenapine groups vs placebo (2.5 mg, -3.2; $p = 0.0008$ vs 5 mg, -5.3; $p < 0.001$ vs 10 mg, -6.2; $p < 0.001$). Weight gain was higher across the asenapine groups, with 8% to 12% of patients experiencing ≥ 7% weight gain vs 1.1% of patients in the placebo group ($p < 0.05$). Fasting glucose, insulin and cholesterol changes were also numerically higher in the asenapine groups vs placebo (p = not reported). Overall, asenapine was well tolerated and

showed efficacy in the treatment of this pediatric population, although the duration of the study period was brief (*Findling et al 2015*).

Depressive Episodes

- Clinical trials measuring the safety and efficacy of atypical antipsychotics in depressive episodes in pediatric patients diagnosed with bipolar disorder are limited. Two trials examined efficacy of quetiapine in this population. In a small trial, a total of 32 patients aged 12 to 18 years were randomized to quetiapine 300 to 600 mg/day or placebo and followed over a period of 8 weeks. The primary endpoint was change in the Children's Depression Rating Scale, Revised Version (CDRS-R) score, in which both quetiapine and placebo groups exhibited statistically significant reductions in the CDRS-R scores from baseline ($p < 0.001$), with no difference between groups (19 vs 20; $p = 0.89$). All other efficacy measures were not statistically different from placebo (*DelBello et al 2009*). A similar 8-week trial enrolled 193 patients aged 10 to 17 years with acute bipolar depression. Patients were randomized to placebo or quetiapine XR 150 to 300 mg/day. The primary endpoint was change in CDRS-R score from baseline, with mean CDRS-R scores decreasing from baseline in both placebo (-29.6) and treatment (-27.3) groups. The difference between groups was not statistically significant (95% CI, -6.22 to 1.65; $p = 0.25$). Triglyceride levels were elevated in 9.3% of the quetiapine XR group vs 1.4% of the placebo group. Mean weight gain was 1.3 kg in the quetiapine XR group vs 0.6 kg in the placebo group (p = not reported) (*Findling et al 2014*).
- In a DB, PC trial, 291 patients aged 10 to 17 years with bipolar I disorder, and depressive episodes were randomized 2:1 to olanzapine/fluoxetine or placebo for 8 weeks. Doses of olanzapine/fluoxetine were titrated to 12/50 mg daily over 2 weeks. The olanzapine/fluoxetine group had a 5-point greater mean decrease in CDRS-R score from baseline vs placebo (-28.4 vs -23.4; $p = 0.003$). A total of 78.2% olanzapine/fluoxetine patients achieved response (defined as ≥ 50% reduction of CDRS-R score from baseline and a YMRS item 1 score ≤ 2) vs 59.2% of placebo group patients ($p = 0.003$). Weight gain was more common in the olanzapine/fluoxetine group vs placebo (4.4 vs 0.5 kg; $p < 0.001$), as well as increase in fasting total cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides (all $p < 0.001$). Mean prolactin increase was higher in the olanzapine/fluoxetine group vs placebo ($p < 0.001$) and increase in heart rate was also statistically significantly higher in the treatment group ($p = 0.013$). This trial demonstrated efficacy in pediatric patients, but also demonstrated serious adverse effects (*Detke et al 2015*).
- In a DB, PC trial, 347 patients aged 10 to 17 years were assigned to flexible doses of lurasidone 20 to 80 mg/day or placebo. The primary endpoint was change from baseline to week 6 in the CDRS-R total score. At week 6 of therapy, treatment with lurasidone was associated with a significant improvement compared with placebo in CDRS-R total score (-21.0 versus -15.3; $p<0.0001$). Lurasidone also was associated with statistically significant improvements in the Clinical Global Impression-Bipolar Severity depression score (key secondary measure) and in measures of anxiety, quality of life, and global functioning (*DelBello et al* 2017).

Schizophrenia and/or Schizoaffective Disorder

- In pediatric patients diagnosed with schizophrenia, FDA-approved treatments include aripiprazole, lurasidone, olanzapine, quetiapine and risperidone for use in patients ≥ 13 years of age and paliperidone oral products in patients aged ≥ 12 years. Many trials include a small sample size of patients, or are not well-designed. However, efficacy has been demonstrated and results are similar to adult trials.
- An SR and network MA of 12 RCTs (N = 2158) evaluated 8 antipsychotics (aripiprazole, asenapine, paliperidone, risperidone, quetiapine, olanzapine, molindone, and ziprasidone) for treatment of children and adolescents with schizophrenia-spectrum disorders. Network MA found that change in Positive and Negative Syndrome Scale (PANSS) total, positive, and negative symptoms did not differ significantly between agents except for ziprasidone, which was inferior on PANSS total symptoms vs molindone, olanzapine, paliperidone, quetiapine, and risperidone, and inferior on PANSS negative symptoms vs molindone, olanzapine, and risperidone. All antipsychotics were superior to placebo on PANSS total symptom change except asenapine and ziprasidone. All antipsychotics, except ziprasidone, were superior to placebo on PANSS positive symptom change; additionally, all antipsychotics, except paliperidone, quetiapine, and ziprasidone, were superior to placebo on PANSS negative symptom change. Weight gain was primarily associated with olanzapine, while prolactin was increased with risperidone, paliperidone, and olanzapine (*Pagsberg et al 2017*).
- In an AHRQ SR of 135 trials evaluating typical and atypical antipsychotics, a total of 39 studies evaluated efficacy and safety in adolescents with schizophrenia. Compared with placebo, atypical antipsychotics as a class probably increase response rates; decrease slightly (not clinically significant for many patients) negative and positive symptoms; and

improve slightly global impressions of improvement, severity, and functioning. Six studies comparing risperidone vs olanzapine found little or no difference in their effects for negative and positive symptoms, response rates, and global impressions of severity (*Pillay et al 2017*).

- A Cochrane review compared atypical antipsychotic medications to placebo, typical antipsychotics, or another atypical antipsychotic in adolescents with psychosis. Compared to typical antipsychotics, there were no significant differences in Brief Psychiatric Rating Scale (BPRS) scores in an analysis of 5 trials with 236 patients. There was no evidence to suggest the superiority of atypical antipsychotics over typical antipsychotics; however, fewer adolescents dropped out due to adverse effects when administered an atypical antipsychotic (RR, 0.65; 95% CI, 0.36 to 1.15). Minimal evidence was available comparing one atypical antipsychotic to another. In terms of the number of patients who did not respond (defined as ≤ 30% reduction in BPRS score), results significantly favored clozapine, but increases in salivation, sweating, and glucose levels were observed vs olanzapine in 1 trial with 39 patients. Treatment with olanzapine, risperidone and clozapine was associated with weight gain. Aripiprazole was not associated with increased prolactin or dyslipidemia. Low-dose risperidone significantly decreased improvement in PANSS total score but also reduced the rate of extrapyramidal symptoms (EPS) vs standard-dose risperidone in 1 trial with 255 patients. Overall, efficacy between atypical and typical antipsychotics may be similar; however, safety benefits may favor treatment with atypical antipsychotics (*Kumar et al 2013*).
- A 6-week, randomized, PC trial evaluating the efficacy of lurasidone in acutely symptomatic adolescents with schizophrenia found that the least squares (LS) mean change in PANSS total score from baseline to week 6 was greater for the lurasidone 40 mg/day group (-18.6; $p < 0.001$; effect size = 0.51) and the lurasidone 80 mg/day group (-18.3; $p < 0.001$; effect size = 0.48) vs the placebo group (-10.5). The LS mean change from baseline to week 6 in CGI-S score was significantly greater for the lurasidone 40 mg/day group (-1.0; $p < 0.001$; effect size = 0.49) and the lurasidone 80 mg/day group (-0.9; $p = 0.0015$; effect size = 0.45) compared with the placebo group (-0.5). The most common adverse events in the lurasidone groups were nausea, anxiety, akathisia, somnolence, and vomiting (*Goldman et al 2017*).

Tourette's Disorder

- Aripiprazole is the only agent indicated for the treatment of Tourette's disorder. Efficacy and safety is based on low quality evidence in one fixed-dose and one flexible-dose trial. There is minimal evidence of safety and efficacy in this population.
- In one published, DB, PC, 10-week trial, aripiprazole significantly reduced total tic score (Yale Global Tic Severity Scale [YGTSS-TTS]; -15 vs -9.6) and phonic tic score (YGTSS-PTS; -7.4 vs -4.2), but not motor tic score, compared with placebo in patients aged 6 to 18 years with Tourette's disorder. The response rate (score of 1 or 2 on the Tourette's syndrome CGI-Improvement scale) was 66% vs 45%, respectively (*Yoo et al 2013*).
- In another similarly designed, unpublished, 8-week trial in patients aged 7 to 17 years who received weight-based aripiprazole, significant improvements compared with placebo were seen on YGTSS-TTS with a change of -13.4 and -16.9 points with low- and high-dose aripiprazole compared to -7.1 with placebo (*Abilify prescribing information 2020*).
- Aripiprazole was associated with increased body weight compared to placebo (range, 0.4 to 1.5 kg). Additional adverse reactions (incidence ≥ 5% and at least twice that for placebo) were sedation, somnolence, nausea, headache, nasopharyngitis, fatigue, and increased appetite (*Abilify prescribing information 2020*). In one safety trial, aripiprazole had a safer cardiovascular profile vs pimozide, and was associated with a lower frequency of QT prolongation (*Gulisano et al 2011*).

ADULTS

- The AHRQ conducted an SR of literature on the safety and efficacy of antipsychotics in adults comparing typical and atypical antipsychotics. The review included studies of atypical antipsychotics (aripiprazole, asenapine, clozapine, olanzapine, quetiapine, risperidone, and ziprasidone), conducted in patients 18 to 64 years of age, and used for the following FDA-approved indications: bipolar disorder, schizophrenia, and schizophrenia-related psychoses. The most frequent comparisons involved haloperidol, with 43 studies comparing haloperidol with risperidone and 37 studies comparing haloperidol with olanzapine. Nevertheless, the number of studies available for each comparison and outcome was often limited. Overall, indications associated with moderate to low strength evidence for the use of atypical antipsychotics included schizophrenia and schizophrenia-related psychoses. Bipolar disorder was associated with low strength of evidence. Few differences of clinical importance for outcomes of effectiveness were found. Patient-important outcomes were rarely assessed. Data were sparse for the 4 key adverse events deemed to be most

clinically important. In terms of efficacy, few differences were found between typical and atypical antipsychotic agents, specifically when compared to haloperidol and clinical significance (defined as ≥ 20% difference between interventions) was rarely found. The evidence regarding safety, particularly those adverse events of most interest (ie, diabetes, tardive dyskinesia, metabolic syndrome, and mortality) were insufficient to draw firm conclusions about the risks among treatment groups. No differences were found in mortality for chlorpromazine vs clozapine and haloperidol vs aripiprazole, or in metabolic syndrome for haloperidol vs olanzapine. The most frequently reported adverse events with significant differences were EPS; in most cases, the atypical antipsychotic had fewer EPS than haloperidol (*Abou-Setta et al 2012*).

Bipolar Disorder

Manic/Mixed Episodes

- All oral atypical antipsychotic agents in this class review are indicated for use in bipolar disorder, except clozapine, iloperidone, lumateperone, paliperidone, brexpiprazole, and pimavanserin. The following summarizes direct comparative evidence and recent MAs and SRs.
- A 2018 AHRQ SR of 156 trials concluded that symptoms of acute mania were modestly improved with asenapine, cariprazine, quetiapine, and olanzapine compared to placebo. Risperidone, ziprasidone, and paliperidone may also be effective for acute mania symptoms. Lithium was effective in the treatment of acute mania and prolonged the time to relapse compared to placebo, and this was the only agent that achieved a minimal clinically important difference in symptoms. All of these results were based on low-strength evidence because moderate and strong evidence was lacking (*Butler et al 2018*).
- In a 2012 AHRQ SR of 125 trials evaluating typical and atypical antipsychotics, a total of 12 measured efficacy and safety in adults with bipolar disorder. Compared to haloperidol, there was no difference in YMRS score for manic episodes for aripiprazole, olanzapine, and risperidone, and no difference in Montgomery-Asberg Depression Rating Scale (MADRS) score for aripiprazole in a total of 9 trials. In one trial of 350 patients, haloperidol was favored in terms of YMRS score over ziprasidone. Haloperidol produced lower relapse rates than aripiprazole in one trial with 347 patients and provided better response rates than ziprasidone in one trial of 350 patients. The most frequently reported adverse effects with significant differences were in the category of EPS and most often involved haloperidol. Haloperidol appears to be an equally effective treatment compared with the atypical antipsychotics; however, it is associated with more incidences of EPS compared to other agents (*Abou-Setta et al 2012*).
- A SR and MA of 15 RCTs and 1 observational study was conducted to evaluate the efficacy of maintenance treatment in bipolar disorder using atypical antipsychotics, either as monotherapy or as adjunctive therapy. As adjunctive therapy to lithium or valproate, MAs showed that treatment with aripiprazole (RR, 0.65; 95% CI, 0.50 to 0.85), quetiapine (RR, 0.38; 95% CI, 0.32 to 0.46), or ziprasidone (RR, 0.62; 95% CI, 0.40 to 0.96) reduced the overall risk of relapses in patients that had responded during the stabilization phase. Quetiapine was the only drug that reduced both manic and depressive episodes. Due to high risk of bias and low levels of evidence, no conclusions could be drawn for olanzapine or risperidone. For monotherapy, quetiapine was shown to be better than lithium/valproate for both manic and depressive relapses; no reliable conclusions could be made for olanzapine due to the low quality of evidence. Monotherapy with olanzapine, quetiapine, and risperidone were shown to be superior vs placebo in reducing the overall risk of relapse; no reliable conclusions could be made for aripiprazole due to the low quality of evidence (*Lindström et al 2017*).
- One SR of 9 RCTs (N = 1289) compared the effectiveness of atypical antipsychotics to placebo, either as monotherapy or as adjunctive treatment with a mood stabilizer. Atypical antipsychotics, either alone or in combination with mood stabilizers, had superior efficacy in treating manic symptoms of mixed episodes compared to placebo in short-term trials lasting 3 to 6 weeks ($p < 0.00001$). Atypical antipsychotics also had superior efficacy in treating depressive symptoms of mixed episodes ($p < 0.001$) (*Muralidharan et al 2013*).
- The efficacy and safety of asenapine in the treatment of manic or mixed bipolar I disorder were evaluated in 6 PC, and active-controlled (olanzapine) studies in adult patients, with or without psychotic features (*McIntyre et al 2009[a], McIntyre et al 2010[a], McIntyre et al 2009[b], McIntyre et al 2010[b], Szegedi et al 2011, Szegedi et al 2018*). In a pooled analysis of patients experiencing bipolar mania, asenapine and olanzapine were comparable in terms of reduction from baseline in YMRS scores at week 52 of therapy (*McIntyre et al 2010[b]*). A MA of various anti-manic therapy options found that asenapine was associated with a statistically significant improvement in YMRS scores from baseline compared to placebo (mean difference [MD], -0.3; 95% CI, -0.53 to -0.07), though it was less effective compared to olanzapine (0.22; 95% CI, 0.08 to 0.37) (*Cipriani et al 2011*). The most commonly reported adverse

events reported with asenapine included sedation, dizziness, somnolence and weight gain. Of note, it was calculated that for every 9 patients treated with olanzapine over asenapine, one would experience clinically significant weight gain with olanzapine (19% vs 31%) (*McIntyre et al 2009[b]*).

- The approval of cariprazine was based on the efficacy and safety from 3 flexible-dose, DB, PC, 3-week trials (*Calabrese et al 2015, Durgam et al 2015[a], Sachs et al 2015*). A total of 1047 adult patients with acute manic or mixed episodes were administered placebo or cariprazine 3 to 12 mg per day based on tolerability. Across trials, the mean daily dose was 8.8 mg per day and the mean final dose was 10.4 mg per day (*FDA/CBER summary review 2015*). All doses were superior to placebo in reducing YMRS and CGI-S scores and a significant reduction in YMRS was observed as early as 4 days in some studies and persisted until week 3. The proportion of YMRS remitters was significantly higher in the cariprazine group than placebo (difference range, 15 to 19%) (*Calabrese et al 2015, Durgam et al 2015[a], Sachs et al 2015*). Of note, doses higher than 6 mg had similar efficacy, but adverse events were less tolerable. Due to the long half-life and pharmacokinetics of the active metabolite, DDCAR, drug steady state was not achieved in trials (*FDA/CBER summary review 2015*). It is anticipated that late-onset of adverse reactions would be observed if assessed for a longer period. In bipolar studies, 4% of patients with normal hemoglobin A1c developed elevated levels (≥ 6.5%). According to a pooled analysis (n = 1940 cariprazine-treated patients) within the FDA summary review, the most frequently observed adverse events include akathisia (14.2%), EPS (20.8%), constipation (7.6%), and nausea/vomiting (6 to 8%). The proportion of patients with weight increase ≥ 7% from baseline ranged from 1 to 3% across cariprazine doses.
- The efficacy and safety of risperidone 1 to 6 mg/day compared to olanzapine 5 to 20 mg/day were evaluated in a 3-week, DB, RCT in patients hospitalized for bipolar I disorder, manic or mixed episode, without psychotic features. Olanzapine and risperidone mean doses were 14.7 mg/day and 3.9 mg/day, respectively. There was no difference between groups in many outcome measures in remission or response in YMRS, 21-item Hamilton Rating Scale for Depression (HAM-D-21), or MADRS scales. More patients given olanzapine completed the trial compared with patients given risperidone (78.7% vs 67%, respectively). In total, 62.1% of patients in the olanzapine group and 59.5% of patients in the risperidone group were categorized as responders (defined as ≥ 50% reduction in the YMRS score at endpoint). Olanzapine-treated patients experienced significantly greater elevations in liver function enzymes and weight gain (2.5 kg vs 1.6 kg). Risperidone-treated patients experienced significantly more prolactin elevations and sexual dysfunction (*Perlis et al 2006[a]*).

Depressive Episodes

- Placebo-controlled trials measuring effects for the treatment of bipolar depression have demonstrated efficacy with lurasidone, quetiapine (immediate- and extended-release [ER]), and olanzapine/fluoxetine as monotherapy and adjunctive treatment (*Calabrese et al 2005, Corya et al 2006, McElvoy et al 2010, Loebel et al 2014[a], Loebel et al 2014[b], Shelton et al 2005, Suppes et al 2010, Thase et al 2007, Young et al 2010*).
- Treatment with olanzapine/fluoxetine was superior to monotherapy with olanzapine and lamotrigine in achieving greater improvements in MADRS and CGI-BP (bipolar version) (*Tohen et al 2003, Brown et al 2009*). Patients treated with olanzapine/fluoxetine had significantly greater rates of treatment response and remission compared to those receiving olanzapine monotherapy (*Tohen et al 2003*). It is not clear if quetiapine outperforms lithium in terms of treatment of bipolar depression, as various studies have produced different results (*Chiesa et al 2012, Young et al 2010*).
- Meta-analyses have found that combination treatment with olanzapine/fluoxetine may be the optimal treatment for bipolar depression compared to other treatment options. However, the overall evidence quality was considered low, trials had limited durations, and a high placebo effect was observed. Olanzapine, quetiapine, lurasidone, valproate, selective-serotonin reuptake inhibitors (SSRIs), lithium, and tricyclic antidepressants (TCAs) also appeared to be effective, but with varied acceptability (*Fornaro et al 2016, Ostacher 2017*, *Silva et al 2013, Taylor et al 2014, Vieta et al 2010*). No notable efficacy differences were identified between atypical antipsychotics, suggesting that lurasidone, quetiapine, and olanzapine/fluoxetine may be reasonable choices.

<u>Major Depressive Disorder (MDD)</u>

Key MDD Meta-Analyses

- A number of MAs and SRs have been conducted evaluating the safety and efficacy of atypical antipsychotics to augment treatment for MDD. Aripiprazole, brexpiprazole, and quetiapine ER are indicated for the treatment of MDD as

adjunctive treatment; and olanzapine, in combination with fluoxetine, is indicated for the treatment of treatment-resistant depression. The most recent, well-designed MAs have been summarized for efficacy and safety evaluations.

- One MA, which followed Cochrane methodologies, evaluated 17 trials of short-term duration ranging from 4 to 12 weeks. The analysis compared adjunctive atypical antipsychotics in combination with an SSRI/serotonin-norepinephrine reuptake inhibitor (SNRI) to SSRI or SNRI monotherapy in patients with refractory or treatment-resistant MDD. Results demonstrated that the augmentation of antidepressants with atypical antipsychotics (olanzapine, quetiapine, aripiprazole, and risperidone [Note: risperidone is not FDA-approved for this indication]) was more effective than antidepressant monotherapy in improving response and remission rates. However, adjunctive atypical antipsychotic therapy was associated with a higher discontinuation rate due to adverse effects (9.1% vs 2.6%). The attributable risk for the discontinuation rate due to adverse effects was 0.07 (number needed to harm [NNH], 16; 95% CI, 12 to 20) (*Wen et al 2014*).
- Another MA evaluated 14 trials in patients with current MDD and an inadequate response to at least 1 course of antidepressant medication treatment. Compared to placebo, the atypical antipsychotics significantly improved remission rates: aripiprazole (odds ratio [OR], 2.01; 95% CI, 1.48 to 2.73), olanzapine/fluoxetine (OR, 1.42; 95% CI, 1.01 to 2), quetiapine (OR, 1.79; 95% CI, 1.33 to 2.42) and risperidone (OR, 2.37; 95% CI, 1.31 to 4.3). In terms of remission, all atypical antipsychotics were efficacious; however, olanzapine/fluoxetine had a higher number needed to treat (NNT) compared to other agents (NNT for olanzapine/fluoxetine, 19 vs NNT for aripiprazole, quetiapine, risperidone, 9). Treatment was associated with several adverse events, including akathisia (aripiprazole), sedation (quetiapine, olanzapine/fluoxetine and aripiprazole), abnormal metabolic laboratory results (quetiapine and olanzapine/fluoxetine), and weight gain (all 4 drugs, especially olanzapine/fluoxetine). However, little to no information was provided in detail regarding the adverse events (*Spielmans et al 2013*).

Adjunctive treatment for MDD

- Aripiprazole, brexpiprazole, and quetiapine ER are indicated for the treatment of MDD as adjunctive treatment. The following information describes the pivotal trials used for FDA-approval.
- The FDA-approval of aripiprazole for the adjunctive treatment of MDD was based on 2 PC, 6-week trials in adult patients (N = 381; N = 362) who had failed 1 to 3 courses of antidepressant therapy, including an inadequate response to 8 weeks of antidepressant treatment. Aripiprazole was superior to placebo in reducing the mean MADRS total scores and remission rates. The NNT to reduce remission rates (defined as MADRS total score ≤ 10 and ≥ 50% reduction in MADRS) was 10 (*Berman et al 2007, Marcus et al 2008*). Increased incidences of akathisia were seen across trials with one trial reporting a NNH of 4 (*Marcus et al 2008*). One pooled analysis of 3 similarly designed trials (N = 409) measured the effects of aripiprazole in older vs younger patients. Results demonstrated adjunctive aripiprazole was effective in improving depressive symptoms in older patients (50 to 67 years), and akathisia was the most commonly reported adverse event in both the older (17.1%) and younger (26%) patient groups (*Steffens et al 2011*). Other trials have demonstrated similar results (*Kamijima et al 2013, Papakostas et al 2005*). In a 12-week, randomized, DB, PC trial evaluating the safety and efficacy of aripiprazole for adjunctive MDD treatment in patients over the age of 60 years (N = 181), a higher percentage of patients achieved remission (defined as a MADRS score of ≤ 10) in the aripiprazole group as compared to placebo (44% vs 29%; p = 0.03; NNT 6.6). Similar to other studies, akathisia was the most common side effect in the aripiprazole group (26% vs 12%), and Parkinsonism was also more often reported (17% vs 2%) (*Lenze et al 2015*).
- The safety and efficacy of brexpiprazole was evaluated in 2 DB, PC, pivotal, 6-week trials in adult patients as an adjunct to antidepressant therapy for MDD. In the pivotal studies, brexpiprazole 2 mg daily doses significantly reduced the mean MADRS score, the primary endpoint, compared with placebo (Study 1 [N = 353], -8.4 points with brexpiprazole 2 mg vs -5.2 points with placebo) (*Thase et al 2015[a]*). In an FDA analysis, the brexpiprazole 1 mg and 3 mg dose did not reduce the mean MADRS score; however, an FDA analysis found evidence of efficacy based on phase 2 data, and per protocol and intention-to-treat analyses of Study 2 (*Thase et al 2015[b], FDA briefing document 2015*). The most common adverse reactions in MDD trials were akathisia (NNH, 15), increased weight (NNH, 20) and somnolence (NNH, 22); and in schizophrenia trials were increased weight (NNH, 48) and tremor (NNH, 51) (*Correll et al 2015, Kane et al 2015[a], Thase et al 2015[b]*). An SR and MA of 4 DB, randomized, PC trials evaluating the efficacy and safety of brexpiprazole for adjunctive treatment of MDD found that it was superior to placebo for MADRS (MD, -1.76; 95% CI, -2.45 to -1.07; p < 0.00001) and the HAM-D-17 (MD, -1.21; 95% CI, -1.71 to -0.72; p < 0.00001). The RRs for response and remission were 1.57 (95% CI, 1.29 to 1.91) and 1.55 (95% CI, 1.22 to 1.96), respectively (*Yoon et al 2017*).

- The FDA-approval of quetiapine fumarate ER as an adjunct to antidepressant therapy for the treatment of MDD was based on two 6-week, PC, fixed dose trials (N = 939) in doses of 150 mg or 300 mg/day. A pooled analysis of the 2 RCTs demonstrated that quetiapine fumarate 300 mg/day (58.3%; p < 0.01; NNT, 9) significantly improved the MADRS response (defined as ≥ 50% decrease in MADRS total score), but quetiapine fumarate 150 mg/day (53.7%; p = 0.06) did not compared to placebo (46.2%). However, MADRS remission was significantly improved for both the quetiapine fumarate 300 mg/day (36.5%; p < 0.001; NNT, 8) and 150 mg/day doses (35.6%; p < 0.01; NNT, 9) vs placebo (24.1%). The most common adverse events leading to discontinuation were somnolence and sedation. For the quetiapine fumarate 300 mg/day, 150 mg/day, and placebo groups, the mean weight gain was 1.3, 0.9, and 0.2 kg, and the incidence of EPS was 6.4, 3.8, and 4.2%, respectively (*Bauer et al 2010*).

Treatment-resistant depression

- Olanzapine, combined with fluoxetine, is the only agent in this class review that is indicated for treatment-resistant depression. Approval of olanzapine/fluoxetine for the acute treatment of treatment-resistant depression was based on 3 clinical trials of 8- (2 trials) and 12-week duration. Treatment with olanzapine/fluoxetine was generally more effective than monotherapy with either olanzapine or fluoxetine in improving MADRS scores; however, results in trials have been mixed (*Corya et al 2006, Shelton et al 2005, Thase et al 2007*). In one 12-week, DB trial, olanzapine/fluoxetine was compared to olanzapine, fluoxetine, or venlafaxine monotherapy. Olanzapine/fluoxetine demonstrated a statistical MADRS advantage over all monotherapy agents after week 1 which was maintained up to week 6; however, this effect was only sustainable over olanzapine monotherapy at week 12 (*Corya et al 2006*). Other trial data demonstrated that olanzapine/fluoxetine was not significantly different compared to other antidepressants such as nortriptyline and fluoxetine monotherapy in improving MADRS scores (*Corya et al 2006, Shelton et al 2005*).
- Treatment with olanzapine/fluoxetine has consistently demonstrated increases in the incidence (≥ 10%) of weight gain, increased appetite, somnolence, and dry mouth. Additional adverse events have varied in trials. Compared to fluoxetine and olanzapine monotherapy, the most common adverse events for olanzapine/fluoxetine (incidence ≥ 10%) included peripheral edema and hypersomnia, which were significantly higher than that of fluoxetine monotherapy (p < 0.001) (*Thase et al 2007*). Compared to olanzapine, fluoxetine or venlafaxine monotherapy, the most common adverse events for olanzapine/fluoxetine (incidence ≥ 10%) included dizziness, asthenia, peripheral edema, and headache. More patients in the combination therapy group discontinued due to weight gain (*Corya et al 2006*). Compared to fluoxetine, olanzapine, and nortriptyline monotherapy, the most common adverse events for olanzapine/fluoxetine combination therapy (incidence ≥ 10%) were asthenia, headache, anxiety, tremor, nervousness, insomnia, and nausea (*Shelton et al 2005*).

<u>Schizophrenia and/or Schizoaffective Disorder</u>

- All oral atypical antipsychotic agents in this class review are indicated for use in schizophrenia with the exception of the combination agent olanzapine/fluoxetine. Clozapine is the only agent indicated for treatment-resistant schizophrenia. Clozapine and paliperidone products, excluding Invega Trinza, are indicated for the treatment of schizoaffective disorder. The following is a summary of recent MAs and SRs, landmark trials in schizophrenia, and study evidence related to newer atypical antipsychotic agents (ie, asenapine, brexpiprazole, cariprazine, iloperidone, and lurasidone) that do not have extensive trial evidence.
- Based on a 2012 AHRQ SR of 125 trials evaluating typical and atypical antipsychotics, a total of 113 measured efficacy and safety in adults with schizophrenia or schizophrenia-related psychoses. Compared to haloperidol, there was no difference in PANSS (and/or Scale for the Assessment of Positive Symptoms [SAPS]) score for positive symptoms for aripiprazole, clozapine, olanzapine, quetiapine, and risperidone. Outcomes measuring negative symptoms demonstrated a significant difference in PANSS scores favoring aripiprazole for 1701 patients in 3 trials, risperidone for 4043 patients in 20 trials, and olanzapine-treatment for 3742 patients in 14 trials. When compared with haloperidol, risperidone yielded lower relapse rates for 1405 patients in 6 trials and olanzapine provided better response rates for 4099 patients in 14 trials and remission rates for 582 patients in 3 trials. The most common adverse effects with significant differences were in the category of EPS and most often involved haloperidol. Haloperidol appears to be equally effective to treatment with the atypical antipsychotics in terms of positive symptoms; however, for negative symptom scores aripiprazole, risperidone, and olanzapine may be better options for treatment. Olanzapine and risperidone may be better options when remission/relapse rates are considered (*Abou-Setta et al 2012*).

- One large Bayesian MA of 212 RCTs compared 15 antipsychotic medications for efficacy and safety outcomes in patients with schizophrenia or related disorders in short-term trials. The primary endpoint was efficacy measured by mean overall change in symptoms after 6 weeks and all antipsychotics were significantly more effective than placebo. Clozapine had the greatest mean difference in the change in symptom scores and was significantly superior to all other antipsychotics, including olanzapine and risperidone which have demonstrated some efficacy in treatment-resistant patients. After clozapine, olanzapine, and risperidone were significantly more effective than the other antipsychotics apart from paliperidone. Overall, effect sizes were small and there were some inconsistencies between results, but the authors did not consider that this was substantial enough to change the results. Safety assessment for the FDA-approved agents indicated that EPS was lowest for clozapine and highest for haloperidol; sedation was lowest for risperidone and highest for clozapine; weight gain was lowest for haloperidol and highest for olanzapine; prolactin increase was lowest for aripiprazole and highest for paliperidone; and QT prolongation was lowest for lurasidone and highest for ziprasidone. The authors concluded that the properties of antipsychotic drugs differed greatly among agents and that treatment should be fit to individual patients' needs. As the MA had many limitations, including substantial differences between studies, and uncertainties surround indirect comparisons, generalizability of the findings and authors' conclusions are limited. This is similar to many large atypical antipsychotic MAs (*Leucht et al 2013*).
- One Cochrane SR evaluated aripiprazole vs other atypical antipsychotics for the treatment of schizophrenia. Differences in efficacy between aripiprazole and other atypical antipsychotics (olanzapine, risperidone, and ziprasidone) demonstrated no advantage in terms of overall global state (defined as MD in CGI-S score) or mental state (defined as MD total change in PANSS score). When compared with any one of several new generation antipsychotic drugs in one RCT (N = 523), the aripiprazole group showed improvement in energy, mood, negative symptoms, somnolence, and weight gain. More nausea was seen in patients given aripiprazole (N = 2881; RR, 3.13; 95% CI, 2.12 to 4.61). Weight gain with aripiprazole-treatment was less common (N = 330; RR, 0.35; 95% CI, 0.19 to 0.64). Attrition ranged from 30% to 40% (no differences between groups). Due to the high attrition rates validity is limited, thereby making it difficult to make strong conclusions. There are limited data on the safety and efficacy of aripiprazole. Based on current available evidence, efficacy of aripiprazole appears to be similar and there may be benefits in terms of weight gain, but there appears to be an increased incidence of nausea compared to other agents (*Khanna et al 2014*).
- One Cochrane SR evaluated quetiapine compared to other atypical antipsychotics for the treatment of schizophrenia. Efficacy and safety were evaluated in 5971 patients across 35 RCTs. For the primary efficacy endpoint, PANSS total score, the comparator drugs may be more effective than quetiapine, but the clinical meaning of these data is unclear. There were no significant differences in efficacy between quetiapine and clozapine, but quetiapine was associated with fewer adverse events. Quetiapine demonstrated fewer movement disorders compared to risperidone (RR, 0.5; 95% CI, 0.36 to 0.69), olanzapine (RR, 0.51; 95% CI, 0.32 to 0.81), and paliperidone (RR, 0.64; 95% CI, 0.45 to 0.91). There are limited studies; however, data provide evidence that quetiapine-treated patients may need to be hospitalized more frequently than those taking risperidone or olanzapine. Quetiapine may be slightly less effective than risperidone and olanzapine in reducing symptoms, and it may cause less weight gain and fewer side effects and associated problems (such as heart problems and diabetes) than olanzapine and paliperidone, but more than risperidone and ziprasidone (*Asmal et al 2013*).
- The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) was a large, multi-center study initiated by the National Institute of Mental Health to examine the effectiveness of SGAs compared to FGAs in patients with chronic schizophrenia. It was intended to include patients treated in typical clinical settings and to reflect typical clinical practice in which individuals with schizophrenia may require multiple medication trials before finding one that is adequately both efficacious and tolerable. The study design allowed for patients who discontinued one study antipsychotic drug to enter subsequent phases of the study to receive additional antipsychotic medications (*Lieberman et al 2005, Stroupe et al 2006, Stroupe et al 2009*). Among the unexpected outcomes was the finding that, with the exception of clozapine, the SGAs did not separate out robustly from the FGAs with respect to overall efficacy and times to treatment discontinuation. However, because of relatively high discontinuation rates across all treatment arms, potential biases regarding optimal dosing of individual drugs, and clear differences in treatment-emergent side effect profiles, the implications of CATIE are subject to interpretation which may preclude definitive guidance in developing pharmacotherapy guidelines for patients with schizophrenia as a whole.
- The efficacy of asenapine in the treatment of schizophrenia in adults was evaluated in 4 published, randomized, DB, PC, and active-controlled (haloperidol, risperidone, and olanzapine) trials, ranging in duration from 6 weeks to 1 year

(*Kane et al 2011, Kane et al 2010[a], Potkin et al 2007, Schoemaker et al 2010*). Asenapine was associated with statistically significant improvement in PANSS scores from baseline compared to placebo, starting from week 2 of therapy. CGI-I and CGI-S scores were also significantly improved with asenapine therapy compared to placebo. Moreover, an extension study demonstrated a reduced risk of relapse associated with continuation of asenapine therapy (*Kane et al 2011*). However, a direct-comparison study suggests that asenapine is less effective than olanzapine in terms of changes from baseline in PANSS and CGI-S scores. Furthermore, study discontinuation due to inadequate efficacy was noted in only 14% of patients receiving olanzapine compared to 25% of patients in the asenapine group. Mean weight gain was 0.9 kg with asenapine and 4.2 kg with olanzapine (*Shoemaker et al 2010*). In another study, while 17% of patients receiving risperidone experienced a weight gain of at least 7% from baseline, 9% of patients in the asenapine group were noted to exhibit clinically significant weight gain (*Potkin et al 2007*).

- The approval of Secuado was based on the unpublished HP-3070-GL-04 clinical trial (N = 614), a 6-week, Phase 3, DB, PC, multinational, inpatient RCT. Patients with schizophrenia in an episode of acute exacerbation lasting ≤ 8 weeks and length of hospitalization ≤ 21 days were randomized to receive Secuado 3.8 mg (n = 204), Secuado 7.6 mg (n = 204), or placebo (n = 206) transdermal system once daily. Compared to placebo, both doses of Secuado demonstrated statistically significant improvements in PANSS total score ($p < 0.001$ for 3.8 mg; $p = 0.003$ for 7.6 mg) and CGI-S ($p < 0.001$ for both doses) (*FDA Secuado review 2020, Secuado prescribing information 2019*).
- The safety and efficacy of brexpiprazole was evaluated in 2 DB, PC, 6-week trials in adults with schizophrenia. In the pivotal studies, brexpiprazole 2 mg and 4 mg daily doses significantly reduced the PANSS score (-20.73 and -19.65 vs -12.01 points with placebo), the primary endpoint, compared with placebo; however, in the BEACON trial, only the brexpiprazole 4 mg dose significantly reduced the PANSS score (-20 vs -13.53 points with placebo) (*Correll et al 2015; Kane et al 2015[a]*). The most common adverse reactions in MDD trials were akathisia (NNH, 15), increased weight (NNH, 20) and somnolence (NNH, 22); in schizophrenia trials, the most common adverse effects were increased weight (NNH, 48) and tremor (NNH, 51) (*Correll et al 2015, Kane et al 2015[a], Thase et al 2015[b]*). The safety and efficacy of brexpiprazole for maintenance therapy of schizophrenia was evaluated in a randomized, DB, MC, PC trial. It enrolled 524 patients with an acute exacerbation of psychotic symptoms to be stabilized on brexpiprazole 1 to 4 mg daily. Patients who achieved stabilization (criteria including PANSS total score ≤ 70, CGI-S score ≤ 4 [moderately ill], no current suicidal behavior, or violent or aggressive behavior) for 12 weeks then entered a 52-week maintenance phase where they were randomized to their stabilization dose of brexpiprazole (N = 97) or placebo (N = 105). The co-primary endpoints were time to exacerbation of psychotic symptoms or impending relapse, defined as worsening of CGI-I and PANSS scores, hospitalization due to worsening of psychotic symptoms, suicidal behavior, or violent/aggressive behavior. In the maintenance phase, 13.5% of patients in the brexpiprazole group experienced impending relapse vs 38.5% of placebo patients ($p < 0.0001$) and time to impending relapse was statistically significantly lower (hazard ratio [HR], 0.34; $p = 0.0008$). However, based on results of an interim analysis, the trial was terminated early. Only a small number of patients were exposed to brexpiprazole for the prescribed 52 weeks and, therefore, conclusions cannot be drawn for long-term use (*Fleischhacker et al 2016*).
- The efficacy and safety of cariprazine in schizophrenia were demonstrated in 3 DB, randomized, PC, 6-week trials (*Durgam et al 2014, Durgam et al 2015[b], Kane et al 2015[b]*). A total of 1792 adult patients with acute exacerbation of schizophrenia were administered placebo or cariprazine 1.5 to 9 mg per day. Two trials were fixed-dose studies and included active comparators, risperidone 4 mg and aripiprazole 10 mg, to assess sensitivity; one study was a flexible-dose study with no active comparator. In the flexible-dose study, the mean daily dose ranged from 5 to 8 mg per day (*Kane et al 2015[b]*). All doses were superior to placebo in reducing PANSS and CGI-S scores and a significant PANSS reduction was observed as soon as 7 days for the higher doses and 2 to 3 weeks for the lower doses (*FDA/CBER summary review 2015*). Of note, higher doses do result in quicker control of symptoms; however, if high doses continue resulting in accumulation of the active metabolite DDCAR, it is not clear how this may influence safety results. Delayed incidences of akathisia occurred. According to pooled analysis (n = 1317 cariprazine-treated patients) within the FDA clinical summary, the most common adverse events reported in schizophrenia trials were EPS (28.5%) and akathisia (11.2%) (*FDA/CBER summary review 2015*). The akathisia observed at cariprazine doses ≤ 6 mg is comparable to those observed with aripiprazole, but accumulation of the DDCAR metabolite may result in later-onset effects. In schizophrenia studies, 4% of patients with normal hemoglobin A1c developed elevated levels (≥ 6.5%). The proportion of patients with weight increase ≥ 7% from baseline ranged from 8 to 17% across cariprazine doses. In an OL 48-week extension (N = 97) of a 6-week trial, safety and tolerability were found to be maintained. The most common adverse events were akathisia (14%), insomnia (14%), and weight gain (11.8%) (*Durgam et al 2014, Durgam et al 2017*). Another study evaluated cariprazine for maintenance therapy for schizophrenia relapse in 765 patients. A

flexible-dose, OL, 8-week, run in phase was followed by a 12-week, fixed-dose, stabilization phase. Patients completing the OL phase (N = 264) entered a DB phase and received cariprazine (3 to 9 mg/day), or placebo for up to 72 weeks. During the DB phase, 24.8% of the cariprazine group experienced relapse vs 47.5% of the placebo group (HR, 0.45; 95% CI, 0.28 to 0.73). Time to relapse was statistically significantly longer for the cariprazine group vs placebo (25th percentile time to relapse, 224 vs 92 days, respectively; p < 0.001). The long-term safety profile of cariprazine was found to be consistent with findings from previous trials (*Durgam et al 2016).*

- Iloperidone has been studied as monotherapy for the treatment of adults with an acute or subacute exacerbation of schizophrenia. Three 6-week, randomized, DB, placebo- and active comparator (risperidone and haloperidol)-controlled studies found iloperidone to be significantly more effective than placebo (*Potkin et al 2008*). Another 4-week, placebo- and active comparator- (ziprasidone) controlled study found a significant improvement in PANSS scores with iloperidone therapy compared to placebo (*Cutler et al 2008*). Two MAs of these 4 studies corroborated earlier data, finding iloperidone more effective than placebo in terms of improvement from baseline in various subscales of the PANSS scale and BPRS scores (*Citrome et al 2011, Citrome et al 2012*). The long-term efficacy and safety of iloperidone in the treatment of schizophrenia was evaluated in an MA that pooled the follow-up data (up to 52 weeks) from 3 prospective RCTs. The MA found the long-term efficacy of iloperidone, assessed via the time to relapse endpoint, to be comparable to haloperidol (p = 0.85), with a more favorable long-term safety profile (*Kane et al 2008*). Moreover, another MA designed to evaluate the short-term safety of iloperidone found the following dose-related adverse effects: dry mouth, dizziness, somnolence and dyspepsia. EPS was noted in association with iloperidone but was more common with haloperidol and risperidone therapies. Iloperidone was also associated with QTc prolongation and weight gain (1.5 to 2.1 kg) (*Weiden et al 2008*). The efficacy of iloperidone for relapse-prevention during maintenance phase of schizophrenia treatment was evaluated in a DB, PC, randomized withdrawal study. Patients were not blinded and were stabilized for 24 weeks. If clinically stable for 12 weeks, they were then randomized to iloperidone (8 to 24 mg/day) (N = 153) or placebo (N = 150) for 26 weeks. The primary endpoints were time to relapse and proportion of patients experiencing relapse (defined as hospitalization due to worsening schizophrenia, worsening of PANSS and CGI-I scores, suicidal or aggressive behavior, or treatment escalation [ie, dose increases or additional medications]). The trial was stopped early due to superior iloperidone relapse prevention. Time to relapse was statistically significantly longer with iloperidone vs placebo (140 vs 95 days, respectively; p < 0.0001). The relapse rate for placebo was 64% vs 17.9% for iloperidone (p < 0.0001). The safety was comparable to other trial results, with dizziness, insomnia, headache, dry mouth, and somnolence being the most common adverse events. Weight gain ≥ 7% occurred in 25.2% of iloperidone-treated patients in the relapse-prevention phase. Mean change in QTcF from baseline was 4.9 ms in the iloperidone group (vs 1 ms in placebo) during the relapse-prevention phase. Rates of EPS (2.5% in stabilization phase/1.3% in relapse-prevention phase) and akathisia (3.7% and 1%, respectively) were consistently low in iloperidone-treated patients as well (*Weiden et al 2016*).
- Lumateperone was evaluated in a Phase 2 and two Phase 3 PC trials. All 3 trials enrolled patients who had demonstrated prior response to antipsychotic drug therapy (ie, not treatment-naïve and not treatment-resistant) who were experiencing an acute exacerbation of psychosis starting within the previous 4 weeks.
  - The Phase 2 trial (Study 005) was a 4-week RCT enrolling 335 patients (*Lieberman et al 2016*). Patients received lumateperone 42 mg daily (the marketed dose), lumateperone 84 mg daily, risperidone 4 mg daily, or placebo.
    - The primary endpoint was the change in total score on the PANSS. Results on the PANSS demonstrated LS mean changes of -7.4, -13.2, -8.3, and -13.4 in the placebo, lumateperone 42 mg, lumateperone 84 mg, and risperidone 4 mg groups, respectively. The difference between lumateperone 42 mg and placebo was -5.8 (95% CI, -10.5 to -1.1; multiplicity-adjusted p = 0.04), which was larger than that of the higher dose tested and comparable to that of risperidone.
  - The first Phase 3 trial (Study 301) was a 4-week RCT enrolling 450 patients (*Correll et al 2020*). Patients received lumateperone 42 mg daily, lumateperone 28 mg daily, or placebo.
    - Results for the PANSS total score (the primary endpoint) demonstrated LS mean changes of -10.3, -14.5, and -12.9 in the placebo, lumateperone 42 mg, and lumateperone 28 mg groups, respectively. The difference between lumateperone 42 mg and placebo was -4.2 (95% CI, -7.8 to -0.6; multiplicity-adjusted p = 0.05).
    - The key secondary endpoint was the change in the CGI-S score. Results demonstrated LS mean changes of -0.5 for the placebo group and -0.8 for both lumateperone groups. The difference between lumateperone 42 mg and placebo was -0.3 (95% CI, -0.5 to -0.1; multiplicity-adjusted p = 0.05).

- The other Phase 3 trial (Study 302) enrolled 696 patients (*FDA Caplyta multidisciplinary review 2019*). It had a similar design to the previous studies but had a duration of 6 weeks rather than 4 weeks. Patients received lumateperone 42 mg, lumateperone 14 mg, risperidone 4 mg, or placebo.
  - Results on the PANSS total score did not demonstrate a statistically significant efficacy benefit for either lumateperone dose vs placebo, with differences of 0.5 (95% CI, -2.9 to 3.8) and 0.1 (95% CI, -3.4 to 3.5) for the 42 mg and 14 mg doses, respectively. A significant difference for risperidone vs placebo was demonstrated (-5.4 [95% CI, -8.9 to -1.9]).
  - Results for secondary endpoints were not reported; the FDA reviewers deemed them irrelevant for discussion based on failure of the primary endpoint.

- Lurasidone was investigated for the treatment of adult patients with acute and chronic symptoms of schizophrenia in 2 PC, 6-week studies and two 21-day studies directly comparing the safety and efficacy of lurasidone 120 mg once daily with ziprasidone 80 mg twice daily. In PC studies, lurasidone 40, 80, or 120 mg once daily was associated with significant improvements from baseline in PANSS and the BPRS scores, compared to placebo (*Meltzer et al 2011, Nakamura et al 2009*). The 2 direct-comparison studies demonstrated comparable improvements in the lurasidone and ziprasidone groups in terms of the reduction in total PANSS, PANSS positive symptom, PANSS general symptom, CGI-S scores, and several cognition scales. Likewise, the 2 groups were comparable in terms of rates of discontinuation for any reason and discontinuation due to adverse events (*Harvey et al 2011, Potkin et al 2011*). Of note, lurasidone was more effective in improving negative symptom PANSS scores compared to ziprasidone (p = 0.046). Both therapies were associated with a small weight loss from baseline and neither therapy was associated with a clinically significant electrocardiogram abnormality. Extrapyramidal adverse events were noted in 3.3% of patients in the ziprasidone group and in 3.3% of patients receiving lurasidone (*Potkin et al 2011*). The efficacy of lurasidone in maintenance treatment was evaluated in a DB, PC, RCT. Patients (N = 676) with schizophrenia experiencing an acute exacerbation entered into an OL stabilization phase for 12 to 24 weeks. Patients achieving stabilization for 12 weeks (N = 285) were randomized into a 28-week, DB phase to receive lurasidone (40 to 80 mg/day) or placebo. The probability of relapse at the 28-week point was 42.2% vs 51.2% in the lurasidone and placebo groups, respectively (NNT = 12). Lurasidone statistically significantly delayed the time to relapse vs placebo (p = 0.039). In patients receiving lurasidone in both the OL and DB phases, the most common adverse events were akathisia (16.7%), insomnia (12.5%), and headache (11.8%) (*Tandon et al 2016*).

Parkinson's Disorder Psychosis

- Pimavanserin is the only oral atypical antipsychotic FDA-approved for the treatment of hallucinations and delusions associated with PD psychosis. The FDA-approval of pimavanserin was based on a 6-week PC, DB, RCT of 199 patients evaluating the safety and efficacy of pimavanserin 40 mg once daily. Compared to placebo, the least-squares mean difference of total PD adapted SAPS (SAPS-PD) score change from baseline at day 43 favored pimavanserin 40 mg (-3.06; 95% CI, -4.91 to -1.20; p = 0.0014). The most common adverse events in the pimavanserin vs the placebo group included urinary tract infection (13 vs 12%), falls (11 vs 9%), peripheral edema (7 vs 3%), hallucinations (7 vs 4%), nausea (6 vs 6%), confusion (6 vs 3%), and headache (1 vs 5%) *(Cummings et al 2014).*
- One MA of pimavanserin included 4 RCTs measuring the efficacy and safety compared to placebo in patients with PD psychosis. Pimavanserin was associated with a significant decrease in SAPS-hallucination and delusions score compared to placebo (weighted mean differences [WMD],-2.26; 95% CI, -3.86 to -0.67; p=0.005). Adverse effects were not significantly different from placebo, except pimavanserin was associated with a significantly lower incidence of orthostatic hypotension (RR, 0.33; 95% CI, 0.15 to 0.75; p = 0.008) *(Yasue et al 2016, Bozymski et al 2017)*.
- In a more recent MA, pimavanserin significantly improved CGI-S score vs placebo (-0.5; 95% CI, -0.9 to -0.2) in patients with PD psychosis; change in motor function based on the Unified Parkinson's Disease Rating Scale part III (UPDRS-III) did not reach statistical significance (0.2; 95% CI, -1.4 to 1.9)*(Iketani et al 2020*). Other agents included in this MA are not FDA-approved for PD psychosis.

Long-Acting Injectable Atypical Antipsychotics:

Bipolar Disorder

- Risperdal Consta (risperidone microspheres) and Abilify Maintena (aripiprazole ER) are the only long-acting injections FDA-approved for bipolar I disorder in adults.
  - Abilify Maintena (aripiprazole ER) long-acting injection is indicated as maintenance monotherapy treatment (*Calabrese et al 2017*).

- Risperdal Consta (risperidone microspheres) long-acting injection is indicated as monotherapy or in combination with lithium or valproate for maintenance therapy. Compared to placebo, risperidone long-acting injection has demonstrated superior efficacy in acute and non-acute patients with similar safety effects to that of oral risperidone (*Macfadden et al 2009, Quiroz et al 2010, Vieta et al 2012, Yatham et al 2007*).

- In a DB, PC, 52-week randomized withdrawal study (N = 266), aripiprazole ER injection significantly delayed recurrence of any mood episode compared with placebo, with a 55% reduction in risk of experiencing a mood episode over 1 year (HR, 0.45; 95% CI, 0.3 to 0.68). The proportion of patients experiencing recurrence of a manic episode was significantly less with aripiprazole ER injection (9.1% vs 30.1%); however, the recurrence rate for either depressive or mixed episodes was not different between treatment groups. After acute treatment of a manic episode with oral aripiprazole and transition to monotherapy with aripiprazole ER 400 mg intramuscularly (IM) once every 4 weeks (reduction to 300 mg was allowed for adverse reactions) for a 12-week stabilization period, patients were randomized to continue aripiprazole IM or withdrawal to placebo for 52 weeks. Of note, a large proportion of patients did not complete the study. Of the 266 randomized patients, 48.1% (N = 64) of the aripiprazole group and 28.6% (N = 38) of the placebo group completed the study. Treatment-emergent adverse effects that lead to discontinuation more commonly occurred with placebo (25.6 vs 17.4%); those that occurred more often with aripiprazole included weight gain of 7% or greater (18 vs 12.9%), akathisia (21.2 vs 12.8%), and anxiety (6.8 vs 4.5%) (*Calabrese et al 2017*).
- For maintenance therapy, risperidone long-acting injection monotherapy has demonstrated inconsistent results regarding the endpoint of delayed time to recurrence of any mood episode compared to placebo (*Quiroz et al 2010, Vieta et al 2012*). When risperidone long-acting injection was used in combination with mood stabilizers (eg, lithium and valproate), antidepressants, or anxiolytics, the time to relapse was significantly longer with fewer proportions of patients relapsing compared to placebo (*Macfadden et al 2009*). An exploratory post hoc analysis showed that the time to recurrence of any mood episode was also significantly longer with oral olanzapine compared with risperidone long-acting injection (p = 0.001) (*Vieta et al 2012*). The adverse effect profile of long-acting injection therapy is not fully understood; however, EPS, weight gain, hyperprolactinemia, and cardiovascular events were observed in risperidone long-acting injection therapy trials (*Macfadden et al 2009, Quiroz et al 2010, Vieta et al 2012, Yatham et al 2007*).

Schizophrenia

- All 8 long-acting injectable atypical antipsychotics are FDA-approved for the treatment of schizophrenia in adults. These agents include Abilify Maintena (aripiprazole ER), Aristada and Aristada Initio (aripiprazole lauroxil), Zyprexa Relprevv (olanzapine pamoate ER), Invega Sustenna (paliperidone palmitate once-a-month injection), Invega Trinza (paliperidone palmitate once-every-3-months injection), Risperdal Consta (risperidone microspheres), and Perseris (risperidone once-a-month injection). Invega Sustenna is the only agent FDA-approved for the treatment of schizoaffective disorder as monotherapy and as an adjunct to mood stabilizers or antidepressants.
- A number of MAs and SRs have been conducted evaluating long-acting injection atypical antipsychotics compared to oral antipsychotics for the treatment of schizophrenia. Comparative effectiveness data between long-acting injectable atypical antipsychotics are lacking, and there is insufficient evidence to draw firm conclusions. The most recent, well-designed MAs have been summarized for efficacy and safety evaluations.
- One MA of atypical antipsychotics included 13 RCTs measuring the efficacy and safety of long-acting injection atypical antipsychotics vs oral antipsychotics or placebo in patients with schizophrenia. Long-acting injectable atypical antipsychotics were not associated with a significant decrease in the PANSS total score from baseline from oral antipsychotics (p = 0.33); therefore, both formulations had similar efficacy. No additional significant differences were noted. The long-acting injectable atypical antipsychotics were associated with a higher incidence of EPS compared to placebo (p < 0.001) and oral antipsychotics (p = 0.048) (*Fusar-Poli et al 2013*).
- One SR and MA of long-acting antipsychotic injectable agents (including typical and atypical agents) measured the safety and efficacy of treatment compared to oral antipsychotics in 21 RCTs (11 trials measured atypical antipsychotic agents). Patients with schizophrenia, schizophreniform, or schizoaffective disorder were evaluated in longer duration trials of greater than or equal to 6 months. Long-acting injectable antipsychotics were similar to oral antipsychotics for relapse prevention in outpatient studies lasting ≥ 1 year (RR, 0.93; 95% CI, 0.71 to 1.07; p = 0.03). Among individual long-acting injectable antipsychotics, only fluphenazine was superior to oral antipsychotics in drug efficacy (p = 0.02) and in preventing hospitalization (p = 0.04). There was no difference between each individual long-acting injectable antipsychotic and pooled long-acting injectable antipsychotics compared to oral antipsychotics regarding discontinuation due to adverse events (p = 0.65) (*Kishimoto et al 2014*).

- One MA compared outcomes for once-monthly long-acting injections of paliperidone palmitate and risperidone across 7 RCTs. Paliperidone palmitate was less likely to show no improvement in global state (defined as reduction in PANSS scores) vs placebo (RR, 0.79; 95% CI, 0.74 to 0.85). When comparing both active treatments, one trial favored paliperidone palmitate and one trial favored risperidone long-acting injection; therefore, conclusions could not be made. In terms of safety, paliperidone palmitate and risperidone long-acting injection were similar. Compared to placebo, paliperidone palmitate led to significant elevations in serum prolactin, regardless of patient gender (*Nussbaum et al 2012*).
- One SR of 41 trials measuring safety concluded that long-acting injectable atypical antipsychotics are associated with similar adverse effects to that of oral formulations, and no clinically significant trends can be conclusively drawn. Data suggested that olanzapine pamoate was associated with dose-dependent weight gain, lipid and glucose metabolism issues, and may increase prolactin levels even at low doses. Post-injection syndrome, due to accidental intravascular injection of olanzapine pamoate, was characterized by delirium and/or excessive sedation (incidence, 1.2%). The risperidone long-acting injection may increase the risk of QT prolongation, although the clinical significance is unknown. Hyperprolactinemia, EPS, cardiovascular events (ie, tachycardia and orthostatic hypotension), and weight gain are known side effects of risperidone long-acting injection and paliperidone palmitate. The most common adverse event associated with paliperidone palmitate was worsening of psychotic symptoms (incidence, 3.5 to 16%) (*Gentile et al 2013*).
- Recently-approved long-acting injectable agents include Aristada and Aristada Initio (aripiprazole lauroxil), Invega Trinza (paliperidone palmitate once-every-3-months injection), and Perseris (risperidone once-a-month injection).
  - The safety and efficacy of aripiprazole lauroxil in adult patients with schizophrenia was established in one PC, DB, RCT of 622 patients over a period of 12 weeks. Oral aripiprazole was administered concomitantly for the first 3 weeks of treatment. The PANSS total score was significantly decreased at day 85 by 10.9 with monthly IM injections of aripiprazole lauroxil 441 mg and by 11.9 with 882 mg IM monthly compared with placebo ($p < 0.001$ for both). PANSS was significantly improved as early as day 8 and maintained throughout the study. In terms of safety, more than double the proportion of patients taking aripiprazole lauroxil experienced akathisia (441 mg, 11.6%; 882 mg, 11.5%) compared to placebo (4.3%). The majority of the akathisia (75%) was experienced before the second injection within the first 3 weeks. Additional treatment-emergent adverse effects (incidence ≥ 2%) included insomnia, headache, and anxiety (*Meltzer et al 2015*). In an indirect comparison of aripiprazole lauroxil (441 or 882 mg) and aripiprazole ER injection (400 mg), all treatment groups had similar reductions in symptoms of schizophrenia as measured by PANSS total score (*Cameron et al 2018*). The incidence of akathisia and changes in weight were also similar between treatments; although, the occurrence of treatment emergent adverse events was potentially lower with aripiprazole lauroxil 882 mg vs aripiprazole ER injection (OR, 0.46; 95% CI, 0.22 to 0.97).
    - Aristada Initio is indicated only to be used as a single dose in conjunction with oral aripiprazole for the initiation of Aristada, when used for the treatment of schizophrenia in adults. Effectiveness of Aristada Initio was established by adequate and well-controlled studies of oral aripiprazole and Aristada in adult patients with schizophrenia and a single pharmacokinetics bridging study (*Aristada Initio prescribing information 2020*).
  - The FDA-approval of Invega Trinza, the 3-month IM paliperidone palmitate injection, was based on one PC, OL, DB trial of 305 patients with schizophrenia experiencing acute symptoms. Prior to administration of paliperidone palmitate once every 3 months injection, patients were administered flexible oral doses for 17 weeks, and then administered the paliperidone palmitate once monthly injection for 12 weeks. If stable, patients were then administered the once-every-3-months injection. Paliperidone palmitate once-every-3-months injection significantly lengthened the median time to first relapse vs placebo. The mean change in PANSS total scores showed greater improvement in the paliperidone group compared to placebo ($p < 0.001$). Due to the low percentage of relapse in treated patients (7.4%), the median time was not estimated; however, in the placebo group, 23% experienced relapse, with a median time of 274 days. The trial was stopped early due to demonstration of efficacy. Those adverse events noted more frequently in the group receiving paliperidone palmitate vs the placebo group included headache (9 vs 4%), increased weight (9 vs 3%), nasopharyngitis (6 vs 1%), and akathisia (4 vs 1%) (*Berwaerts et al 2015*).
  - The efficacy of risperidone ER monthly injection (Perseris) was evaluated in an 8-week, DB, randomized, PC trial in 354 patients who were experiencing an acute schizophrenia exacerbation. Patients received risperidone 90 mg, 120 mg, or placebo subcutaneously on days 1 and 29. LS mean change from baseline in PANSS total score (the primary outcome) was significantly greater with risperidone 90 mg (-6.148, $p = 0.004$) and 120 mg (-7.237, $p < 0.001$) compared to placebo. Compared to placebo, CGI-S scores were also significantly decreased in both

risperidone dose groups (p = 0.0002 and p < 0.0001, respectively). Adverse effects were similar between groups, with the exception of weight gain (13% in the risperidone 90 mg group, 12.8% in the risperidone 120 mg group, and 3.4% in the placebo group) (*Nasser et al 2016*).

- The AHRQ conducted an SR of 71 studies on the pharmacological and psychosocial treatment for schizophrenia. Most evidence was for older SGAs, with clozapine, olanzapine, and risperidone superior on more outcomes than other SGAs. Older SGAs were similar to haloperidol on benefit outcomes but had fewer adverse event outcomes. Additionally, results from a subgroup analysis found that that patients experiencing a first episode of schizophrenia did not show significant differences in response or remission when treated with olanzapine, quetiapine, risperidone, ziprasidone, aripiprazole, or paliperidone (*McDonagh et al 2017).*
- A SR and MA of 402 RCTs (N= 53,463) evaluated the comparative efficacy of 32 antipsychotics for the treatment of adults with multi-episode schizophrenia. For the majority of medications, treatment was associated with a statistically significant reduction in overall symptoms vs placebo, and there were few significant differences between drugs. clozapine, olanzapine, and risperidone exhibited greater efficacy in reducing negative symptoms than many other antipsychotic medications for overall symptoms, with the greatest benefit noted with clozapine. Overall, the authors concluded that antipsychotics vary more in side effect profile than efficacy, thus choice of medication should be individualized for each patient (*Huhn et al 2019*).

CLINICAL GUIDELINES

- The use of these agents for the treatment of schizophrenia is recognized by national and international guidelines as a mainstay in therapy. Guidelines vary by indication and the following outlines use in children, adolescents, and adults:

  Adults
  - Bipolar disorders
    - The 2018 Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) guideline recommends: lithium, quetiapine, divalproex, asenapine, aripiprazole, paliperidone, risperidone, and cariprazine monotherapy or in combination as first line treatments for acute mania. Quetiapine, lurasidone plus lithium or divalproex, lithium, lamotrigine, lurasidone, or adjunctive lamotrigine are recommended first line for bipolar 1 depression. When initiating or switching during maintenance phase, lithium, quetiapine, divalproex, lamotrigine, asenapine, and aripiprazole monotherapy or combination should be considered first-line (*Yatham et al 2018*).
    - The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the biological treatment of bipolar disorders (acute and long term treatment of mixed states in bipolar disorder) suggest that the best evidence for manic symptoms in bipolar mixed states is with olanzapine. For depressive symptoms, the addition of ziprasidone may be beneficial; however, the evidence is much more limited than for the treatment of manic symptoms. For maintenance treatment, olanzapine, quetiapine, valproate and lithium can be considered (*Grunz et al 2017*).
  - MDD – The Veteran Administration and Department of Defense (VA/DoD) clinical practice guideline for the management of MDD and the American Psychiatric Association (APA) guideline for the treatment of patients with MDD indicate for the majority of patients, an SSRI, SNRI, bupropion or mirtazapine is optimal for first-line treatment (*APA 2010, VA/DoD 2016*). The American College of Physicians (ACP) guideline for the treatment of adult patients with MDD recommends cognitive behavioral therapy or second generation antidepressants (eg, SSRI or SNRI) as first line treatment (*Qaseem et al 2016).* While all 3 guidelines suggest that atypical antipsychotics may be useful to augment antidepressant therapy, the VA/DoD suggests they should be considered only when other strategies have failed because of their significant side effects.
  - Schizophrenia –Per the 2020 APA practice guideline for the treatment of patients with schizophrenia, an evidence-based ranking of atypical antipsychotics or an algorithmic approach to antipsychotic selection is not possible due to the significant heterogeneity in clinical trial designs, the limited number of head-to-head comparisons, and the limited clinical trial data for a number of antipsychotics. The guideline notes that there may be clinically meaningful distinctions in response or tolerability of the various atypicals in an individual patient; however, there is no definitive evidence that one typical or atypical antipsychotic will have consistently superior efficacy compared with another, with the possible exception of clozapine. Specific factors that may influence choice of an atypical antipsychotic include available formulation, drug interactions, pharmacokinetic properties, and adverse effects. The choice of an atypical antipsychotic is based on patient-specific factors such as symptoms, prior treatment response, and benefits and risks of treatment (*Keepers et al 2020*).

- The initial goal of acute treatment with an antipsychotic medication is to reduce acute symptoms, to return individuals to their baseline level of functioning. Maintenance treatment aims to prevent recurrence of symptoms and maximize functioning and quality of life.

- Parkinson's disease psychosis – The American Academy of Neurology (AAN) practice parameter on the treatment of depression, psychosis, and dementia in PD states that clozapine should be considered for the treatment for PD and psychosis, quetiapine may be considered, and olanzapine should not be routinely considered (*Miyasaki et al 2006*).

Children and Adolescents

- Use of atypical antipsychotics - According to guidelines from the American Academy of Child and Adolescent Psychiatry (AACAP), prior to the initiation of antipsychotic therapy patients should undergo a thorough diagnostic assessment and evaluation for comorbid medical conditions and concomitant medications. Furthermore, a multidisciplinary plan that includes education and psychotherapy should be established. The prescriber should also have a thorough discussion about the risks and benefits of psychotropic treatment (*Findling et al 2011*).
- Autism Spectrum Disorders (ASD) –
  - AACAP guidelines state that pharmacotherapy may be considered in children with ASD when there is a specific target symptom or comorbid condition. Risperidone and aripiprazole are FDA-approved for irritability associated with autism; other drugs that have been studied include: clonidine, olanzapine, valproic acid, lamotrigine, levetiracetam, clomipramine, amantadine, pentoxifylline (in combination with risperidone), and naltrexone (*Volkmar et al 2014*).
  - The 2019 American Academy of Pediatrics (AAP) guideline for the identification, evaluation, and management of children with ASD suggests that pharmacotherapy is used to help manage coexisting behavioral health disorders (eg, ADHD, mood disorders, or anxiety disorders) and problem behaviors or symptoms causing significant impairment and distress including: aggression, self-injurious behavior, sleep disturbance, mood lability, anxiety, hyperactivity, impulsivity, inattention. The guideline recommends the use of SGAs (aripiprazole or risperidone) to manage irritability and/or aggression in ASD. There less evidence for the use of SGAs in decreasing hyperactivity, thus stimulants are recommended first line (*Hyman et al 2020*).
- Bipolar disorder – According to AACAP guidelines for treatment of children and adolescents with bipolar disorder, pharmacotherapy is the primary treatment for bipolar mania. Standard therapy includes lithium, valproate, and/or atypical antipsychotic agents, with other adjunctive medications used as indicated (*McClellan et al 2007*).
- Schizophrenia – According to the AACAP guidelines, antipsychotics are a primary treatment for schizophrenia spectrum disorders in children and adolescents. The choice of agent is typically based on factors such as FDA-approval status, side effect profile, patient and family preference, and cost (*McClellan et al 2013*).
- Tourette's disorder
  - According to AACAP guidelines for the treatment of children and adolescents with tic disorders, pharmacotherapy should be considered for moderate to severe tics causing severe impairment in quality of life, or when psychiatric comorbidities are present that can also be targeted. Most clinicians use atypical antipsychotics before first-generation agents and some prefer α-agonists over antipsychotic medications due to the adverse effect profile. Commonly used drugs include risperidone, aripiprazole, and clonidine (*Murphy et al 2013*).
  - The 2019 AAN guideline for the treatment of tics in people with Tourette syndrome and chronic tic disorders (*Pringsheim et al 2019*) recommends:
    - Providing information to families about the natural history of a disorder can help inform treatment decisions (Level A). Tics usually begin in childhood and demonstrate a waxing and waning course. Tics generally peak between 10 to 12 years old, with many children experiencing an improvement in tics in adolescence. Additionally, it is important that clinicians assess for co-morbid conditions that are common in people with TS, including attention-deficit/hyperactivity disorder (ADHD), obsessive-compulsive disorder (OCD), and other psychiatric disorders (eg, anxiety, mood).
    - Treatment options for tics include: watchful waiting, comprehensive behavioral intervention for tic (CBIT), and pharmacotherapy.
      - People with tics receiving CBIT are more likely than those receiving psychoeducation and supportive therapy to have reduced tic severity. CBIT is a manualized treatment program consisting of habit reversal training (HRT), relaxation training, and a functional intervention to address situations that sustain or worsen tics.

- The use of antipsychotics is recommended when benefits outweigh the risks. No one drug is recommended over another due to insufficient evidence. Haloperidol, risperidone, aripiprazole, and tiapride (not available in the United States) are probably more likely than placebo to reduce tic severity.

SAFETY SUMMARY

- Ziprasidone is contraindicated in patients with recent acute myocardial infarction (MI), uncompensated heart failure (HF), and history of QT prolongation, or those taking drugs that have demonstrated QT prolongation. Lurasidone is contraindicated for concomitant use with strong cytochrome (CYP) 3A4 inducers and/or inhibitors. Olanzapine/fluoxetine is contraindicated in patients taking concurrent pimozide or thioridazine due to the potential for QT prolongation, and in patients taking concurrent monoamine oxidase inhibitors due to the potential for serotonin syndrome. Lastly, asenapine is contraindicated in patients with severe hepatic impairment.
- All atypical antipsychotic agents, including pimavanserin, have a boxed warning for increased mortality in elderly patients with dementia-related psychosis. Those agents (ie, aripiprazole, lurasidone, brexpiprazole, quetiapine, quetiapine ER, olanzapine/fluoxetine) indicated for depressive episodes carry a boxed warning for an increased risk of suicidal thoughts and behaviors. Zyprexa Relprevv has a boxed warning for incidences of post-injection delirium and/or sedation syndrome; this agent should not be used in patients with dementia-related psychosis. Lastly, clozapine-containing agents (ie, Clozaril and Versacloz) have a boxed warning for severe neutropenia, orthostatic hypotension, bradycardia, syncope, seizures, myocarditis, and cardiomyopathy.
- The atypical antipsychotics have warnings relating to risks of neuroleptic malignant syndrome, tardive dyskinesia, metabolic changes, falls, orthostatic hypotension, leukopenia/neutropenia/agranulocytosis, seizures, cognitive and motor impairment, body temperature dysregulation, suicide, and dysphagia. Additional warnings for various agents include:
  - Aripiprazole: Pathological gambling and other compulsive behaviors and cerebrovascular adverse events in elderly patients with dementia-related psychosis
  - Brexpiprazole: Pathological gambling and other compulsive behaviors.
  - Clozapine-containing products: Eosinophilia, hepatotoxicity, QT prolongation, pulmonary embolism, fever, gastrointestinal hypomotility, and anticholinergic toxicity
  - Iloperidone: QT prolongation, hyperprolactinemia, and priapism
  - Ziprasidone: QT prolongation, severe cutaneous reactions (eg, Drug Reaction with Eosinophilia and Systemic Symptoms [DRESS] and Stevens-Johnson syndrome), hyperprolactinemia, and priapism
  - Paliperidone: QT prolongation, hyperprolactinemia, priapism, and potential for gastrointestinal obstruction (due to non-deformable tablet)
  - Lurasidone: Hyperprolactinemia and activation of mania/hypomania
  - Risperidone: Priapism, hyperprolactinemia, increased sensitivity in patients with PD or dementia with Lewy bodies, and recent myocardial infarction or unstable cardiac disease
  - Asenapine: QT prolongation, hyperprolactinemia, and hypersensitivity reactions
  - Quetiapine: QT prolongation, cataracts, hypothyroidism, hyperprolactinemia, increased blood pressure in children and adolescents, leukopenia, neutropenia and agranulocytosis, and anticholinergic effects
  - Olanzapine: DRESS and hyperprolactinemia
  - Pimavanserin: QT prolongation
- Clozapine-containing products and Zyprexa Relprevv are a part of the Risk Evaluation and Mitigation Strategies (REMS) program. Registry, training, and counseling are required as part of both programs (*REMS@FDA 2021*). Clozapine products also require certain laboratory levels prior to prescribing. Zyprexa Relprevv requires patients to be observed in clinic for 3 hours after administration.
  - In September 2015, the FDA made modifications to the clozapine REMS program. The absolute neutrophil count (ANC) requirements were modified to a lower ANC level. Benign ethnic neutropenia (BEN) patients were also included as now eligible for clozapine-treatment (*FDA safety communication [clozapine] 2015*).
- Post-marketing reports of intense urges, particularly for gambling, have been reported in patients taking aripiprazole and brexpiprazole. Other compulsive urges include: sexual urges, shopping, eating or binge eating, and other compulsive behaviors. Dose reductions or stopping aripiprazole and brexpiprazole should be considered.
- In 2018, the FDA completed an analysis of reported postmarketing deaths and serious adverse events with the use of pimavanserin, including those reported to the FDA Adverse Event Reporting System (FAERS). The FDA did not identify any new or unexpected safety findings, or findings inconsistent with the established safety labeling. The FDA's

conclusion was that the benefits of pimavanserin outweighed its risks for patients with hallucinations and delusions of Parkinson's disease psychosis (*FDA Drug Safety and Availability 2018*).
  - In assessing the reports of deaths, FDA considered that patients with Parkinson's disease have psychosis, a higher mortality rate due to their older age, advanced Parkinson's disease, and other medical conditions. In FAERS reports that included a cause of death, there was no evident pattern to suggest a drug effect (*FDA Drug Safety and Availability 2018*).
- Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at an increased risk of extrapyramidal and/or withdrawal symptoms. Neonates exposed to fluoxetine, a component of Symbyax, late in the third trimester have developed complications arising immediately upon delivery requiring prolonged hospitalization, respiratory support, and tube feeding. These drugs should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In general, a decision should be made whether to discontinue nursing or to discontinue the antipsychotic drug, taking into account the importance of the drug to the mother. It is recommended that women do not breastfeed during treatment with clozapine, iloperidone, lumateperone, and olanzapine,.
- Many factors are taken into consideration when prescribing an atypical antipsychotic, including co-morbid conditions and safety risks. Common adverse events observed within the class include EPS, sedation, increased prolactin levels, autonomic effects, metabolic effects, and cardiac risks including the risk of ventricular arrhythmias (QT prolongation). Table 3 outlines the relative adverse event trends observed between the various atypical antipsychotic agents:

Table 3. Relative adverse event risk observed in trials for atypical antipsychotic agents

Adverse Event	Aripiprazole	Asenapine	Brexpiprazole	Cariprazine	Clozapine*	Iloperidone	Lumateperone	Lurasidone	Olanzapine	Paliperidone	Pimvanserin	Quetiapine	Risperidone	Ziprasidone
Sedation – sleepiness	Low	Moderate	Moderate	Moderate	High	Moderate	Low	Moderate	High	Low	Low	High	Moderate	Moderate
Diabetes	Low	Moderate	Low	Low	High	Moderate	Low	Moderate	High	Low	Low	Moderate	Moderate	Low
EPS – akathisia (motor restlessness), parkinsonism (tremor, rigidity, and slow movements), dystonia (continuous muscle spasms or contractions), and tardive dyskinesia (jerky movements)	Low	Low to moderate	Low to moderate	Low to moderate	Low	Low	Low	Moderate	Low to moderate	Moderate	Low	Low	Moderate	Low to moderate
Anticholinergic – blurred vision, constipation, dry mouth, drowsiness, memory impairment, etc.	Low	Low	Low	Moderate	High	Low	Low	Low	Moderate	Low	Low	Moderate	Low	Low
Orthostasis – low blood pressure resulting in dizziness when standing up	Low	Moderate	Low	Low	High	High	Low	Low	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Weight Gain	Low	Moderate	Low	Moderate	High	Moderate	Low	Low	High	Moderate	Negligible	Moderate	Moderate	Low
Prolactin – high levels linked to gynecomastia, sexual dysfunction, menstrual disruption, acne, amenorrhea, hirsutism, osteoporosis, increased risk of hip fracture, etc.	Low	Moderate	Low	Low	Low	Moderate	Low	Low	Moderate	High	Low	Low	High	Moderate
QT prolongation	Negligible to low	Low	Negligible to low	Negligible to low	Moderate	Low	Negligible to low	Negligible to low	Moderate	Low	Low	Moderate	Moderate	High
Hypercholesterolemia	Low	Moderate	Moderate	Low	High	Low	Low	Moderate	High	Moderate	Low	High	Low	Low

Abbreviation: EPS = extrapyramidal side effects
Note: Information is based on indirect comparisons and expert assessments; however, more head-to-head trials are warranted to substantiate observations
*Granulocytopenia or agranulocytosis has been reported in 1% of patients. Clozapine is associated with an excess risk of myocarditis and venous thromboembolism (VTE), including fatal pulmonary embolism (PE).

(*Jibson et al 2021*)

DOSING AND ADMINISTRATION

Table 4. Dosing and administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Abilify (aripiprazole)	Tablet, tablet with sensor (drug/device), orally disintegrating tablet, oral solution	Oral	Daily Tablet with sensor has a patch which should be changed weekly or sooner, as needed.	Dose adjustments are recommended in known CYP2D6 poor metabolizers, or with concomitant CYP2D6 inhibitors, and/or CYP3A4 inhibitors/inducers. The MyCite (tablet with sensor) system is composed of an ingestible event marker (IEM) sensor, MyCite patch (wearable sensor), MyCite app, and a web-based portal for healthcare professionals and caregivers. Tablets with sensor may be administered with or without food. Most ingestions will be detected in 30 minutes to 2 hours. Patients should be instructed not to repeat doses if not detected.
Abilify Maintena (aripiprazole ER)	Injection	IM	Monthly	Must be administered by a healthcare professional. Dose adjustments are recommended in known CYP2D6 poor metabolizers, or with concomitant CYP2D6 inhibitors, and/or CYP3A4 inhibitors/inducers. Aripiprazole-naïve patients should establish tolerability with oral formulations prior to initiating long-acting injections.
Aristada (aripiprazole lauroxil)			Monthly (441 mg, 662 mg, or 882 mg) or every 6 weeks (882 mg) or every 2 months (1064 mg)	
Aristada Initio (aripiprazole lauroxil)			One dose of Aristada Initio 675 mg and aripiprazole 30 mg orally with the first Aristada injection	
Saphris (asenapine)	Sublingual tablet	Oral	Twice daily	Sublingual tablets should be placed under the tongue and left to dissolve completely; they should not be swallowed. Eating and drinking should be avoided for 10 minutes after administration.
Secuado (asenapine)	Patch	Transdermal	Daily	Patch should be applied once daily and left in place for 24 hours.
Rexulti (brexpiprazole)	Tablet	Oral	Daily	Dose adjustments are recommended in known CYP2D6 poor metabolizers and in

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				concomitant CYP3A4 or CYP2D6 inhibitors, and/or strong CYP3A4 inducers. Dosage adjustments are recommended for hepatic and renal impairment.
Vraylar (cariprazine)	Capsule, therapy pack	Oral	Daily	Dose adjustments are recommended with concomitant CYP3A4 inhibitors. Concomitant use is not recommended with CYP3A4 inducers. Use of the drug is not recommended in severe hepatic or renal impairment since it has not been studied in these populations.
Clozaril (clozapine)	Tablet	Oral	Once or twice daily	Prior to initiating, a baseline ANC must be ≥ 1500/mcL (≥ 1000/mcL for patients with BEN). To continue treatment, ANC must be monitored regularly. Dose adjustments are recommended in patients with renal/hepatic impairment, CYP2D6 poor metabolizers, taking concomitant CYP2D6, CYP1A2, CYP3A4 inhibitors and/or CYP3A4, CYP1A2 inducers.
Clozapine	Orally disintegrating tablet			
Versacloz (clozapine)	Suspension			
Fanapt (iloperidone)	Tablet	Oral	Twice daily	Dose adjustments are recommended in patients with hepatic impairment, CYP2D6 poor metabolizers, taking concomitant CYP2D6 and/or CYP3A4 inhibitors.
Caplyta (lumateperone)	Capsule	Oral	Once Daily	Should be administered with food. Moderate or strong CYP3A4 inhibitors and CYP3A4 inducers; moderate or severe hepatic impairment: Avoid concomitant use.
Latuda (lurasidone)	Tablet	Oral	Daily	Dose adjustment recommended with concomitant use with a moderate CYP3A4 inhibitor and renal/hepatic impairment. Do not use with strong CYP3A4 inhibitors/inducers. Should be administered with food (≥ 350 calories).
Zyprexa (olanzapine)	Tablet	Oral	Daily	
Zyprexa Zydis (olanzapine)	Orally disintegrating tablet			

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Zyprexa IntraMuscular (olanzapine)	Injection	IM	As needed; max. 3 doses 2 to 4 hrs apart	
Zyprexa Relprevv (olanzapine ER)	Injection	IM	Every 2 weeks (initial: 210 mg or 300 mg; maintenance: 150 mg, 210 mg, or 300 mg) or every 4 weeks (initial: 405 mg; maintenance: 300 mg or 405 mg)	This product is available only through a restricted distribution program and must be administered by a healthcare professional; patient observation is required for at least 3 hours after injection due to the potential for Post-Injection Delirium/Sedation Syndrome. Tolerability with oral olanzapine must be established prior to initiating therapy with this long-acting injection.
Symbyax (olanzapine/fluoxetine)	Capsule	Oral	Daily	The safety of doses above 18 mg/75 mg has not been evaluated in clinical studies. The safety of doses above 12 mg of olanzapine and 50 mg of fluoxetine has not been evaluated in pediatric clinical studies. Start olanzapine/fluoxetine at 3 mg/25 mg or 6 mg/25 mg in patients with a predisposition to hypotensive reactions, patients with hepatic impairment, or patients who exhibit a combination of factors that may slow the metabolism of olanzapine/fluoxetine (female gender, geriatric age, nonsmoking status).
Invega (paliperidone ER)	Tablet	Oral	Daily	Tablets should be swallowed whole and should not be chewed, divided, or crushed.
Invega Sustenna (paliperidone ER)	Injection	IM	Monthly	Must be administered by a healthcare professional. Dosage adjustment for renal impairment. For patients naïve to oral paliperidone or oral or injectable risperidone, tolerability with oral paliperidone or oral risperidone must be established prior to initiating therapy with this long-acting injection.
Invega Trinza (paliperidone ER)	Injection	IM	Every 3 months	Must be administered by a healthcare professional. Prior to initiation, patients must have been adequately treated with Invega Sustenna for at least 4 months. Dosage adjustment for renal impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Nuplazid (pimavanserin)	Tablet, capsule	Oral	One 34 mg capsule once daily; or one 10 mg tablet with strong CYP3A4 inhibitors	No initial dosage titration. Dosage adjustment is required with concomitant use with strong CYP3A4 inhibitors; avoid use with strong or moderate CYP3A4 inducers.
Seroquel (quetiapine)	Tablet	Oral	Daily to twice daily	Dosage adjustment for hepatic impairment, geriatric use, and with concomitant CYP3A4 inhibitors and/or inducers.
Seroquel XR (quetiapine ER)	Tablet	Oral	Daily	Tablets should be swallowed whole and not split, chewed, or crushed. Dosage adjustment for hepatic impairment, geriatric use, and with concomitant CYP3A4 inhibitors and/or inducers
Risperdal (risperidone)	Tablet, oral solution	Oral	Daily to twice daily	Dosage adjustment for renal/hepatic impairment.
Risperdal M-Tabs (risperidone)	Orally disintegrating tablet			
Risperdal Consta (risperidone microspheres)	Injection	IM	Every 2 weeks	Must be administered by a healthcare professional. Tolerability to oral risperidone must be established prior to initiating therapy with this long-acting injection.
Perseris (risperidone ER)		SC	Monthly	
Geodon (ziprasidone)	Capsule	Oral	Twice daily	Give capsules with food. IM ziprasidone should be administered with caution to patients with impaired renal function as the cyclodextrin excipient is cleared by renal filtration.
	Injection	IM	As needed; 10 mg every 2 hrs or 20 mg every 4 hrs up to a maximum of 40 mg/day	

See the current prescribing information for full details.

CONCLUSION

- The antipsychotics are divided into 2 distinct classes: typical antipsychotics, also called FGAs, and atypical antipsychotics, also called SGAs (*Miyamato et al 2005*).
- There are a number of atypical antipsychotic formulations available as both branded and generic products. These agents are available in various dosage forms including capsules, tablets, injections, oral solutions, sublingual tablets, and orally disintegrating tablets.
- FDA-approved indications for the atypical antipsychotics include irritability associated with autistic disorder, bipolar disorder, Tourette's disorder, MDD, schizophrenia, schizoaffective disorder, and PD psychosis. The indications vary by diagnosis, age, or by use as mono- or adjunctive-therapy. All agents in this class are indicated for use in schizophrenia with the exception of the combination agent Symbyax (olanzapine/fluoxetine) and pimavanserin. Clozapine and paliperidone products, excluding Invega Trinza, are indicated for the treatment of schizoaffective disorder, and clozapine

is the only agent in this class FDA-approved for treatment-resistant schizophrenia. Aripiprazole, lurasidone, olanzapine, quetiapine and risperidone are approved for use in patients ≥ 13 years of age and paliperidone oral products are approved for patients ≥ 12 years of age with schizophrenia. All oral agents in this class are indicated for use in bipolar disorder, except clozapine, iloperidone, lumateperone, paliperidone, pimavanserin, and brexpiprazole. Risperdal Consta and Abilify Maintena are the only long-acting injectables indicated for the treatment of bipolar disorder. Aripiprazole, olanzapine/fluoxetine, risperidone, quetiapine, lurasidone, and asenapine are approved for use in pediatric patients ≥ 10 years of age with bipolar disorder. Olanzapine is approved for use in patients ≥ 13 years of age with bipolar disorder. Aripiprazole and risperidone are the only agents indicated for the treatment of irritability associated with autistic disorder in pediatric patients (aged 6 to 17 years, and 5 to 17 years, respectively). Aripiprazole is the only agent indicated for the treatment of Tourette's disorder in pediatric patients, aged ≥ 6 years. Aripiprazole, brexpiprazole, and quetiapine ER are indicated as adjunctive treatment for MDD in patients already taking an antidepressant. Olanzapine, when prescribed in combination with fluoxetine, is indicated for treatment-resistant depression. Pimavanserin is the only agent in the class FDA-approved for treatment of PD psychosis.

- Comparative effectiveness data are most available for the treatment of schizophrenia and schizophrenia-like psychosis in adults; however, outcomes are often inconsistent. Study evidence demonstrates that there are no consistent differences in the efficacy between the atypical antipsychotics in acute or short-term trials, although clozapine has often been touted as significantly more effective for patients with treatment-resistant schizophrenia compared to all other atypical antipsychotics (*Leucht et al 2013, Lieberman et al 2005, Stroupe et al 2006, Stroupe et al 2009, Huhn et al 2019*). In general, clozapine is often followed by olanzapine and risperidone in terms of improved efficacy (*Leucht et al 2013*). There is also very little evidence evaluating the long-acting injection agents and newer agents brexpiprazole, cariprazine, iloperidone, and lurasidone. Challenges associated with comparative effectiveness reviews are mainly due to high attrition rates, internal validity study concerns, and small sample sizes within trials. In general, antipsychotics differ more in their side effects than efficacy, thus choice of therapy should be individualized.
- Each atypical antipsychotic has a distinctive chemical structure, mechanism of action, and neuropharmacologic and adverse event profile. It should be noted that paliperidone is an active metabolite of risperidone and therefore carries some similarity in chemical structure and pharmacologic effects with the parent drug. Plasma levels of cariprazine and its metabolite accumulate over time; adverse reactions may not appear until after several weeks of drug administration.
- Safety profiles vary between agents and are often an important component of treatment selection. The long-acting injection antipsychotics are often prescribed for patients who demonstrate adherence issues with oral formulations. Common adverse events observed within the class include EPS, increased prolactin levels, autonomic effects, metabolic effects, and cardiac risks including risk of ventricular arrhythmias (QT prolongation). When compared to the typical antipsychotics, the atypical antipsychotics are associated with a lower risk of EPS and tardive dyskinesia, making them a generally better-tolerated treatment option (*Abou-Setta et al 2012, Clinical Pharmacology 2021*). However, certain atypical antipsychotic agents appear to have varying levels of risk according to the side effect profile (*Jibson et al 2021*). The following factors may be considered when selecting certain agents in patients:
  - Metabolic syndrome – Metabolic effects influencing weight gain, glycemic effects, and lipid profiles have been reported to fluctuate with all atypical antipsychotics. Clozapine and olanzapine have been associated with the highest risks; aripiprazole, lurasidone, and ziprasidone have been associated with lower risks. Despite the stratified risks, routine monitoring of metabolic measures is recommended for patients on all antipsychotics.
  - EPS or tardive dyskinesia – Atypical antipsychotics have a lower risk of these side effects compared to typical antipsychotic agents. Tardive dyskinesia risks have been reported to be similar to the prevalence of EPS. Risperidone has been associated with a higher risk of EPS (up to 25% in adults); clozapine and quetiapine carry the lowest risk.
  - Anticholinergic effects – Anticholinergic side effects include dry mouth, constipation, blurred vision, and urinary retention. Clozapine has the strongest affinity for muscarinic receptors among the agents in this class review; therefore, anticholinergic side effects are reported most often. This is followed by olanzapine and quetiapine.
  - QT prolongation – QT prolongation has been reported with a number of atypical antipsychotic agents, but to a lesser degree than other classes of medications. Iloperidone and ziprasidone have been reported to prolong the QT interval (average increase in QTc of 9 to 10 msec) most often, and should be avoided in high risk patients. Those less likely to cause cardiac arrhythmias include aripiprazole, lurasidone, and cariprazine; however, very few studies have been conducted with lurasidone and cariprazine.
  - Myocarditis and cardiomyopathy – Clozapine has been associated with fatal cases, often within the first few months of treatment.

- Orthostatic hypotension and tachycardia – Changes in heart rate and blood pressure are most frequently observed with clozapine (9% to 25%) and iloperidone (3% to 12%). In pediatric patients, quetiapine has been associated with increased systolic/diastolic pressure in 15% to 41% of patients, but in adults orthostatic hypotension and tachycardia have been reported in up to 7% of patients. Tachycardia has been reported in up to 16% of paliperidone-treated adult patients. Hypotension has been reported less frequently with aripiprazole, asenapine, brexpiprazole, cariprazine, lurasidone, and pimavanserin. However, fewer studies have been conducted with the newer agents.
- Seizure – All atypical antipsychotics carry a risk for seizures; however, this appears to be associated with lowering the seizure threshold vs new-onset seizures. Incidences of seizure are most often reported with clozapine (3% to 5%), and to a lesser degree risperidone (0.3%).
- Prolactin levels and sexual side effects – Elevations of prolactin have been most associated with risperidone and paliperidone. This is particularly concerning in pediatric patients as it is associated with changes in estrogen and testosterone levels and may result in gynecomastia and menstrual disturbances. In pediatric patients administered risperidone, hyperprolactinemia has been reported in 49% to 87% of patients versus adults in which incidences range from 1% to 4% depending on formulation (IM or oral routes). Abnormal prolactin levels have also been associated with sexual dysfunction, infertility and galactorrhea. Of the atypical antipsychotics that are well studied, prolactin abnormalities are less frequently reported with olanzapine and ziprasidone. For patients in which sexual dysfunction is a concern, a number of MAs have referred to aripiprazole as the drug of choice (*Serretti et al 2011*).
- Sedation – Clozapine is most associated with sedation (46%), followed by olanzapine (20% to 52%) and quetiapine (18% to 57%). In this class, aripiprazole is unique as insomnia was reported in ≥ 10% of adult patients, but somnolence/fatigue and insomnia were reported in ≥ 10% of pediatric patients.
- Agranulocytosis – Agranulocytosis, leukopenia, and neutropenia are associated with use of clozapine. Within the first few months of treatment, this is particularly evident in patients with pre-existing low blood counts or those who had prior drug-induced blood dyscrasias.
- Hypersensitivity – Olanzapine and ziprasidone have a specific warning for a fatal drug reaction with eosinophilia and systemic symptoms or DRESS. Asenapine has a warning for hypersensitivity reactions.

- Cariprazine, has demonstrated safe and effective use in doses ≤ 6 mg/day for the treatment of bipolar disorder or schizophrenia in short-term adult trials (*Calabrese et al 2015, Durgam et al 2015[a], Durgam et al 2014, Durgam et al 2015[b], Earley et al 2020, FDA/CBER summary review 2015, Kane et al 2015[b], Sachs et al 2015*). The most common adverse events with treatment are EPS and akathisia. The clinical implications of the long half-life have not been well characterized and some experts have cited safety concerns associated with the accumulating active metabolite. One 72-week (N = 264) and one 48-week (N = 97) extension trial in patients with schizophrenia have demonstrated comparable results to short-term trials of 6 weeks. Patients who are able to persist on treatment maintained efficacy and tolerability at cariprazine doses of 1.5 mg to 9 mg daily during maintenance therapy (*Durgam et al 2016, Durgam et al 2017*).
- For the treatment of Tourette's disorder, aripiprazole has demonstrated safe and effective use compared to placebo in trials of 8 to 10 weeks in pediatric patients aged ≥ 6 years. Adverse events most frequently observed included sedation-like effects, nausea, headache, nasopharyngitis, and increased appetite (*Abilify prescribing information 2020*, *Gulisano et al 2011, Yoo et al 2013*).
- For the treatment of irritability associated with autism, one small, low quality study (N = 59) compared the effects of aripiprazole and risperidone in patients aged 4 to 18 years over a period of 8 weeks, although FDA-approval stipulates therapy should be initiated for ages 5 to 6 years. No differences were detected in terms of safety or efficacy; however, the ABC-I scores numerically favored risperidone (p = 0.06) (*Ghanizadeh et al 2014*). Both agents have demonstrated safe and effective use in PC trials (*Marcus et al 2009, McCracken et al 2002, Owen et al 2009, Shea et al 2004, McDougle et al 2005*). Based on current data, both agents appear to have similar efficacy and safety.
- For the treatment of PD psychosis, pimavanserin has demonstrated safe and effective use compared to placebo. Pimavanserin was associated with a significantly lower incidence of orthostatic hypotension *(Cummings et al 2014, Yasue et al 2016, Bozymski et al 2017).*
- For the treatment of MDD, aripiprazole, brexpiprazole, and quetiapine ER have demonstrated effectiveness when combined with adjunctive treatment, generally in trials with a 6-week duration and combined with an SSRI or SNRI. Olanzapine/fluoxetine (Symbyax) has also demonstrated effectiveness in treatment-resistant depression. Most studies have been PC trials. Brexpiprazole is the newest agent to be FDA approved; results from RCTs and an MA demonstrate efficacy vs placebo, and the safety profile appears to be similar to aripiprazole (*Thase et al 2015[a], Thase et al 2015[b]*, *Yoon et al 2017*). One MA found all agents were more effective than antidepressant monotherapy in improving response and remission rates, although adjunctive atypical antidepressant therapy was associated with a higher discontinuation

rate due to adverse effects (*Wen et al 2014*). Another MA concluded aripiprazole and quetiapine may have an advantage in reducing remission (NNT, 9) compared to olanzapine/fluoxetine (NNT, 19) (*Spielmans et al 2013*). More well-designed, head-to-head trials are needed to validate conclusions. Treatment was associated with several medication-specific adverse events, including akathisia (aripiprazole), sedation (quetiapine, olanzapine/fluoxetine, and aripiprazole), abnormal metabolic laboratory results (quetiapine and olanzapine/fluoxetine), and weight gain (all drugs, especially olanzapine/fluoxetine).

- For the treatment of bipolar disorder, a number of atypical antipsychotics have demonstrated effective use for managing symptoms associated with manic or mixed episodes; however, only a few agents have demonstrated efficacy for depressive episodes. In adolescents and children, aripiprazole, olanzapine, olanzapine/fluoxetine, risperidone, quetiapine, and asenapine are FDA-approved for manic or mixed episodes, although only quetiapine and olanzapine/fluoxetine have been studied for depressive episodes. An AHRQ SR found that atypical antipsychotics decrease mania, decrease depression symptoms slightly, and improve symptom severity and global functioning to a small extent vs placebo. In addition, they probably increase response and remission rates vs placebo for manic/mixed phases (*Pillay et al 2017*). For depressive episodes, evidence is less clear, but point to efficacy with the FDA approved agents (*Findling et al 2014, Detke et al 2015*). Support for use of atypical antipsychotics in adult patients with bipolar disorder has been demonstrated in several MAs (*Abou-Setta et al 2012, Muralidharan et al 2013, Lindström et al 2017*). Risperdal Consta (risperidone microspheres) and Abilify Maintena are the only long-acting injection agents in this class that have demonstrated safe and effective use (*Calabrese et al 2017, Macfadden et al 2009, Quiroz et al 2010, Vieta et al 2012, Yatham et al 2007*). Although only lurasidone, quetiapine (immediate- and extended-release), and olanzapine/fluoxetine have demonstrated efficacy for depressive episodes, MAs have concluded that olanzapine/fluoxetine may be the optimal treatment compared to other treatment options for depressive episodes (*Fornaro et al 2016, Silva et al 2013, Taylor et al 2014, Vieta et al 2010*).
- For the treatment of schizophrenia, MAs evaluating the roles of available atypical antipsychotics in the treatment of schizophrenia suggest that all agents are significantly more effective than placebo. Most analyses and studies have demonstrated that with the exception of clozapine, the atypical antipsychotics do not separate out robustly from the typical antipsychotics with respect to overall efficacy and times to treatment discontinuation. The trends for respective efficacy suggest that clozapine, olanzapine, and risperidone may be more effective agents based on relapse and remission rates compared to typical antipsychotics or placebo; however, many atypical antipsychotics haven't been studied to the same extent as these agents. In general, due to high attrition rates in trials, validity is limited, thereby making it difficult to make strong conclusions (*Abou-Setta et al 2012, Asenjo Lobos et al 2010, Asmal et al 2013, Cipriani et al 2011, Citrome et al 2009, Durgam et al 2014, Durgam et al 2015[b], Glick et al 2011, Jones et al 2010, Kane et al 2015[b], Khanna et al 2014, Klemp et al 2011, Komossa et al 2009[a], Komossa et al 2010[a], Komossa et al 2009[b], Komossa et al 2010[b], Komossa et al 2011, Kumar et al 2013, Leucht et al 2009[a], Leucht et al 2009[b], Leucht et al 2013, Lieberman et al 2005, Pagsberg et al 2017, Perlis et al 2006[b], Pillay et al 2017, Riedel et al 2010, Stroupe et al 2006, Stroupe et al 2009, Tarr et al 2011, Vieta et al 2010, Yildiz et al 2011*).
- The use of these agents for the treatment of schizophrenia is recognized by national and international guidelines as a mainstay in therapy. Guidelines vary by indication and the following outlines use in children, adolescents, and adults:

<u>Adults</u>

  - MDD – For the majority of patients, an SSRI, SNRI, bupropion or mirtazapine is optimal for first-line treatment. Atypical antipsychotics may be useful to augment antidepressant therapy (*APA 2010, Qaseem et al 2016, Va/DoD 2016*).
  - Bipolar Disorders - recent guidelines from CANMAT/ISBD and WFSBP have recommended clear first line pharmacological therapies for various stages of bipolar disease. These include second generation antipsychotics, lithium, valproate, divalproex and lamotrigine as monotherapy or combination therapy.
  - Schizophrenia –Guidelines state that an evidence-based ranking of atypical antipsychotics or an algorithmic approach to antipsychotic selection is not possible due to the significant heterogeneity in clinical trial designs, the limited number of head-to-head comparisons, and the limited clinical trial data for a number of antipsychotics (*Keepers et al 2021*). There may be clinically meaningful distinctions in response or tolerability of the various atypicals in an individual patient; however, there is no definitive evidence that one atypical antipsychotic will have consistently superior efficacy compared with another, with the possible exception of clozapine. Specific factors that may influence choice of an atypical antipsychotic include available formulation, drug interactions, pharmacokinetic properties, and adverse effects.

- Parkinson's disease psychosis – The American Academy of Neurology Practice Parameter on the treatment of depression, psychosis, and dementia in PD states that clozapine should be considered for the treatment for PD and psychosis, quetiapine may be considered, and olanzapine should not be routinely considered (*Miyasaki et al 2006*).

Children and Adolescents

- Use of atypical antipsychotics - According to guidelines from the American Academy of Child and Adolescent Psychiatry (AACAP), prior to the initiation of antipsychotic therapy, patients should undergo a thorough diagnostic assessment and evaluation for comorbid medical conditions and concomitant medications. Furthermore, a multidisciplinary plan that includes education and psychotherapy should be established. The prescriber should also have a thorough discussion about the risks and benefits of psychotropic treatment (*Findling et al 2011*).
- Autism Spectrum Disorders (ASD) –
  - AACAP guidelines state that pharmacotherapy may be considered in children with ASD when there is a specific target symptom or comorbid condition. Risperidone and aripiprazole are FDA-approved for irritability associated with autism; other drugs that have been studied include: clonidine, olanzapine, valproic acid, lamotrigine, levetiracetam, clomipramine, amantadine, pentoxifylline (in combination with risperidone), and naltrexone (*Volkmar et al 2014*).
  - The 2019 (AAP) guideline for children with ASD suggests that pharmacotherapy is used to help manage coexisting behavioral health disorders (eg, ADHD, mood disorders, or anxiety disorders) and problem behaviors or symptoms causing significant impairment and distress including: aggression, self-injurious behavior, sleep disturbance, mood lability, anxiety, hyperactivity, impulsivity, inattention. The guideline recommends the use of SGAs (aripiprazole or risperidone) to manage irritability and/or aggression in ASD. There less evidence for the use of SGAs in decreasing hyperactivity; stimulants are recommended first line.
- Bipolar disorder – According to AACAP guidelines for treatment of children and adolescents with bipolar disorder, pharmacotherapy is the primary treatment for bipolar mania. Standard therapy includes lithium, valproate, and/or atypical antipsychotic agents, with other adjunctive medications used as indicated (*McClellan et al 2007*).
- Schizophrenia – According to AACAP guidelines, antipsychotics are a primary treatment for schizophrenia spectrum disorders in children and adolescents. The choice of agent is typically based on factors such as FDA-approval status, side effect profile, patient and family preference, and cost (*McClellan et al 2013*).
- Tourette's disorder– According to AACAP guidelines for the treatment of children and adolescents with tic disorders, pharmacotherapy should be considered for moderate to severe tics causing severe impairment in quality of life, or when psychiatric comorbidities are present that can also be targeted. Most clinicians use atypical antipsychotics before first-generation agents and some prefer α-agonists over antipsychotic medications due to the adverse effect profile. Commonly used drugs include risperidone, aripiprazole, and clonidine (*Murphy et al 2013*).

- Pharmacologic therapy treatment is highly individualized and dependent on a number of patient characteristics and response to treatment. In certain patient groups, such as pediatric patients, liquid formulations are useful for better dose-control, so clinicians may titrate and taper doses in those that may have sensitive responses to treatment. Agents with different chemical structures have different clinical responses and adverse events; therefore, access to the atypical antipsychotic medication class is important in order to tailor therapies to individual patients.

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Therapeutic Class Overview
Opioid Use Disorder Agents

INTRODUCTION

Products for Treatment of Opioid Dependence

- The American Psychiatric Association (APA) defines opioid use disorder as a syndrome characterized by a problematic pattern of opioid use, leading to clinically significant impairment or distress (*APA 2013*).
  - In 2015, approximately 2 million Americans had a substance use disorder involving prescription pain relievers and 591,000 had a substance use disorder involving heroin (*American Society of Addiction Medicine [ASAM] 2016*).
- Methadone, buprenorphine (with or without naloxone), and naltrexone are Food and Drug Administration (FDA)-approved for the detoxification and maintenance treatment of opioid dependence (*Micromedex 2021*).
  - Methadone products, when used for the treatment of opioid addiction in detoxification or maintenance programs, may be dispensed only by opioid treatment programs (and agencies, practitioners, or institutions by formal agreement with the program sponsor) certified by the Substance Abuse and Mental Health Services Administration (SAMHSA) and approved by the designated state authority. Certified treatment programs may dispense and use methadone in oral form only and according to the treatment requirements stipulated in the Federal Opioid Treatment Standards (Code of Federal Regulations, Title 42, Sec 8).
  - The Drug Addiction Treatment Act (DATA) of 2000 expanded the clinical context of medication-assisted opioid addiction treatment by allowing qualified physicians to dispense or prescribe specifically approved medications, like buprenorphine, for the treatment of opioid addiction in treatment settings other than the traditional Opioid Treatment Program. In addition, DATA reduced the regulatory burden on physicians who choose to practice opioid addiction therapy by permitting qualified physicians to apply for and receive waivers of the special registration requirements defined in the Controlled Substances Act (*SAMHSA statutes, regulations, and guidelines 2021*).
  - Naltrexone, an opioid antagonist, is only indicated for the prevention of relapse after opioid detoxification; patients must be opioid-free for at least 7 to 10 days prior to initiation of naltrexone therapy in order to avoid precipitation of withdrawal.
- All buprenorphine products are Schedule III controlled substances (*Drugs@FDA 2021*).
- In 2012, Reckitt Benckiser Pharmaceuticals notified the FDA that they were voluntarily discontinuing production of Suboxone (buprenorphine/naloxone) sublingual tablets as a result of increasing concerns over accidental pediatric exposure with the tablets; the unique child-resistant, unit-dose packaging of the film formulation is believed to be a contributing factor to reduce exposure rates in children. Generic formulations of the sublingual tablets remain available.
- In November 2017, the FDA approved Sublocade (buprenorphine ER) SC injection for the treatment of moderate to severe opioid use disorder in patients who have initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for a minimum of 7 days.
  - Sublocade is injected as a liquid and the subsequent precipitation of the polymer creates a solid depot, which contains buprenorphine. Buprenorphine is released via diffusion from, and the biodegradation of, the depot.
- On September 7, 2018, a new dosage strength of buprenorphine/naloxone sublingual films was approved by the FDA under the brand name Cassipa. However, the launch of this product has been delayed due to patent infringement claims made by the manufacturer of Suboxone. The current estimated launch date of Cassipa is unknown, and the FDA shows that the product has been discontinued (*Drugs@FDA 2021*).
- Lofexidine, an oral central alpha-2 agonist, was approved in May 2018 for the mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation in adults. This product is indicated for short-term use, up to 14 days, during the period of peak opioid withdrawal symptoms.
- Included in this review are the products that are FDA-approved to be used in the treatment of opioid dependence; however, methadone products are not included since they must be dispensed in an opioid treatment program when used for the treatment of opioid addiction in detoxification.
- Medispan Class: Opioid Use Disorder Agents; Agents for Chemical Dependency

Table 1. Medications for Treatment of Opioid Dependence Included Within Class Review

Drug	Generic Availability
Single-Entity Agents	
buprenorphine* sublingual tablet	✔
Lucemyra (lofexidine) tablet	-
naltrexone hydrochloride (HCl)* tablet	✔
Sublocade (buprenorphine) subcutaneous (SC) injection	-
Vivitrol (naltrexone) intramuscular (IM) injection	-
Combination Products	
Bunavail (buprenorphine/naloxone) buccal film‡	-
buprenorphine/naloxone* sublingual tablets	✔
Suboxone (buprenorphine/naloxone) sublingual film	✔
Zubsolv (buprenorphine/naloxone) sublingual tablets	-

* Brand name product was discontinued; however, generic formulations are available.
‡ Product was discontinued; the expiration dates of the last manufactured batches range from February to October 2021.

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

Products for Emergency Treatment of Opioid Overdose

- Opiate overdose continues to be a major public health problem in the United States (U.S.). It has contributed significantly to accidental deaths among those who use or abuse illicit and prescription opioids. Overdose deaths involving opioids accounted for more than 70% of the nearly 71,000 drug overdose deaths in 2019, exceeding the number of deaths caused by motor vehicle crashes (*Centers for Disease Control and Prevention 2021*).
- Death following opioid overdose can be averted by emergency basic life support and/or the timely administration of an opioid antagonist such as naloxone. Naloxone is a narcotic antagonist that displaces opiates from receptor sites in the brain and reverses respiratory depression, which is usually the cause of overdose deaths (*SAMHSA 2018, World Health Organization [WHO] 2014*).
- Naloxone is provided to patients through the regular course of medical care, by pharmacist-initiated collaborative practice agreements, or through community-based opioid overdose prevention programs (*Doe-Simkins 2014*).
- Recognizing the potential value of providing naloxone to laypersons, most states have passed laws and changed regulations authorizing prescribers to provide naloxone through standing orders and/or to potential overdose witnesses as well as protecting those who administer naloxone from penalties for practicing medicine without a license (*Morbidity and Mortality Weekly Report [MMWR] 2012, Coffin 2021*).
- In December 2018, the U.S. Department of Health & Human Services (HHS) recommended prescribing or co-prescribing naloxone to all patients who are at risk for opioid overdose, including: patients receiving opioids at a dosage of 50 milligram morphine equivalents (MME) per day or greater; patients with respiratory conditions who are prescribed opioids; patients who have been prescribed benzodiazepines along with opioids; and patients prescribed opioids who have a non-opioid substance use disorder, report excessive alcohol use, or have a mental health disorder (*HHS 2018*).
- In patients with opioid overdose, naloxone begins to reverse sedation, respiratory depression, and hypotension within 1 to 2 minutes after intravenous (IV) administration, 2 to 5 minutes after IM or SC administration, and 8 to 13 minutes after intranasal (IN) administration. Since the half-life of naloxone is much shorter than that of most opioids, repeated administration may be necessary (*Lexicomp 2021)*.
- Naloxone was first approved by the FDA in 1971. In November 2015, the FDA approved the first IN formulation of naloxone (Narcan nasal spray). Prior to the approval of these products, naloxone was only available in glass vials and ampules, which were distributed with syringes and needles for manual injection or with syringes and atomizers for off-label IN administration.
- Included in this review are the naloxone products that are FDA-approved for opioid overdose.
- Medispan Class: Opioid Antagonists

Table 2. Medications for Emergency Treatment of Opioid Overdose Included Within Class Review

Drug	Generic Availability
naloxone HCl* injection	✔
Narcan (naloxone HCl) nasal spray	-†
Kloxxado, (naloxone HCl) nasal spray	-

* Brand name product was discontinued; however, generic formulations are available.
† Generic product for Narcan approved by the FDA, but not yet launched due to patent litigation.

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

INDICATIONS

Table 3. FDA-Approved Indications for Buprenorphine and Buprenorphine/Naloxone Products

Indication	Single-Entity Agents		Combination Products			
	Sublocade (buprenorphine) SC injection	buprenorphine sublingual tablets	Bunavail (buprenorphine/ naloxone) film	buprenorphine/ naloxone sublingual tablets	Suboxone (buprenorphine/ naloxone) Film	Zubsolv (buprenorphine/ naloxone) sublingual tablets
Treatment of opioid dependence			✔		✔	✔
Treatment of opioid dependence and is preferred for induction		✔				
Maintenance treatment of opioid dependence				✔		
Treatment of moderate to severe opioid use disorder*	✔					

*For use in patients who initiated treatment with a transmucosal buprenorphine-containing product, followed by dose adjustment for at least 7 days.
(*Prescribing information: buprenorphine sublingual tablets 2021, buprenorphine/naloxone sublingual tablets 2021, Bunavail 2021, Sublocade 2021, Suboxone film 2021, Zubsolv 2021*)

Table 4. FDA-Approved Indications for Naltrexone Agents Used in Opioid Dependence

Indication	naltrexone HCl tablets	Vivitrol (naltrexone HCl) injection
Blockade of the effects of exogenously administered opioids	✔	
Treatment of alcohol dependence	✔	✔
Prevention of relapse to opioid dependence following opioid detoxification		✔

(*Prescribing information: naltrexone tablets 2017, Vivitrol 2021*)

Table 5. FDA-Approved Indications for Other Agents Used in Opioid Dependence

Indication	Lucemyra (lofexidine) tablets
Mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation	✔

(*Prescribing information: Lucemyra 2020*)

Table 6. FDA-Approved Indications for Naloxone Products

Indication	Kloxxado (naloxone HCl) nasal spray	naloxone HCl injection	Narcan (naloxone HCl) nasal spray
Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or CNS depression			✔
Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or CNS depression, for adult and pediatric patients	✔		
Complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids, including propoxyphene, methadone, and certain mixed agonist-antagonist analgesics: nalbuphine, pentazocine, butorphanol, and cyclazocine.		✔	
Diagnosis of suspected or known acute opioid overdosage		✔	
Adjunctive agent to increase blood pressure in the management of septic shock		✔	

Abbreviations: CNS= central nervous system

(*Prescribing information: Kloxxado 2021, naloxone injection 2021, Narcan nasal spray 2020*)

Limitations of use

- Prescription of Narcan nasal spray 2 mg should be restricted to opioid-dependent patients expected to be at risk for severe opioid withdrawal in situations where there is a low risk for accidental or intentional opioid exposure by household contacts.
- Naloxone nasal spray (Narcan, Kloxxado) is not a substitute for emergency medical care.

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

CLINICAL EFFICACY SUMMARY

Products for Treatment of Opioid Dependence

- Clinical trials have demonstrated that buprenorphine/naloxone is practical and safe for use in diverse community treatment settings including primary care offices (*Amass et al 2004, Fiellin et al 2014*).
- Studies have shown that in adult patients with opioid dependence, the percentage of opioid-negative urine tests was significantly higher for both buprenorphine and buprenorphine/naloxone compared to placebo, while no significant difference was seen between the 2 active treatment groups (*Daulouède et al 2010, Fudala et al 2003*). In addition, a small randomized controlled trial (n = 32) also showed no significant difference in withdrawal symptoms between buprenorphine and buprenorphine/naloxone (*Strain et al 2011*).
- Several studies have compared the effectiveness of short-term detoxification to medium- or long-term maintenance treatment with buprenorphine monotherapy or buprenorphine/naloxone. Three studies have shown higher treatment retention rates or lower self-reported drug use rates with longer treatment duration compared to detoxification; however, 1 of the studies showed no significant difference in the percentage of positive urine tests between the 2 treatment groups at 12 weeks (*Kakko et al 2003, Weiss et al 2011, Woody et al 2008*).
- In a meta-analysis of 21 randomized controlled trials, patients receiving buprenorphine at doses ≥ 16 mg/day were more likely to continue treatment compared to patients receiving doses < 16 mg/day; however, no significant difference was seen in the percentage of opioid-positive urine tests between the high- and low-dose groups (*Fareed et al 2012*).
- Studies that compared different dosing regimens of buprenorphine showed no difference in rate of treatment retention, percentage of urine tests positive for opioids, or withdrawal symptoms (*Bickel et al 1999, Gibson et al 2008, Petry et al 1999, Schottenfeld et al 2000*).
- One study found that buprenorphine/naloxone sublingual film was comparable to the sublingual tablet form in dose equivalence and clinical outcomes (*Lintzeris et al 2013*).

- A randomized, parallel-group, noninferiority trial (n = 758) found that for the treatment of patients with opioid dependence, Zubsolv (buprenorphine/naloxone) sublingual tablets was noninferior to generic buprenorphine sublingual tablets during induction and was noninferior to buprenorphine/naloxone sublingual film during early stabilization (*Gunderson et al 2015*).
- Buprenorphine has been compared to methadone in several clinical studies and reviewed in multiple meta-analyses. Most studies have demonstrated that buprenorphine-based therapy was as effective as methadone in the management of opioid dependence; however, some newer data suggest that buprenorphine may be superior in this regard (*Bahji et al 2019, Dalton et al 2019*, *Farré et al 2002, Gibson et al 2008, Gowing et al 2017, Johnson et al 1992, Kamien et al 2008, Law et al 2017, Meader 2010, Perry et al 2015, Petitjean et al 2001, Soyka et al 2008, Strain et al 2011).* In a 2019 meta-analysis (n = 150,235 patients across 32 cohort studies), overall mortality rates were higher with methadone vs buprenorphine; however, when comparing time in-treatment to time out-of-treatment, methadone significantly reduced mortality vs buprenorphine (*Bahji et al 2019*). In another meta-analysis that same year (n = 370,611 patients across 30 studies), buprenorphine demonstrated lower all-cause mortality post-medication assisted therapy (MAT) vs methadone or naltrexone. However, all-cause mortality during MAT was lowest with naltrexone, followed by buprenorphine and methadone (*Ma et al 2019*).
- A meta-analysis of 4 randomized controlled trials compared methadone versus buprenorphine (3 studies) or methadone versus slow-release morphine (1 study) in pregnant women with opioid-dependence *(Minozzi et al 2020).* Although the comparison of methadone versus buprenorphine was based on limited evidence, methadone and buprenorphine were generally found to be similar in safety and efficacy for pregnant women and their children based on available data.
- When low doses of buprenorphine were studied (≤ 8 mg/day), high doses of methadone (≥ 50 mg/day) proved to be more efficacious *(Farré et al 2002, Ling et al 1996, Mattick et al 2014, Schottenfeld et al 1997*).
- In another 2019 meta-analysis (n = 847 overdose events across 4 studies), there was no statistically significant difference for retention in treatment between patients who received buprenorphine/naloxone vs buprenorphine or methadone alone (*Dalton et al 2019*).
- In a 24-week, Phase 3, double-blind, placebo-controlled, randomized controlled trial (n = 504), the efficacy and safety of multiple SC injections of buprenorphine (100 mg and 300 mg) over 24 weeks were assessed in treatment-seeking patients with opioid use disorder. Buprenorphine injection was shown to be superior to placebo in achieving more illicit opioid-free weeks ($p < 0.0001$). The proportion of patients achieving treatment success (defined as any patient with at least 80% of urine samples negative for opioids combined with negative self-reports for illicit opioid use from week 5 through week 24) was statistically significantly higher in both groups receiving buprenorphine compared to the placebo group (28% [300 mg/100 mg], 29% [300 mg/300mg], and 2% [placebo]) ($p < 0.0001$) *(FDA Advisory Committee Briefing Document 2017, Haight et al 2019)*.
- Extended-release IM naltrexone was compared to buprenorphine/naloxone sublingual film in a 24-week, open-label, randomized controlled trial (n = 570). More induction failures were seen with extended-release IM naltrexone; as a result, in the intention-to-treat analysis, relapse-free survival was lower with extended-release IM naltrexone compared to sublingual buprenorphine/naloxone. However, among patients who were able to successfully initiate treatment, extended-release IM naltrexone had similar efficacy to buprenorphine/naloxone in terms of relapse prevention (*Lee et al 2018*). A longitudinal secondary analysis of this trial examined urine testing data for non-study opioids from the last 22 weeks of the 24-week trial. Investigators found that in the per protocol sample (n=474) of patients who took at least one dose of medication, patients who were taking buprenorphine/naloxone had significantly greater proportions of opioid-positive tests in 14 out of the 22 weeks, suggesting that extended-release naltrexone may offer benefit over buprenorphine/naloxone in reducing illicit opioid use during treatment in this sample. However, this difference was not noted in patients who completed (n=211) the entirety of treatment (*Mitchell et al 2021)*. A 12-week, randomized, open-label, noninferiority trial (n = 159) similarly found that extended-release IM naltrexone was noninferior to oral buprenorphine/naloxone in terms of negative urine drug tests and days of opioid use (*Tanum et al 2017).*
- In a meta-analysis examining the efficacy of oral naltrexone for maintenance treatment of opioid dependence, oral naltrexone was no better than placebo or any pharmacologic treatment in terms of treatment retention or use of the primary substance of abuse. Based on the results of 1 study, it was also not significantly different from buprenorphine for retention, abstinence, and side effects (*Minozzi et al 2011*). A small, randomized, open-label study (n = 60) found that patients receiving extended-release IM naltrexone were twice as likely to remain in treatment for 6 months compared to patients receiving oral naltrexone (*Sullivan et al 2019*).
- The safety and efficacy of lofexidine for inpatient treatment of opioid withdrawal symptoms was examined in an 8-day, randomized, double-blind, placebo-controlled trial (n = 264). In this study, patients treated with lofexidine had lower

scores on the Short Opioid Withdrawal Scale (SOWS) Gossop scale on day 3 compared to placebo. More patients in the placebo group terminated study participation early (*Gorodetzky et al 2017).* Similar results were found in another placebo-controlled trial *(Fishman et al 2019)*. Meta-analyses have found that although lofexidine reduces withdrawal symptoms compared to placebo, it is less effective than buprenorphine for managing opioid withdrawal in terms of withdrawal severity, withdrawal duration, and likelihood of treatment completion *(Gowing et al 2016, Gowing et al 2017)*. It is likely to be less effective than buprenorphine or methadone for opioid detoxification (*Meader 2010*).

Products for Emergency Treatment of Opioid Overdose

- The approval of Narcan nasal spray and Kloxxado nasal spray were based on pharmacokinetic bioequivalence studies comparing these products to a generic naloxone product, delivered SC or IM. No clinical studies were required by the FDA (*Prescribing information: Kloxxado 2021, Narcan 2020*).
  - The manufacturers also conducted a human factors validation study in which participants were asked to deliver a simulated dose of the drug to a mannequin without training and most demonstrated appropriate use of the device (*FDA Summary Review: Narcan nasal spray 2015*).
- Studies have suggested that IN naloxone is an effective option in the treatment of opioid overdose (*Kelly et al 2005, Kerr et al 2009, Merlin et al 2010, Robertson et al 2009, Sabzghabaee et al 2014*). However, results from a recent double-blind, double-dummy, randomized clinical trial found that IN naloxone may not reverse overdose as efficiently as IM naloxone, replicating findings from previous unblinded trials (*Dietze et al 2019*). Kloxxado nasal spray delivers 8 mg of naloxone, a higher dose than what is delivered by Narcan nasal spray, to treat opioid overdose (*Kloxxado Prescribing information 2021).* Future clinical trials are required to determine if this increased dose of IN naloxone impacts reversal compared to previous studies.
- A meta-analysis of naloxone studies found that lay administration of naloxone was associated with significantly increased odds of recovery compared with no naloxone administration (odds ratio, 8.58; 95% confidence interval [CI], 3.90 to 13.25) (*Giglio et al 2015*).
- A 2-year, non-randomized intervention study found that prescribing naloxone to patients who were prescribed long-term opioids for chronic pain was associated with a 47% decrease in opioid-related emergency visits per month after 6 months and a 63% decrease after 1 year compared to those who did not receive naloxone (*Coffin et al 2016*).
- A retrospective cohort study including 3,085 patients found that of out-of-hospital naloxone administration improved outcomes for approximately 73% of patients with presumed opioid overdose (*Ashburn et al 2020*).

CLINICAL GUIDELINES

- The American Academy of Pediatrics (AAP), APA, ASAM, SAMHSA, and the Veterans Health Administration (VHA) have published guidelines for the treatment of opioid dependence. In general, these guidelines support access to all FDA-approved pharmacological therapies for the management of opioid dependence. Buprenorphine/naloxone combination products may be used for induction and maintenance. In pregnant women for whom buprenorphine therapy is selected, buprenorphine alone (ie, without naloxone) is recommended. Naltrexone may be considered for the prevention of relapse, although outcomes with this medication are often adversely affected by poor adherence. Extended-release injectable naltrexone may reduce, but not eliminate, some of the problems with oral naltrexone adherence. The VHA guideline recommends extended-release injectable naltrexone if opioid agonist treatment is not feasible. (*CSUP 2016, Cunningham et al 2020, Kampman et al 2015, Kleber et al 2006, SAMHSA treatment improvement protocol 2021, VHA 2015*).
- Updated 2020 clinical practice guidelines from ASAM recommend against opioid withdrawal management on its own (ie, detoxification) due to the associated high risk of relapse and other safety concerns; treatment with ongoing maintenance medication therapy in combination with psychosocial treatment as appropriate is the standard of care for opioid use disorder *(Cunningham et al 2020).*
  - The ASAM specifically recommends using methadone or buprenorphine for opioid withdrawal management over abrupt cessation of opioids.
  - Opioid withdrawal management with buprenorphine should not be initiated until objective signs of opioid withdrawal are present.
  - Alpha-2 adrenergic agonists (eg, lofexidine and clonidine) are safe and effective for withdrawal management; however, methadone and buprenorphine are more effective in reducing withdrawal symptoms.

- Various organizations including the WHO and the ASAM have endorsed the availability of naloxone for patients, bystanders, and first responders for the emergency management of suspected opioid overdose. It is recommended that people who are likely to witness an overdose should have access to and be trained in the use of naloxone (*Cunningham et al 2020, WHO 2014*).
  - According to the WHO guidelines for community management of opioid overdose, naloxone is effective when delivered by IV, IM, SC, and IN routes of administration. Persons using naloxone should select a route of administration based on the formulation available, their skills in administration, the setting, and local context.

SAFETY SUMMARY

- In July 2020, the FDA issued a drug safety communication recommending that healthcare professionals discuss the availability of naloxone with all patients receiving opioid pain relievers and consider prescribing it for patients who are at high risk or have a close contact at risk of overdose or accidental ingestion (*FDA Drug Safety Communication 2020*).

Products for Treatment of Opioid Dependence

- Buprenorphine and buprenorphine/naloxone products are contraindicated in patients with known hypersensitivity to the active ingredients.
  - Buprenorphine products have several warnings and precautions, including abuse potential; respiratory depression; CNS depression; unintentional pediatric exposure; neonatal opioid withdrawal; adrenal insufficiency; risk of opioid withdrawal with abrupt discontinuation of treatment; hepatitis and hepatic events; hypersensitivity reactions; precipitation of opioid withdrawal signs and symptoms; use in patients with impaired hepatic function; impairment of ability to drive or operate machinery; orthostatic hypotension; elevation of cerebrospinal fluid pressure; elevation of intracholedochal pressure; and effects in acute abdominal conditions. It is strongly recommended to prescribe naloxone at the same time as buprenorphine (if not dispensing a combination buprenorphine/naloxone product) due to the potential for relapse and opioid overdose.
  - Concomitant use of buprenorphine with benzodiazepines or other CNS depressants increases the risk for adverse events, including overdose, respiratory depression, and death. Cessation of benzodiazepines or other CNS depressants is preferred in most cases of concomitant use. This additional warning was added to opioid products in February 2018 after data demonstrated an increased risk of mortality in patients receiving benzodiazepines while on opioid maintenance treatment (*Abrahamsson et al 2017, FDA Drug Safety Communication 2017*).
  - The buprenorphine SC injection also has several unique warnings and precautions, including serious harm or death if administered IV (boxed warning); risks associated with treatment of emergent acute pain; and use in patients at risk for arrhythmia.
  - In the treatment of addiction involving opioid use in pregnant women, the buprenorphine/naloxone combination product is not recommended for use (insufficient evidence); however, the buprenorphine monoproduct is a reasonable and recommended option for use.
  - Similar to other opiate products, these products may increase intracholedochal pressure, increase cerebrospinal fluid pressure, and obscure diagnosis or exacerbate acute abdominal symptoms.
  - These products should not be used as analgesics.
  - The most common adverse reactions observed with buprenorphine and buprenorphine/naloxone products include headache, insomnia, nausea, pain, sweating, and withdrawal syndrome.
  - All of the buprenorphine-containing products have an associated risk evaluation and mitigation strategy (REMS) program (*REMS@FDA 2021*).
- Lofexidine has several warnings and precautions, including risk of hypotension, bradycardia, and syncope; risk of QT prolongation; increased risk of CNS depression with concomitant use of CNS depressant drugs; and increased risk of opioid overdose in patients who complete opioid discontinuation and resume opioid use.
  - Sudden discontinuation of lofexidine can cause a marked rise in blood pressure and symptoms that include diarrhea, insomnia, anxiety, chills, hyperhidrosis, and extremity pain. Lofexidine should be discontinued by gradually reducing the dose.
  - The most common adverse reactions observed with lofexidine include orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth.
  - The safety of lofexidine in pregnancy has not been established.
- Naltrexone products are contraindicated in patients receiving opioid analgesics; patients currently dependent on opioids (including those currently maintained on opioid agonists); patients in acute opioid withdrawal; individuals who have failed

a naloxone challenge test or have a positive urine screen for opioids; individuals with a history of sensitivity to naltrexone or other components of the product; and individuals with acute hepatitis or liver failure (oral naltrexone only). Extended-release injectable naltrexone is contraindicated in patients with hypersensitivity to polylactide-co-glycolide (PLG), carboxymethylcellulose, or any other component of the diluent.
- Naltrexone can precipitate withdrawal if given to an opioid-dependent patient. Prior to initiating naltrexone, an opioid-free interval of 7 to 10 days is recommended for patients previously dependent on short-acting opioids; patients transitioning from buprenorphine or methadone may be vulnerable to precipitation of withdrawal symptoms for up to 2 weeks. A naloxone challenge test may be helpful to determine whether or not the patient has had a sufficient opioid-free period prior to initiating naltrexone.
- Patients may be more vulnerable to opioid overdose after discontinuation of naltrexone due to decreased opioid tolerance.
- Monitor patients on naltrexone for the development of depression or suicidality.
- Warnings unique to extended-release IM naltrexone include injection site reactions, which may be severe; eosinophilic pneumonia; hypersensitivity reactions, including anaphylaxis; use in patients with thrombocytopenia or any coagulation disorder; and interference with certain immunoassay methods of urine opioid detection.
- The most common adverse reactions observed with oral naltrexone include difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea/vomiting, low energy, joint and muscle pain, and headache. The most common adverse reactions observed with extended-release IM naltrexone include hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache.
- There are no adequate and well-controlled studies of naltrexone in pregnant women; it should be used only if the potential benefit justifies the potential risk to the fetus.
- Extended-release IM naltrexone has a REMS program due to the risk of severe injection site reactions (*REMS@FDA 2021*).

Products for Emergency Treatment of Opioid Overdose
- These products are contraindicated in patients with hypersensitivity to naloxone or to any of the other ingredients.
- These products carry warnings and precautions for risks of recurrent respiratory and CNS depression, limited efficacy with partial agonists or mixed agonists/antagonists (eg, buprenorphine, pentazocine), and precipitation of severe opioid withdrawal, and increased risk of adverse cardiovascular events.
- Naloxone may precipitate acute withdrawal symptoms in opioid-dependent patients including anxiety, tachycardia, sweating, piloerection, yawning, sneezing, rhinorrhea, nausea, vomiting, diarrhea, increased blood pressure, and abdominal or muscle cramps. Opioid withdrawal signs and symptoms in neonates also include convulsions, excessive crying, and hyperactive reflexes.

DOSING AND ADMINISTRATION

Table 7a. Dosing and Administration for Products for Treatment of Opioid Dependence

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single Entity Agents				
buprenorphine	Sublingual tablets	Oral	Single daily dose	• Severe hepatic impairment: Consider reducing the starting and titration incremental dose by half and monitor for signs and symptoms of toxicity or overdose
Lucemyra (lofexidine)	Tablet	Oral	Four times daily at 5- to 6-hour intervals	• May be continued for up to 14 days with dosing guided by symptoms • Adjust dose for patients with hepatic or renal impairment

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
naltrexone hydrochloride	Tablet	Oral	Single daily dose May also be dosed every other day or every 3 days	• Contraindicated in patients with acute hepatitis or liver failure • Use caution in patients with hepatic or renal impairment
Sublocade (buprenorphine)	SC injection	SC	Monthly (minimum 26 days between doses) May be instances where a 2-month dosing interval is appropriate	• Can only be administered by a healthcare provider • Patients with moderate or severe hepatic impairment are not candidates for this product
Vivitrol (naltrexone extended-release)	IM injection	IM	Monthly or every 4 weeks	• Can only be administered by a healthcare provider • Use caution in patients with moderate to severe renal impairment
Combination Products				
Bunavail, Suboxone, Zubsolv (buprenorphine/ naloxone)	Buccal film (Bunavail) Sublingual film (Suboxone) Sublingual tablet (Zubsolv; generics equivalent to Suboxone tablet)	Oral	Bunavail: Single daily dose (except day 1 of induction for patients dependent on heroin or other short-acting opioid products: start with an initial dose of 2.1 mg/0.3 mg and repeat at approximately 2 hours, under supervision, to a total dose of 4.2 mg/0.7 mg based on the control of acute withdrawal symptoms) Suboxone: Single daily dose (except day 1 of induction: titrate in buprenorphine 2 mg to 4 mg increments at approximately 2-hour intervals based on the control of acute symptoms) Sublingual tablet generics (Suboxone): Single daily dose Zubsolv: Single daily dose (except day 1 of induction: divided into doses of 1 to 2 tablets of 1.4 mg/0.36 mg at 1.5 to 2-hour intervals)	• These products should generally be avoided in patients with severe hepatic impairment and may not be appropriate for patients with moderate hepatic impairment.

See the current prescribing information for full details

Table 7b. Equivalent Doses of Buprenorphine/Naloxone Combination Products*

buprenorphine/naloxone sublingual tablets and/or Suboxone sublingual film	Zubsolv sublingual tablets
2 mg/0.5 mg	1.4 mg/0.36 mg
4 mg/1 mg	2.9 mg/0.71 mg
8 mg/2 mg	5.7 mg/1.4 mg
12 mg/3 mg	8.6 mg/2.1 mg
16 mg/4 mg	11.4 mg/2.9 mg

*Systemic exposures of buprenorphine and naloxone may differ when patients are switched from tablets to films or vice versa.

Table 8. Dosing and Administration for Products for Emergency Treatment of Opioid Overdose

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Kloxxado (naloxone HCl)	Nasal spray	IN	A single spray should be administered into 1 nostril Additional doses should be administered, using a new nasal spray device in alternating nostrils, if the patient does not respond or responds and then relapses into respiratory depression. Additional doses may be given every 2 to 3 minutes until emergency medical assistance arrives.	Kloxxado delivers a single dose of 8 mg of naloxone HCl Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance
naloxone HCl	Vials, prefilled syringe, solution cartridge	IV	*Adults:* An initial dose may be administered IV. It may be repeated at 2 to 3-minute intervals if the desired degree of counteraction and improvement in respiratory functions are not obtained. *Children:* The usual initial dose in children is given IV; a subsequent dose may be administered if the desired degree of clinical improvement is not obtained.	IM or SC administration may be necessary if the IV route is not available.
Narcan (naloxone HCl)	Nasal spray	IN	A single spray should be administered into 1 nostril. Additional doses should be administered, using a new nasal spray device in alternating nostrils, if the patient does not respond or responds and then relapses into respiratory depression. Additional doses may be given every 2 to 3 minutes until emergency medical assistance arrives.	Narcan delivers single doses of 2 mg or 4 mg naloxone HCl Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance

See the current prescribing information for full details

CONCLUSION

Products for Treatment of Opioid Dependence

- Buprenorphine sublingual tablets, buprenorphine/naloxone sublingual tablets, Bunavail (buprenorphine/naloxone) buccal film, Sublocade (buprenorphine) SC injection, Suboxone (buprenorphine/naloxone) sublingual film, and Zubsolv (buprenorphine/naloxone) sublingual tablets are used for the treatment of opioid dependence. Some products are indicated for maintenance treatment only, while others are indicated for both induction and maintenance.
- Buprenorphine is suggested as a first-line maintenance treatment for moderate-to-severe opioid use disorder; it may be preferred over methadone because it is safer and does not require clinic-based treatment. Buprenorphine is typically administered in a combination product with naloxone, an opioid antagonist, to discourage abuse. These agents are Schedule III controlled substances (*Strain 2021*).
- Clinical trials have demonstrated that buprenorphine/naloxone is practical and safe for use in diverse community treatment settings including primary care offices (*Amass et al 2004, Fiellin et al 2014*).
- Physicians prescribing buprenorphine for opioid dependency must undergo specialized training due to the potential for abuse and diversion. Because of these risks, buprenorphine monotherapy should be reserved for patients who are pregnant or have a documented allergy to naloxone (*DATA 2000*).
- Most studies have demonstrated that buprenorphine-based therapy was as effective as methadone in the management of opioid dependence; however, some newer data suggest that buprenorphine may be superior in this regard (*Bahji et al 2019, Dalton et al 2019, Farré et al 2002, Gibson et al 2008, Gowing et al 2017, Johnson et al 1992, Kamien et al 2008, Meader 2010, Petitjean et al 2001, Soyka et al 2008, Mattick et al 2014, Strain et al 2011*).
- The most common adverse reactions observed with buprenorphine and buprenorphine/naloxone products include headache, insomnia, nausea, pain, sweating, and withdrawal syndrome. These products also have REMS criteria.
- Lofexidine is an oral central alpha-2 agonist indicated for mitigation of opioid withdrawal symptoms to facilitate abrupt opioid discontinuation.
- Meta-analyses have found that although lofexidine reduces withdrawal symptoms compared to placebo, it is less effective than buprenorphine for managing opioid withdrawal in terms of withdrawal severity, withdrawal duration, and likelihood of treatment completion *(Gowing et al 2016, Gowing et al 2017)*. It is likely to be less effective than buprenorphine or methadone for opioid detoxification (*Meader 2010*).
- The most common adverse reactions observed with lofexidine include orthostatic hypotension, bradycardia, hypotension, dizziness, somnolence, sedation, and dry mouth.
- Naltrexone is an opioid antagonist. Oral naltrexone is indicated for the treatment of alcohol dependence and blockade of the effects of exogenously administered opioids. Extended-release IM naltrexone is indicated for the treatment of alcohol dependence and the prevention of relapse to opioid dependence following opioid detoxification. In order to initiate naltrexone treatment, patients must be opioid-free for at least 7 to 10 days to avoid precipitation of withdrawal.
- In a meta-analysis examining the efficacy of oral naltrexone for maintenance treatment of opioid dependence, oral naltrexone was no better than placebo or any pharmacologic treatment in terms of treatment retention or use of the primary substance of abuse. Based on the results of 1 study, it was also not significantly different from buprenorphine for retention, abstinence, and side effects (*Minozzi et al 2011*). Extended-release IM naltrexone has been shown to have similar efficacy to oral buprenorphine/naloxone among patients who are able to successfully initiate treatment (*Lee et al 2018, Tanum et al 2017*). Retention rates with extended-release IM naltrexone are better than those seen with oral naltrexone (*Sullivan et al 2019*).
- The most common adverse reactions observed with oral naltrexone include difficulty sleeping, anxiety, nervousness, abdominal pain/cramps, nausea/vomiting, low energy, joint and muscle pain, and headache. The most common adverse reactions observed with extended-release IM naltrexone include hepatic enzyme abnormalities, injection site pain, nasopharyngitis, insomnia, and toothache. Extended-release IM naltrexone also has a REMS program.
- The AAP, APA, ASAM, SAMHSA, and VHA publish guidelines for the treatment of opioid dependence. These guidelines support access to all FDA-approved pharmacological therapies for the management of opioid dependence. Buprenorphine/naloxone combination products may be used for induction and maintenance. In pregnant women for whom buprenorphine therapy is selected, buprenorphine alone (ie, without naloxone) is recommended. Naltrexone may be considered for the prevention of relapse, although outcomes with this medication are often adversely affected by poor adherence. Extended-release injectable naltrexone may reduce, but not eliminate, some of the problems with oral naltrexone adherence. The VHA guideline recommends extended-release injectable naltrexone if opioid agonist

treatment is not feasible; it does not recommend for or against oral naltrexone (*CSUP 2016, Cunningham et al 2020, Kampman et al 2015, Kleber et al 2006, SAMHSA treatment improvement protocol 2021, VHA 2015).*

- Updated 2020 clinical practice guidelines from ASAM recommend against opioid withdrawal management on its own (ie, detoxification) due to the associated high risk of relapse and other safety concerns; treatment with ongoing maintenance medication therapy in combination with psychosocial treatment as appropriate is the standard of care for opioid use disorder *(Cunningham et al 2020).*
  - The ASAM specifically recommends using methadone or buprenorphine for opioid withdrawal management over abrupt cessation of opioids.
  - Opioid withdrawal management with buprenorphine should not be initiated until objective signs of opioid withdrawal are present.
  - Alpha-2 adrenergic agonists (eg, lofexidine and clonidine) are safe and effective for withdrawal management; however, methadone and buprenorphine are more effective in reducing withdrawal symptoms.

Products for Emergency Treatment of Opioid Overdose

- Naloxone is the standard of care to treat opioid overdose. It has been used by medical personnel for over 40 years and its use outside of the medical setting has gained traction through improvements in legislation and community-based opioid overdose prevention programs.
- Naloxone HCl injection, Kloxxado (naloxone HCl) nasal spray, and Narcan (naloxone HCl) nasal spray are approved for treatment of known or suspected opioid overdose. Prior to the approval of Narcan nasal spray, naloxone was only available in glass vials and ampules, which were distributed with syringes and needles for manual injection or with syringes and atomizers for off-label IN administration.
  - Naloxone injection can be administered IV, IM, or SC. Potential advantages of IN administration of naloxone include easier disposal, no needle stick risk, and avoidance of needle anxiety. Kloxxado nasal spray and Narcan nasal spray are designed for use by laypersons.
- The approvals of Kloxxado nasal spray and Narcan nasal spray were based on pharmacokinetic bioequivalence studies. No new clinical studies were required by the FDA. Kloxxado nasal spray, the most recently approved dosage form of naloxone, delivers 8 mg of naloxone, a higher dose than what is delivered by Narcan nasal spray, to treat opioid overdose.
- Various organizations including WHO and ASAM have endorsed the availability of naloxone for patients, bystanders, and first responders for the emergency management of suspected opioid overdose. It is recommended that people who are likely to witness an overdose should have access to and be trained in the use of naloxone (*WHO 2014, Cunningham et al 2020*).
  - According to the WHO guidelines for community management of opioid overdose, naloxone is effective when delivered by IV, IM, SC, and IN routes of administration. Persons using naloxone should select a route of administration based on the formulation available, their skills in administration, the setting, and local context.
- The U.S. HHS has recommended prescribing or co-prescribing naloxone to all patients who are at risk for opioid overdose, including: patients receiving opioids at a dosage of 50 MME per day or greater; patients with respiratory conditions who are prescribed opioids; patients who have been prescribed benzodiazepines along with opioids; and patients prescribed opioids who have a non-opioid substance use disorder, report excessive alcohol use, or have a mental health disorder (*HHS 2018*).

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

Therapeutic Class Overview
Neuropathic Pain and Fibromyalgia Agents

INTRODUCTION

- Neuropathic pain is commonly described by patients as burning or electrical in nature and results from injury or damage to the nervous system (*Herndon et al 2021*). Management of neuropathic pain may prove challenging due to unpredictable patient response to drug therapy (*Attal et al 2010*).
- Fibromyalgia is characterized by chronic musculoskeletal pain with unknown etiology and pathophysiology. Patients typically complain of widespread musculoskeletal pain, fatigue, cognitive disturbance, psychiatric symptoms, and multiple somatic symptoms (*Goldenberg 2020a*). Fibromyalgia is often difficult to treat and requires a multidisciplinary, individualized treatment program (*Goldenberg 2020b)*.
- This review focuses on medications that are approved by the Food and Drug Administration (FDA) for the treatment of fibromyalgia, neuropathic pain, and/or post-herpetic neuralgia (PHN). The products in this review include Cymbalta (duloxetine), Gralise (gabapentin ER), Horizant (gabapentin enacarbil ER), Lidoderm (lidocaine 5% patch), Lyrica (pregabalin), Lyrica CR (pregabalin ER), Neurontin (gabapentin), Nucynta ER (tapentadol ER), Qutenza (capsaicin), Savella (milnacipran), and ZTlido (lidocaine 1.8% topical system). These agents represent a variety of pharmacologic classes, including anticonvulsants, serotonin-norepinephrine reuptake inhibitors (SNRIs), extended-release (ER) opioids, and topical analgesics. As such, these agents hold additional FDA-approved indications that are outlined in Table 2; however, clinical information included within this review will not address the use of these agents for these additional indications (*Prescribing information: Cymbalta 2020, Gralise 2020, Horizant 2020, Lidoderm 2018, Lyrica 2020, Lyrica CR 2020, Neurontin 2020, Nucynta ER 2021, Qutenza 2021, Savella 2017, ZTLido 2021*).
- Medispan classes: Anticonvulsants - Misc.; Fibromyalgia Agents; Local Anesthetics – Topical; Opioid Agonists; Postherpetic Neuralgia (PHN) Agents; Restless Leg Syndrome (RLS) Agents; Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

Diabetic Neuropathy

- Approximately 50% of patients with diabetes will eventually develop neuropathy. The high rate of diabetic neuropathy results in substantial patient morbidity, which includes recurrent lower extremity infections, ulcerations, and subsequent amputations (*Feldman 2021b*).
- The condition is categorized into distinct syndromes based on the neurologic distribution, although syndromes may overlap in some patients. The most frequently encountered diabetic neuropathies include distal symmetric polyneuropathy, autonomic neuropathy, polyradiculopathies, and mononeuropathies (*Feldman et al 2021b*).
- The 3 main components to the management of diabetic neuropathy are glycemic control, foot care, and pain management (*Feldman et al 2021a*).
  - Optimal glucose control is important for the prevention of diabetic neuropathy. Clinical trial evidence demonstrates that rigorous blood glucose control in patients with type 1 diabetes reduces the occurrence of diabetic neuropathy. In contrast, the role of glycemic control in patients with type 2 diabetes is less certain. Limited evidence suggests that neuropathic symptoms may improve with intensive antidiabetic therapy (*Feldman et al 2021a*).
  - Patients with diabetes should be counseled on the importance of daily foot care, including the inspection of feet for the presence of dry or cracking skin, fissures, and plantar callus formation. Regular foot examinations by a healthcare provider are also important (*Feldman et al 2021a*).
  - A small proportion of patients with diabetic neuropathy will experience painful symptoms, and in some instances the condition is self-limited. When treatment is necessary, options include antidepressants, anticonvulsants, capsaicin cream, lidocaine patches, alpha-lipoic acid, spinal cord stimulation, and transcutaneous electrical nerve stimulation (*Feldman et al 2021a*).

Fibromyalgia

- Fibromyalgia is a chronic functional illness marked by widespread musculoskeletal pain for which no alternative cause can be identified. Fibromyalgia patients often experience neuropsychological symptoms of fatigue, unrefreshing sleep, cognitive dysfunction, anxiety, and depression (*Clauw et al 2009*).

- Patients with fibromyalgia have pain that is typically above and below the waist on both sides of the body and involves the axial skeleton (neck, back, or chest). The pain attributable to fibromyalgia is poorly localized, difficult to ignore, severe in its intensity, and associated with a reduced functional capacity (*Crofford 2018*).

- The prevalence of fibromyalgia in the general U.S. population is estimated to be 2% to 3% and increases with age *(Goldenberg 2020a)*. It is more common in women than in men, with a ratio of approximately 9:1 (*Crofford 2018)*.
- There is an increased prevalence of other syndromes associated with pain and fatigue, including chronic fatigue syndrome, temporomandibular disorder, chronic headaches, irritable bowel syndrome, interstitial cystitis/painful bladder syndrome, and other pelvic pain syndromes in fibromyalgia patients (*Clauw et al 2009, Crofford 2018*).

PHN

- PHN refers to the persistence of the pain of herpes zoster beyond 4 months from the initial onset of the rash. Among patients with acute herpes zoster infection, the major risk factors for PHN are older age, greater acute pain, and greater rash severity. The duration of PHN is highly variable among individuals and may persist for months, years, or life (*Bajwa et al 2019*).
- PHN, as well as acute herpetic neuralgia, can be a severe condition associated with profound psychological dysfunction, including impaired sleep, decreased appetite, and decreased libido (*Bajwa et al 2019*).
- Prevention of PHN involves either treatment of acute herpes zoster infection or use of a vaccine (*Bajwa et al 2019*). Although evidence suggests that antiviral therapy hastens resolution of lesions and acute neuritis of herpes zoster, it is unclear if it decreases the risk of PHN *(Albrecht 2020).*
- A number of treatment modalities have been evaluated in the management of PHN and include tricyclic antidepressants, anticonvulsants, opioids, capsaicin, topical lidocaine, intrathecal glucocorticoids, N-methyl-D-aspartate receptor antagonists, botulinum toxin, cryotherapy, and surgery (*Bajwa et al 2019*).

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Cymbalta (duloxetine delayed-release)	✔
Gralise (gabapentin ER)*	-
Horizant (gabapentin enacarbil ER)*	-
Lidoderm (lidocaine transdermal patch)	✔
Lyrica (pregabalin)	✔
Lyrica CR (pregabalin ER)	✔
Neurontin (gabapentin)	✔
Nucynta ER (tapentadol ER)	-
Qutenza (capsaicin transdermal patch)	-
Savella (milnacipran)	-
ZTlido (lidocaine topical system)	-

* Medication is not interchangeable with other gabapentin products because of differing pharmacokinetic profiles that affect the frequency of administration.

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

INDICATIONS

Table 2. FDA-Approved Indications

Indication	Cymbalta (duloxetine)	Gralise (gabapentin ER)	Horizant (gabapentin enacarbil ER)	Lidoderm, ZTlido (lidocaine)	Lyrica (pregabalin)	Lyrica CR (pregabalin ER)	Neurontin (gabapentin)	Nucynta ER (tapentadol)	Qutenza (capsaicin)	Savella (milnacipran)
Adjunctive therapy for adult patients with partial onset seizures					✔					
Adjunctive therapy in the treatment of partial seizures with and without secondary generalization in patients > 3 years of age with epilepsy							✔			
Adjunctive therapy for patients 1 month of age and older with partial onset seizures					✔					
Management of chronic musculoskeletal pain	✔ †									
Management of fibromyalgia in adults	✔				✔					✔
Management of fibromyalgia in adults and pediatric patients 13 years of age and older	✔									
Management of neuropathic pain associated with diabetic peripheral neuropathy	✔				✔	✔		✔ §	✔	
Management of neuropathic pain associated with spinal cord injury					✔					
Management of PHN		✔	✔		✔	✔	✔			
Relief of pain associated with PHN				✔					✔	
Moderate-to-severe primary restless legs syndrome			✔ ‡							
Treatment of generalized anxiety disorder	✔									
Treatment of major depressive disorder	✔									
Management of moderate to severe chronic pain in adults								✔ §		

† This has been established in studies of patients with chronic low back pain and chronic pain due to osteoarthritis.
‡ Gabapentin enacarbil is not indicated for patients who are required to sleep during the day and remain awake at night.
§ Medication is not for use as an as-needed analgesic. Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release opioid formulations, reserve use for patients in whom alternative treatment options (eg, non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.

(*Prescribing information: Cymbalta 2020, Gralise 2020, Horizant 2020, Lidoderm 2018, Lyrica 2020, Lyrica CR 2020, Neurontin 2020, Nucynta ER 2021, Qutenza 2021, Savella 2017, ZTlido 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

Neuropathic Pain

- Pregabalin demonstrated significant improvements in pain relief, functional outcomes, and quality of life compared to placebo for the treatment of diabetic peripheral neuropathic pain. Commonly reported adverse events (AEs) in patients receiving pregabalin include dizziness, somnolence, infection, headache, dry mouth, weight gain, and peripheral edema (*Dworkin et al 2003, Freynhagen et al 2005, Guan et al 2011, Lesser et al 2004, Moon et al 2010, Rosenstock et al 2004, Roth et al 2010, Sabatowski et al 2004, Semel et al 2010, Sharma et al 2010, Skvarc et al 2010*).
- Tapentadol ER demonstrated superiority over placebo in alleviating pain and improving quality of life in patients with diabetic peripheral neuropathy. Tapentadol ER is associated with significant improvements in pain intensity scores, responder rates, and Patient Global Impression of Change (PGIC). Commonly reported AEs in patients receiving tapentadol ER include nausea, vomiting, and constipation (*Schwartz et al 2011*).
- Duloxetine demonstrated consistent superiority over placebo in alleviating pain, improving functional outcomes, and improving quality of life in patients with diabetic peripheral neuropathic pain. Specifically, duloxetine is associated with significant improvements in Brief Pain Inventory (BPI), Clinician and Patient Global Impression of Improvement and Severity, Short Form-36 Health Survey (SF-36), Pain-Related Sleep Interference, and Euro Quality of Life assessment (EQ-5D) scores. Commonly reported AEs in patients receiving duloxetine include nausea, somnolence, anorexia, and dysuria (*Armstrong et al 2007, Kajdasz et al 2007, Lunn et al 2014, Parsons et al 2016, Yan et al 2010*).
- Head-to-head trials among the neuropathic pain and fibromyalgia agents are rare. In a 52-week, open-label trial comparing duloxetine to routine care (gabapentin, amitriptyline, and venlafaxine) for the treatment of diabetic peripheral neuropathic pain, there were no significant differences observed between groups in EQ-5D questionnaire scores; however, results differed with regards to SF-36 subscale scores. In another trial, there were no significant between-group differences in SF-36 subscale scores; however, other subscale scores for physical functioning, bodily pain, mental health, and vitality favored duloxetine (*Raskin et al 2006, Wernicke et al 2007[b]*). A second head-to-head trial demonstrated duloxetine to be noninferior to pregabalin for the treatment of pain in patients with diabetic peripheral neuropathy who had an inadequate pain response to gabapentin (*Tanenberg et al 2011*). A post-hoc analysis of study patients who were taking concomitant antidepressants and those who were not taking antidepressants found duloxetine may provide better pain reduction in those patients who were not taking concomitant antidepressants (*Tanenberg et al 2014*). Another head-to-head trial found no significant differences between high-dose duloxetine or pregabalin monotherapy and combination duloxetine/pregabalin therapy, as measured by BPI Modified Short Form (BPI-MSF) average pain (*Tesfaye et al 2013*).
- Several large meta-analyses and systematic reviews have been conducted evaluating the neuropathic pain and fibromyalgia agents, which further support the safety and efficacy of these agents in FDA-approved indications (*Chou et al 2009, Derry et al 2019, Edelsberg et al 2011, Lunn et al 2014, Meng et al 2014, Quilici et al 2009, Wernicke et al 2007[a], Wiffen et al 2017, Liampas et al 2021*). In a meta-analysis by Quilici et al, limited available clinical trial data suitable for indirect comparison demonstrated that duloxetine provides comparable efficacy and tolerability to that of gabapentin and pregabalin for the treatment of diabetic peripheral neuropathic pain (*Quilici et al 2009*).
- The efficacy of pregabalin in patients with neuropathic pain associated with spinal cord injury was established in 2 placebo-controlled trials, 1 of 12 weeks duration and the other of 16 weeks duration. Patients had neuropathic pain associated with spinal cord injury for at least 3 months or with relapses and remissions for at least 6 months. Patients were allowed to take opioids, non-opioid analgesics, antiepileptic drugs, muscle relaxants, and antidepressant drugs if doses were stable for 30 days prior to screening. Patients were also allowed to take acetaminophen and nonsteroidal anti-inflammatory drugs during the trial. In both trials, pregabalin (150 to 600 mg/day) significantly improved weekly pain scores compared to placebo, and increased the proportion of patients with at least a 30 or 50% reduction from baseline in pain score (*Lyrica prescribing information 2020*, *Siddall et al 2006, Vranken et al 2008*).
- The efficacy of capsaicin 8% in diabetic peripheral neuropathy was assessed in a placebo-controlled trial *(Simpson et al 2016)*. The primary endpoint, percentage reduction in average daily pain score from baseline through 8 weeks, was significantly improved with capsaicin 8%. Patients treated with capsaicin also had significant improvements in median time to treatment response and in sleep interference scores through week 8.

Fibromyalgia

- From the agents included in this review, the agents that have several randomized controlled trials (RCTs) and meta-analyses demonstrating their efficacy in the treatment of fibromyalgia include duloxetine, pregabalin, and milnacipran (*Arnold et al 2007, Arnold et al 2008, Arnold et al 2009, Clauw et al 2008, Crofford et al 2005, Hauser et al 2009[a], Hauser et al 2009[b], Hauser et al 2010, Lunn et al 2014, Mease et al 2009, Mease et al 2010, Russell et al 2008, Vitton et al 2004, Welsch et al 2018*).
  - A 2009 meta-analysis on the treatment of fibromyalgia syndrome with antidepressants found that antidepressants were associated with improved health-related quality of life. The largest effect size for pain reduction was seen with the tricyclic antidepressant, amitriptyline, followed by monoamine oxidase inhibitors, moclobemide and pirlindole (medium effect size). Small effect sizes were observed with the selective serotonin reuptake inhibitors (SSRIs), fluoxetine and paroxetine, and the SNRIs, duloxetine and milnacipran. The authors concluded that short-term treatment with amitriptyline and duloxetine could be considered for fibromyalgia-associated pain and sleep disturbances (*Hauser et al 2009[a]*).
  - In a meta-analysis of 5 RCTs, gabapentin and pregabalin reduced pain and improved sleep in patients with fibromyalgia. The pooled number-needed-to-treat to achieve ≥ 30% reduction in pain was 8.5. Anxiety, depressed mood, and fatigue were not improved with gabapentin or pregabalin treatment (*Hauser et al 2009[b]*).
  - Results from another 2010 meta-analysis noted that duloxetine, milnacipran, and pregabalin have short-term (up to 6-month) efficacy data. The authors concluded that the choice of medication may be dependent on the occurrence of key symptoms of fibromyalgia syndrome and the specific AEs that are associated with each drug (*Hauser et al 2010*).
  - A systematic review of 6 randomized trials involving 2249 patients concluded that for the treatment of fibromyalgia, duloxetine 60 and 120 mg/day are effective with a similar magnitude of effect (low quality evidence). The effect in fibromyalgia may be achieved through a greater improvement in mental symptoms than somatic physical pain (*Lunn et al 2014*).
  - A 2016 network meta-analysis of 9 RCTs (N = 5140) indirectly compared duloxetine, pregabalin, and milnacipran in the treatment of fibromyalgia. The probability of achieving > 30% improvement in pain scores was numerically highest with duloxetine 60 mg, followed by pregabalin 300 mg, milnacipran 100 mg, and milnacipran 200 mg. While the aforementioned treatment groups each demonstrated superiority over placebo, differences between active treatments did not achieve statistical significance (*Lee et al 2016*).
  - A systematic review and meta-analysis of 18 randomized trials involving 7903 patients concluded that duloxetine and milnacipran provided a small incremental benefit over placebo in pain reduction and provided no clinically relevant benefit over placebo in improving health-related quality of life or in reducing fatigue. Dropout rates for duloxetine and milnacipran due to AEs were higher than placebo (*Welsch et al 2018*).
  - Duloxetine is approved for treatment of fibromyalgia in patients age 13 years and older. Pediatric approval was supported by findings of a 13-week, placebo-controlled RCT (N = 184) of patients age 13 to 17 years with juvenile fibromyalgia *(Upadhyaya et al 2019)*. The primary outcome, mean change in BPI average pain severity, was not statistically different between groups; however, significantly more duloxetine- vs placebo-treated patients had a treatment response of ≥ 30% reduction (52% vs 36%) and ≥ 50% reduction (40% vs 24%) on BPI average pain severity.

PHN

- In patients with PHN, treatment with lidocaine 5% resulted in significant pain relief compared to placebo (*Galer et al 1999, Galer et al 2002, Meier et al 2003*). In addition, treatment with lidocaine 5% was associated with higher rates of patient preference, less use of rescue medication, and decreases in allodynia and neuropathic symptoms compared to placebo (*Galer et al 1999, Meier et al 2003*). An open-label trial evaluating lidocaine 5% for the management of PHN supports the findings of placebo-controlled trials (*Katz et al 2002*).
- Lidocaine 1.8% was approved via the 505(b)(2) pathway with no new efficacy trials. However, in a single-dose, crossover study conducted in 53 healthy volunteers, lidocaine 1.8% topical system demonstrated equivalent exposure (AUC) and peak concentration (C_{max}) of lidocaine to lidocaine 5% patch. In addition, based on a clinical study in 54 subjects, 47 subjects (87%) had adhesion scores of 0 (≥ 90% adhered) for all evaluations performed every 3 hours during the 12 hours of lidocaine 1.8% administration, 7 subjects (13%) had adhesion scores of 1 (≥ 75% to < 90% adhered) for at least 1 evaluation, and no subjects had scores of 2 or greater (< 75% adhered) *(ZTlido prescribing information 2021)*.
- In patients with PHN, treatment with capsaicin resulted in significant pain relief compared to low dose capsaicin 0.04% (*Backonja et al 2008, Derry et al 2017, Irving et al 2012*). Treatment with capsaicin was associated with improvement in

PGIC, reduction in numeric pain rating scale (NPRS) scores, and reduction in neuropathic symptoms compared to low-dose capsaicin for up to 12 weeks of treatment (*Backonja et al 2008, Derry et al 2017, Irving et al 2012*). The long-term tolerability and safety of capsaicin was also demonstrated in a 52-week study, which found that repeat treatment with capsaicin (30 and 60 minutes) in addition to the standard of care therapies (antidepressants, antiepileptics, and/or opioids) was well tolerated with no negative functional or neurological effects when compared to standard of care therapies alone (*Vinik et al 2016*).

- Gabapentin also demonstrated superiority over placebo in alleviating pain, improving functional outcomes, and improving quality of life in patients with PHN. Treatment with gabapentin significantly improved average daily pain and sleep, short-form McGill Pain Questionnaire (SF-MPQ), Patient and Clinician Global Impression of Change, SF-36, and Prolife of Mood States (POMS) scores in RCTs. Commonly reported AEs in patients receiving gabapentin included somnolence, drowsiness, dizziness, ataxia, peripheral edema, and infection (*Rice et al 2001, Rowbotham et al 1998*). In a trial comparing placebo, gabapentin monotherapy, morphine sustained-release monotherapy, and gabapentin and morphine sustained-release combination therapy, combination therapy achieved better analgesia at lower doses of each agent compared to monotherapy with either agent in patients with PHN. Combination therapy was most commonly associated with constipation, sedation, and dry mouth (*Gilron et al 2005*). Within these clinical trials, doses of gabapentin of up to 3,600 mg/day were evaluated (*Gilron et al 2005, Rice et al 2001, Rowbotham et al 1998*).
- In 2 placebo-controlled trials, gabapentin ER achieved significant improvements in average daily pain and sleep interference scores (*Irving et al 2009, Wallace et al 2010*). In one of these trials, a larger proportion of patients receiving gabapentin ER reported ≥ 50% reduction from baseline in average daily pain scores compared to placebo (*Irving et al 2009*). In general, treatment with gabapentin ER was well tolerated; dizziness, headache, somnolence, and peripheral edema were the most commonly reported AEs (*Irving et al 2009, Wallace et al 2010*). Another placebo-controlled trial concluded that gabapentin ER may be particularly effective in patients with PHN presenting with sharp, dull, sensitive, or itchy pain (*Jensen et al 2009*). Within these clinical trials, doses of gabapentin ER of up to 1,800 mg/day were evaluated (*Irving et al 2009, Jensen et al 2009, Wallace et al 2010*).
- The efficacy of gabapentin enacarbil ER (1200, 2400, and 3600 mg/day) was established in a randomized, placebo-controlled, 12-week trial in adult patients with a documented medical diagnosis of PHN for ≥ 3 months (n = 371) and significant pain, as demonstrated by a minimum baseline 24-hour average Pain Intensity Numerical Rating Scale score ≥ 4 on the 11-point scale. Treatment with gabapentin enacarbil ER significantly improved the mean pain score and increased the proportion of patients with ≥ 50% reduction in pain score from baseline at all doses evaluated. A benefit over placebo was observed for all 3 doses of gabapentin enacarbil ER as early as Week 1 and was maintained at Week 12. Additional benefit of using doses of gabapentin enacarbil ER > 1200 mg/day was not demonstrated (*Zhang et al 2013*). Results of a second, published, placebo-controlled trial confirms these findings. Reported AEs were similar to those of gabapentin and gabapentin ER (ie, dizziness, headache, and nausea) (*Backonja et al 2011*).
- A meta-analysis of 7 trials evaluating gabapentin, gabapentin enacarbil ER, and gabapentin ER was conducted to determine the efficacy and safety of all gabapentin formulations for management of PHN. Although gabapentin was found to be superior to placebo in terms of pain reduction, global impression of change, and sleep quality, patients taking gabapentin were significantly more likely to experience AEs such as dizziness, somnolence, peripheral edema, ataxia, and diarrhea (*Meng et al 2014*).
- Pregabalin demonstrated consistent superiority over placebo in alleviating diabetic peripheral neuropathic pain and PHN-related pain. Two noncomparative, open-label trials evaluating pregabalin for the management of PHN support the findings of placebo-controlled trials (*Ogawa et al 2010, Xochilcal-Morales et al 2010*). In one of these noncomparative trials, long-term treatment of PHN with pregabalin (52 weeks) was found to be safe and effective (*Ogawa et al 2010*). Patients with PHN who were transitioned to pregabalin from gabapentin demonstrated no significant difference in pain scores, based on a visual analog scale, with pregabalin compared to gabapentin. However, in a subset of patients who required an increase in the dosage of pregabalin to improve the analgesic effect after the transition, significant improvement in pain scores was observed (*Ifuku et al 2011*).
- Support for efficacy of pregabalin ER in PHN and diabetic peripheral neuropathy was based on the efficacy of pregabalin in these indications and 1 clinical trial in PHN (*Lyrica CR prescribing information 2020*). In this trial, pregabalin ER demonstrated a significantly longer time to loss of therapeutic response compared with placebo over a 13-week randomized withdrawal phase in a phase 3, double-blind, randomized trial *(Huffman et al 2017).*

CLINICAL GUIDELINES

Diabetic Neuropathy

- The 2011 American Academy of Neurology (AAN) guidelines, which were reaffirmed in 2016 (update in progress 2021), recommend the following:
  - If clinically appropriate, pregabalin should be offered for treatment. Gabapentin and sodium valproate are other anticonvulsants that should be considered for treatment (*Bril et al 2011*).
  - Amitriptyline, venlafaxine, and duloxetine should be considered for treatment; there is insufficient evidence available to recommend one of these agents over another. Combination therapy with venlafaxine and gabapentin may be utilized for a better response.
  - Dextromethorphan, morphine sulfate, tramadol, and oxycodone should be considered for treatment; there is insufficient evidence available to recommend one of these agents over another.
  - With regards to other pharmacologic options, capsaicin and isosorbide dinitrate spray should be considered for treatment, while lidocaine patch may be considered.
- The 2021 American Diabetes Association (ADA) guideline acknowledges the lack of quality of life outcomes and recommends that treatment decisions follow a trial-and-error approach (*ADA 2021*).
  - Pregabalin, duloxetine, and tapentadol ER have been approved for relief of diabetic peripheral neuropathy; however, none of these agents affords complete relief, even when used in combination.
  - Either pregabalin or duloxetine is recommended as initial pharmacologic therapy for neuropathic pain in diabetes. The use of tapentadol ER is generally not recommended as a first or second-line therapy due to safety concerns such as high-risk for addiction, and the evidence for its use is considered weaker. Although not FDA-approved for diabetic peripheral neuropathy, gabapentin has been reported to be effective for pain control and is included in the guidelines as an initial treatment for neuropathic pain associated with diabetes.
  - Tricyclic antidepressants, venlafaxine, carbamazepine, and topical capsaicin are not approved for the treatment of painful diabetic peripheral neuropathy, but may be effective and can be considered as treatment options.
- In general, other published guidelines support recommendations from the AAN and ADA concerning the use of the neuropathic pain and fibromyalgia agents in the management of diabetic neuropathy (*Dworkin et al 2007, Handelsman et al 2015, Pop-Busui et al 2017*).

PHN

- According to the 2010 European Federation of Neurological Societies guideline on the pharmacological treatment of neuropathic pain, tricyclic antidepressants or gabapentin/pregabalin are recommended as first-line treatment for PHN. Topical lidocaine may be considered first line in the elderly, especially if there are concerns regarding AEs of oral medications. Capsaicin cream and opioids may be considered a second-line choice; capsaicin patches are promising, but the long-term effects of repeated applications on sensation are unclear *(Attal et al 2010).*

Fibromyalgia

- According to the evidence-based recommendations for the management of fibromyalgia syndrome from the European League Against Rheumatism, non-pharmacologic interventions should be considered first-line therapy for the management of fibromyalgia symptoms. Pharmacologic therapy should only be initiated if there is a lack of effect with non-pharmacologic therapies, and should be tailored to meet the patient's needs. Recommended pharmacologic agents include low-dose amitriptyline, cyclobenzaprine, duloxetine, milnacipran, pregabalin, and tramadol (*Macfarlane 2017*).
- According to the 2012 Canadian guidelines for the diagnosis and management of fibromyalgia syndrome, all classes of antidepressants are options for treatment of pain and other symptoms of fibromyalgia. Anticonvulsants are also options, though the guideline does not recommend specific agents (*Fitzcharles et al 2013*).

SAFETY SUMMARY

- The following key contraindications are included in the prescribing information:
  - Concomitant use or use within the last 14 days of monoamine oxidase inhibitors (MAOIs) is contraindicated with duloxetine, milnacipran, and tapentadol ER.
  - Duloxetine is contraindicated for use by patients treated with linezolid or intravenous methylene blue.

  - Tapentadol ER is contraindicated in significant respiratory depression, acute or severe bronchial asthmas, or hypercarbia in an unmonitored setting or in the absence of resuscitative equipment, and in known or suspected paralytic ileus.
- Duloxetine and milnacipran carry a boxed warning for clinical worsening, suicidality, and unusual changes in behavior. There is an increased risk of suicidal thinking and behavior in children, adolescents, and young adults taking antidepressants. All SNRIs are not approved for use in pediatric populations. All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely, especially during the initial few months of a course of drug therapy and following changes in dosage.
- Duloxetine and milnacipran may increase the risk of bleeding events due to interference with serotonin reuptake. Concomitant use with aspirin and other antithrombotics may increase risk of bleeding.
- Tapentadol ER has a boxed warning for the potential for abuse, life-threatening respiratory depression, accidental exposure, risk of neonatal opioid withdrawal syndrome with prolonged use, and interactions with alcohol, benzodiazepines, or other central nervous system depressants that can cause profound sedation, respiratory depression, coma, and death.
- The FDA requires a Risk Evaluation and Mitigation Strategy (REMS) program for opioid analgesics, including tapentadol ER, to assure safe use of these medications.
- Tapentadol ER p
- Gabapentin, pregabalin, and pregabalin ER carry warnings regarding the risk of anaphylaxis and/or angioedema after the first dose or during therapy.
- Gabapentin, gabapentin enacarbil, pregabalin, and pregabalin ER carry warnings regarding the risk of respiratory depression when co-administered with CNS depressants, including opioids, or in the setting of underlying respiratory impairment.
- Topical lidocaine products have a warning for excessive dosing/overexposure, increased absorption on non-intact skin, risk of overexposure with external heat sources, and hypersensitivity reactions. Methemoglobinemia has been reported in association with local anesthetic use.
- Topical capsaicin carries warnings for severe irritation with unintended exposure or exposure to eyes or mucous membranes, pain associated with application, potential respiratory exposure from inhalation of airborne capsaicin upon rapid removal of the patch, and temporary reductions in sensory function. It is recommended that healthcare workers wear nitrile gloves, a face mask, and protective glasses and administer capsaicin in a well-ventilated treatment area.
- The following monitoring parameters are recommended with treatment:
  - Monitor for clinical worsening of depression, suicidality, or unusual changes in behavior with duloxetine, milnacipran, gabapentin ER, gabapentin enacarbil ER, pregabalin, pregabalin ER, and gabapentin.
  - Patients receiving tapentadol ER, duloxetine, or milnacipran should be monitored for signs of serotonin syndrome when used concurrently with other serotonergic agents (eg, SSRIs, SNRIs, tricyclic antidepressants, triptans, fentanyl, lithium, tramadol, tryptophan, buspirone, amphetamines, and St. John's Wort). Tapentadol ER, duloxetine or milnacipran should not be used with drugs that impair metabolism of serotonin (eg, MAOIs, linezolid, and methylene blue).
  - Monitor for signs of misuse, abuse, and addiction during tapentadol ER therapy. Patients should also be closely monitored for 72 hours after initiating tapentadol ER treatment and monitored throughout treatment due to an increased risk of respiratory depression.
  - Patients receiving tapentadol ER, duloxetine, capsaicin, or milnacipran should have their blood pressure monitored prior to initiating treatment and periodically throughout treatment.
  - Monitor for worsened seizure control in patients with a history of seizure disorder with the treatment of tapentadol ER, duloxetine, or milnacipran.
  - Patients receiving tapentadol ER should be monitored for signs and symptoms of worsening biliary tract disease, including acute pancreatitis.
- In general, oral neuropathic pain and fibromyalgia agents are commonly associated with central nervous system-related AEs (eg, dizziness, drowsiness, somnolence). Peripheral edema and weight gain may also occur with use of these agents.
  - Caution is advised when prescribing pregabalin, gabapentin, or gabapentin enacarbil concomitantly with opioids due to risk of CNS depression.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Cymbalta (duloxetine delayed-release)	Capsule	Oral	Once daily	• Not recommended in ESRD, severe renal impairment (CrCl < 30 mL/min), or hepatic insufficiency
Gralise (gabapentin ER)	Tablet	Oral	Once daily	• Should be administered with evening meal • Dose should be reduced in CrCl of 30 to 60 mL/min; not recommended in CrCl < 30 mL/min or hemodialysis
Horizant (gabapentin enacarbil ER)	Tablet	Oral	Twice daily	• Should be administered with food • Dose should be reduced in CrCl < 60 mL/min or hemodialysis
Lidoderm, ZTlido (lidocaine)	Patch, topical system	Transdermal	Once daily	• Should be applied for up to 12 hours within a 24-hour period. • Caution advised in patients with severe hepatic disease
Lyrica (pregabalin)	Capsule, oral solution	Oral	2 or 3 times daily	• Schedule V controlled substance • Dose should be reduced in CrCl < 60 mL/min
Lyrica CR (pregabalin ER)	Tablet	Oral	Once daily	• Schedule V controlled substance • Dose should be reduced in CrCl < 60 mL/min; not recommended in CrCl < 30 mL/min or hemodialysis • Should be administered after evening meal
Neurontin (gabapentin)	Capsule, oral solution, tablet	Oral	3 times daily	• Dose should be reduced in CrCl < 60 mL/min or hemodialysis
Nucynta ER (tapentadol ER)	Tablet	Oral	Twice daily	• Schedule II controlled substance • Should not be used in severe renal impairment (CrCl < 30 mL/min) or severe hepatic impairment • Dose should be reduced in moderate hepatic impairment
Qutenza (capsaicin)	Patch	Transdermal	30-minute (DPN) or 60-minute (PHN) application of up to 4 patches every 3 months	• Only administered by physicians or health care professionals
Savella (milnacipran)	Tablet	Oral	Twice daily	• Dose should be reduced in CrCl < 30 mL/min • Caution advised in patients with moderate renal impairment or severe hepatic impairment

Abbreviations: CrCl = creatinine clearance; DPN = diabetic peripheral neuropathy; ESRD = end-stage renal impairment; PHN = postherpetic neuralgia

See the current prescribing information for full details.

CONCLUSION

- Included in this review are the neuropathic pain and fibromyalgia agents, duloxetine, gabapentin ER, gabapentin enacarbil ER, lidocaine, pregabalin, pregabalin ER, gabapentin, tapentadol ER, capsaicin, and milnacipran. In general, these agents are FDA-approved for the treatment of diabetic peripheral neuropathic pain, PHN, and/or fibromyalgia.
- Clinical trials support the use of the neuropathic pain and fibromyalgia agents for their FDA-approved indications. Available data demonstrated that neuropathic pain and fibromyalgia agents provide relief from pain; some studies have demonstrated improvement in functional outcomes and quality of life. Direct comparisons among the various agents are rare, and consistent benefit of one agent over another has not been demonstrated.
- According to the available literature, tricyclic antidepressants and duloxetine demonstrate an ability to provide pain relief in patients with painful diabetic neuropathy. While pregabalin and valproate have both demonstrated usefulness in the management of diabetic neuropathy, available literature suggests that the utility of gabapentin is less certain. There is minimal evidence evaluating the use of topical lidocaine and capsaicin for the management of painful diabetic neuropathy. Strong opioids have demonstrated efficacy compared to placebo; however, prescribers may consider this as last line therapy due to concerns regarding long-term safety, including addiction potential and misuse (*Attal et al 2010, Feldman et al 2021a, Schwartz et al 2011*).
  - Of the neuropathic pain and fibromyalgia agents included in the review, capsaicin, duloxetine, pregabalin, pregabalin ER, and tapentadol ER are approved for the management of diabetic neuropathy.
- For the management of PHN, available literature demonstrates that tricyclic antidepressants, gabapentin, pregabalin, opioids, topical capsaicin, botulinum toxin, and topical lidocaine are more effective compared to placebo (*Bajwa et al 2019*).
  - Of the neuropathic pain and fibromyalgia agents included in this review, gabapentin ER, gabapentin enacarbil ER, lidocaine, pregabalin, pregabalin ER, gabapentin, and capsaicin are approved for the management or relief of pain associated with PHN.
- For the management of fibromyalgia, available literature demonstrates that amitriptyline, cyclobenzaprine, duloxetine, gabapentin, milnacipran, and pregabalin are all appropriate treatment options. The choice of therapy is guided by specific symptoms, comorbidities, and patient preference (*Goldenberg 2020b*).

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Therapeutic Class Overview
Angiotensin-Converting Enzyme (ACE) Inhibitors

INTRODUCTION

- Approximately 126.9 million American adults are living with some form of cardiovascular (CV) disease (coronary heart disease, heart failure [HF], stroke, and hypertension), according to the American Heart Association (AHA) Heart Disease and Stroke Statistics 2021 update *(Virani et al 2021).* Cardiovascular disease is the number one cause of death in the United States.
- Hypertension (HTN) is an independent risk factor for CV disease and increases the mortality risks of CV disease and other diseases *(Virani et al 2021).* The 2017 American College of Cardiology (ACC)/AHA Clinical Practice Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults defines HTN as a blood pressure (BP) ≥ 130/80 mm Hg (*Whelton et al 2018).* Nearly half of American adults have HTN based on this definition.
- Lowering of BP has been shown to reduce the risk of fatal and nonfatal CV events including stroke and myocardial infarctions (MIs). Lipid control, diabetes mellitus (DM) management, smoking cessation, exercise, weight management, and limiting sodium intake may also reduce CV risk *(Eckel et al 2013, Virani et al 2021).*
- Numerous classes of antihypertensives are available to reduce BP. Some examples of antihypertensives include diuretics, angiotensin converting enzyme inhibitors (ACE-Is), angiotensin II receptor blockers (ARBs), beta (β)-blockers, and calcium channel blockers (CCBs). Selection of antihypertensive therapy for a specific patient is determined by patient characteristics such as ethnic group, and the presence of compelling indications such as HF, DM, chronic kidney disease (CKD), history of stroke or MI, and risk factors for coronary heart disease (CHD). Some patients require 2 or more antihypertensives from different pharmacological classes to achieve BP control *(Go et al 2014, Whelton et al 2018, Unger et al 2020).*
- In general, guideline-recommended BP goals in hypertensive adults range from < 130/80 mm Hg to < 140/90 mm Hg *(American Diabetes Association [ADA] 2021, Arnett et al 2019, de Boer et al 2017, Unger et al 2020, Whelton et al 2018).*
  - Blood pressure goals for older patients have long been a point of debate. The SPRINT trial followed patients ≥ 50 years with high BP and increased CV risks under intense hypertensive treatment (systolic blood pressure [SBP] goal of < 120 mm Hg) compared to standard HTN treatment (SBP goal of < 140 mm Hg) over a period of 3.2 years. The trial ended early; however, results demonstrated a reduced primary composite outcome of MI, acute coronary syndrome (ACS), stroke, HF, or CV death driven mainly by reduced HF events and CV death with intense treatment compared to standard treatment. The SPRINT trial pointed to potential clinical benefits associated with more intensive treatment in certain patients, although early termination of the trial and variations in the BP-measurement technique employed have called into question the generalizability of the results *(SPRINT Research Group 2015).*
  - A guideline from the American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP) on treatment of HTN in adults aged ≥ 60 years recommends standard and intense SBP treatment goals of < 150 mm Hg and < 140 mm Hg, respectively, with more intense BP reduction reserved for patients with a history of stroke or transient ischemic attack *(Qaseem et al 2017).*
- This review includes the ACE-Is and the ACE-I combination products.
  - The ACE-Is are Food and Drug Administration (FDA)-approved to treat HTN, HF, left ventricular (LV) dysfunction, diabetic nephropathy, acute myocardial infarction (AMI) to improve survival, and stable coronary artery disease (CAD) to reduce the risk of CV mortality or nonfatal MI.
  - The ACE-I combinations are products that combine an ACE-I with the diuretic hydrochlorothiazide (HCTZ), or a CCB (amlodipine or verapamil) in a fixed-dose formulation. By combining agents from different classes, these combination products are meant to increase the effectiveness of antihypertensive therapy through complementary mechanisms of action while minimizing the potential for dose-related adverse effects. All of the combination ACE-Is are FDA-approved for the treatment of HTN; however, with the exceptions of captopril/HCTZ and perindopril/amlodipine, none are FDA-approved for initial treatment of HTN.
- The single entity and combination ACE-Is included in this review are listed in Table 1.
- Medispan class: Antihypertensives - ACE Inhibitors; ACE Inhibitors & Thiazide/Thiazide-Like; ACE Inhibitor & Calcium Channel Blocker Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single-Entity ACE-Inhibitors	
Accupril (quinapril)	✔
Altace (ramipril)	✔
captopril*	✔
enalaprilat*	✔
fosinopril*	✔
Lotensin (benazepril)	✔
moexipril*	✔
perindopril*	✔
Prinivil, Qbrelis, Zestril (lisinopril)	✔ (Prinivil and Zestril only)
trandolapril*	✔
Vasotec, Epaned (enalapril)‡	✔
ACE-I/HCTZ Combinations	
Accuretic (quinapril/HCTZ)	✔
captopril/HCTZ*	✔
fosinopril/HCTZ*	✔
Lotensin HCT (benazepril/HCTZ)	✔
Vaseretic (enalapril/HCTZ)	✔
Zestoretic (lisinopril/HCTZ)†	✔
ACE-I/CCB Combinations	
Lotrel (benazepril/amlodipine)	✔
Prestalia (perindopril/amlodipine)	-
Tarka (trandolapril/verapamil ER)	✔

*Branded Aceon (perindopril), Capoten (captopril), Monopril (fosinopril), Univasc (moexipril), Vasotec (enalaprilat), Mavik (trandolapril), Capozide (captopril/HCTZ), and Monopril HCT (fosinopril/HCTZ) are no longer marketed.

†Branded Prinzide (lisinopril/HCTZ) is no longer marketed; however, branded Zestoretic and generic products are available.

‡As of August 2021, a generic for Epaned (enalapril) oral solution launched. All enalapril formulations are available as brand or generics.

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

INDICATIONS

Table 2. FDA-Approved Indications for Single-Entity ACE-Is

Indication	benazepril	captopril	enalapril/ enalaprilat	Epaned (enalapril)	fosinopril	lisinopril	moexipril	perindopril	Qbrelis (lisinopril)	quinapril	ramipril	trandolapril
Acute MI to improve survival						✔			✔			
Asymptomatic left ventricular dysfunction			✔ †	✔ §								
Diabetic nephropathy		✔										
Heart failure		✔	✔ †	✔ ‡	✔	✔			✔	✔	✔ *	✔ *
Hypertension in adults	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Hypertension in children aged > 1 month			✔ †	✔ **								
Hypertension in children aged ≥ 6 years	✔				✔	✔			✔			
Left ventricular dysfunction after MI		✔										✔
Stable coronary artery disease to reduce the risk of CV mortality or nonfatal MI								✔				

Indication	benazepril	captopril	enalapril/ enalaprilat	Epaned (enalapril)	fosinopril	lisinopril	moexipril	perindopril	Qbrelis (lisinopril)	quinapril	ramipril	trandolapril
Reduce risk of MI, stroke, and death from CV causes in patients ≥ 55 years of age at high risk for a major CV event											✔	

Abbrv: CV=cardiovascular, MI=myocardial infarction
*Post-MI.
**Epaned is not recommended in neonates (ie, infants 1 month of age or less), preterm infants who have not reached a corrected post-conceptual age of 44 weeks, and in pediatric patients with glomerular filtration rate < 30 mL/min/1.73m^2.
†Enalapril oral tablets only.
‡For symptomatic heart failure usually in combination with diuretics and digitalis.
§For clinically stable asymptomatic patients with ejection fraction ≤35%.

(Prescribing Information: Accupril 2019, Altace 2017, captopril 2020, enalaprilat 2021, Epaned 2020, fosinopril 2021, Lotensin 2019, moexipril 2015, perindopril 2019, Prinivil 2019, Qbrelis 2020, trandolapril 2018, Vasotec 2020, Zestril 2020)

Table 3. FDA-Approved Indications for Combination ACE-Is

Generic Name	Hypertension; not for initial therapy	Hypertension in patients not adequately controlled on monotherapy with either agent	Hypertension as either initial therapy or substituted for previously titrated doses of the individual products	Hypertension as either initial therapy or in patients not adequately controlled on monotherapy
ACE-I/HCTZ Combinations				
benazepril/HCTZ	✔			
captopril/HCTZ			✔	
enalapril/HCTZ	✔			
fosinopril/HCTZ	✔			
lisinopril/HCTZ	✔			
quinapril/HCTZ	✔			
ACE-I/CCB Combinations				
benazepril/amlodipine		✔		
perindopril/amlodipine*				✔
trandolapril/verapamil ER	✔			

Abbrv: ACE=angiotensin converting enzyme, CCB=calcium channel blocker, ER=extended release, HCTZ=hydrochlorothiazide
*Perindopril/amlodipine may be used as initial therapy in patients likely to need multiple drugs to achieve blood pressure goals.

(Prescribing Information: Accuretic 2021, captopril/HCTZ 2020, fosinopril/HCTZ 2020, Lotensin HCT 2020, Lotrel 2021, Prestalia 2019, Tarka 2019, Vaseretic 2020, Zestoretic 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

- ACE-Is have demonstrated efficacy for the treatment of HTN in adults. A Cochrane systematic review of 92 randomized, placebo-controlled trials evaluated the BP-lowering ability of 14 different ACE-Is (N = 12,954). On average, SBP was lowered by 8 mm Hg and diastolic blood pressure (DBP) by 5 mm Hg. There were no clinically meaningful BP lowering differences among the various ACE-Is *(Heran et al 2008)*.
  - Enalapril has demonstrated efficacy for the treatment of HTN in children aged 6 to 16 years *(Wells et al 2002)*.

- Meta-analyses have shown that ACE-Is and ARBs have similar long-term effects on BP *(Sanders et al 2011, Savarese et al 2013).* Additionally, a Cochrane review involving 11,007 subjects with primary HTN found no evidence of a difference in total mortality or CV outcomes for ACE-Is in comparison to ARBs (*Li 2014*).

- ACE-Is have been shown to be effective for CAD and in reducing the risk for CV mortality, MI, and stroke in clinical trials *(ADVANCE Collaborative Group 2007, Blood Pressure Lowering Treatment Trialists' Collaboration 2007, Dahlof et al 2005, Fox et al 2003, Nissen et al 2004, ONTARGET Investigators 2008, Pilote et al 2004, Pitt et al 2003, PREAMI Investigators 2006, PROGRESS Collaborative Group 2001, Sanders et al 2011, Savarese et al 2013, Swedberg et al 1992, The Heart Outcomes Prevention Evaluation Study Investigators 2000, The PEACE Trial Investigators 2004, van Vark et al 2012, Zoungas et al 2014).*
  - Additionally, in a retrospective analysis of patients > 65 years of age, ramipril was associated with significantly lower mortality 1 year after MI compared to captopril, enalapril, fosinopril, lisinopril, and quinapril. There were no significant differences between ramipril and perindopril *(Pilote et al 2004).*
  - In meta-regression analyses of 26 large-scale trials, ACE-Is and ARBs appeared to have similarly beneficial BP-dependent effects for risk reduction of stroke, CHD, and HF *(Blood Pressure Lowering Treatment Trialists' Collaboration 2007).*
  - For patients with mitral regurgitation secondary to MI, both ACE-Is and ARBs have been shown to improve prognosis *(Okura et al 2016).*
- Clinical trials have demonstrated the efficacy of ACE-Is in reducing mortality associated with congestive HF *(Cohn et al 1991, Dickstein et al 2002, Dobre et al 2008, Kober et al 1995, Lee et al 2004, McKelvie et al 1999, Packer et al 1999, Pfeffer et al 1992, Pfeffer et al 2003, Pitt et al 1997, Pitt et al 2000, The Acute Infarction Ramipril Efficacy [AIRE] Study Investigators 1993, The CONSENSUS Trial Study Group 1987, The SOLVD Investigators 1991, The SOLVD Investigators 1992, Tu et al 2005).*
  - No significant differences were noted when ACE-Is and ARBs were compared *(Dickstein et al 2002, Lee et al 2004, McKelvie et al 1999, Pfeffer et al 2003, Pitt et al 1997, Pitt et al 2000).*
- ACE-Is have also shown efficacy for protection against the development of progressive nephropathy in patients with DM *(Barnett et al 2004, Casas et al 2005, Hou et al 2007, Morgensen et al 2000, Ruggenenti et al 2004, The GISEN Group 1997, Wright et al 2002).*
  - In patients with type 2 DM, combination treatment with perindopril and indapamide reduced SBP and significantly decreased micro- and macrovascular events vs placebo *(ADVANCE Collaborative Group 2007, Zoungas et al 2014).*
  - In a meta-analysis comparing ACE-Is to ARBs for preventing the progression of diabetic kidney disease, the effects on renal outcomes were similarly beneficial between the groups *(Strippoli et al 2006).* In a meta-analysis of patients with CKD, including those with diabetic and nondiabetic nephropathy, both ACE-Is and ARBs reduced the risk of kidney failure compared to other active agents and placebo, and reduced CV events compared to placebo *(Xie et al 2016).* However, only ACE-Is reduced the risk of all-cause mortality compared to other active agents.
  - A meta-analysis of randomized antihypertensive trials in patients with DM and microalbuminuria found that reduction in albuminuria among normotensive patients was greatest with trandolapril plus candesartan, followed by trandolapril monotherapy. In hypertensive patients, reduction in albuminuria was greatest with fosinopril plus amlodipine, followed by fosinopril monotherapy. However, the combination therapies had inferior safety profiles when compared to ACE-I monotherapy with respect to dry cough, presyncope, and peripheral edema *(Huang et al 2017).*
  - In a recent trial enrolling adolescents with type 1 DM, the addition of an ACE-I did not change the albumin-to-creatinine ratio over 2 to 4 years of treatment vs placebo. However, the use of an ACE-I was associated with a lower incidence of microalbuminuria. The short duration of the trial was cited as an important limitation, and follow-up to evaluate the potential benefits of early intervention in this population is necessary *(Marcovecchio et al 2017).*
- Clinical trials have demonstrated the effectiveness of some ACE-I combination products compared to other ACE-I combination products or when compared to monotherapy *(Chrysant et al 2004, Chrysant et al 2007, Fogari et al 1997, Hilleman et al 1999, Jamerson et al 2004, Kuschnir et al 1996, Messerli et al 2000, Neutel et al 2005).*
  - Benazepril/amlodipine has demonstrated superior CV outcomes compared to benazepril/HCTZ *(Bakris et al 2010, Jamerson et al 2008, Weber et al 2010)*. In addition, benazepril/amlodipine has demonstrated higher antihypertensive efficacy compared to captopril/HCTZ *(Malacco et al 2002)* and olmesartan/HCTZ *(Kereiakes et al 2007).* Benazepril/amlodipine also demonstrated noninferiority to valsartan/HCTZ in lowering of DBP over 16 weeks in patients with HTN and DM *(Lee et al 2012).*

- When lisinopril/HCTZ was compared to a combination ARB, candesartan/HCTZ, no significant difference in antihypertensive efficacy was identified; however, the proportion of patients reporting at least 1 adverse event was significantly greater in the lisinopril/HCTZ group *(McInnes et al 2000)*.
- Trandolapril/verapamil has been associated with a significantly greater reduction of BP compared to either component as monotherapy *(Brunner et al 2007, Cifkova et al 2000, Karlberg et al 2000, Pepine et al 2003, Pepine et al 2006, Ruggenenti et al 2004)*.
- In 728 black patients from sub-Saharan Africa, blood pressure reductions were greater with amlodipine/HCTZ and amlodipine/perindopril than perindopril/HCTZ at 6 months (*Ojji et al 2019*).

- Studies have demonstrated that the combination of 2 renin angiotensin-aldosterone system (RAAS) inhibitors, including an ACE-I combined with an ARB, provides no renal or CV benefits and may lead to significant adverse events, particularly in patients with diabetes and/or renal insufficiency. Most notably, patients receiving combination therapy had increased rates of hyperkalemia, hypotension, and renal dysfunction. All agents in this class have safety warnings against combined use *(Fried et al 2013, ONTARGET Investigators 2008, Parving et al 2012, Pfeffer et al 2003, Sakata et al 2015)*.
- One meta-analysis compared the effectiveness of ACE-Is with ARBs and found that the 2 drug classes had similar effectiveness in lowering SPB and DBP, all-cause mortality, essential hypertension, fatal and non-fatal MI, and stroke. ACE-Is were more helpful in the prevention of and/or during hospitalization for heart failure than ARBs (*Dimou et al 2019*).

CLINICAL GUIDELINES

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

Table 4. Classification of BP measurements

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

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

- In patients with stage 1 HTN, it is reasonable to initiate therapy with a single antihypertensive agent. In patients with stage 2 HTN and BP more than 20/10 mm Hg higher than their target, 2 first-line agents of different classes should be initiated.
  - First-line antihypertensive agents include thiazide diuretics, CCBs, and ACE-Is or ARBs.
  - Diuretics, ACE-Is, ARBs, CCBs, and β-blockers have been shown to prevent CVD compared with placebo.
    - ACE-Is were notably less effective in preventing HF and stroke compared with CCBs in black patients. ARBs may be better tolerated than ACE-Is in black patients, with less cough and angioedema, but they offer no proven advantage over ACE-Is in preventing stroke or CVD in this population; thiazide diuretics (especially chlorthalidone) or CCBs are the best initial choice for single-drug therapy in this population, or as initial agents in a multidrug regimen.

  - An ACE-I is a preferred drug for treatment of HTN for those with CKD stage 3, or for stage 1 or 2 with albuminuria.
- The 2019 ACC/AHA guideline on the primary prevention of CVD recommends using BP-lowering medications in hypertensive adults: with an estimated 10-year ASCVD risk ≥ 10% and a SBP ≥ 130 mm Hg or DBP ≥ 80 mm Hg; with diabetes and a BP > 130/80 mm Hg; or with an estimated 10-year ASCVD risk < 10% and a SBP ≥ 140 mm Hg or DBP ≥ 90 mm Hg (*Arnett et al 2019*). A target BP of < 130/80 mm Hg is recommended for most patients.
- The ADA position statement on DM and HTN recommends that most patients with DM and HTN be treated to a goal BP of < 140/90 mm Hg. Target BPs should be individualized and lower BP targets such as < 130/80 mm Hg may be appropriate for individuals at high risk of CVD *(ADA 2021, de Boer et al 2017)*.
  - Treatment for HTN should include drug classes demonstrated to reduce CV events in patients with DM: ACE-Is, ARBs, thiazide diuretics, or dihydropyridine CCBs.
  - Patients with BP ≥ 160/100 mm Hg should have prompt initiation of 2 drugs or a single-pill combination of drugs demonstrated to reduce CV events in patients with DM.
  - An ACE-I or ARB, at the maximum tolerated dose indicated for BP treatment, is the recommended first-line treatment for HTN in patients with DM and a urine albumin-to-creatinine ratio ≥ 30 mg/g creatinine.
- The American Academy of Pediatrics clinical practice guideline for high BP in children and adolescents recommends that the treatment goal with nonpharmacologic and pharmacologic therapy should be a reduction in SBP and DBP to < 90th percentile and < 130/80 mm Hg in adolescents ≥ 13 years old *(Flynn et al 2017)*.
  - In hypertensive children and adolescents who have failed lifestyle modifications, clinicians should initiate pharmacologic treatment with an ACE-I, ARB, long-acting CCB, or thiazide diuretic.
  - Children and adolescents with CKD, HTN, and proteinuria should be treated with an ACE-I or ARB.
- Various other guidelines and position statements place ACE-Is as first-line therapy in patients with DM and microalbuminuria; with stable CAD and HTN; with HF; and after an MI. ACE-Is have demonstrated clinical benefit and reductions in morbidity and mortality in these populations *(Amsterdam et al 2014, Arnold et al 2020, Go et al 2014, Rosendorff et al 2015, Unger et al 2020, Yancy et al 2017).*
  - Due to differences in the activity of the RAAS, ACE-Is are often less effective as HTN monotherapy in black patients (African or Caribbean descent). Alternative first-line options for these patients include CCBs and thiazide diuretics (or a CCB with an ARB) *(Unger et al 2020).*

SAFETY SUMMARY

Boxed Warnings

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

Contraindications

- ACE-Is are contraindicated in patients with angioedema or with a history of hereditary or idiopathic angioedema.
- ACE-Is are contraindicated in combination with a neprilysin inhibitor (eg, sacubitril). An ACE-I should not be administered within 36 hours of a neprilysin inhibitor.
- ACE-Is are contraindicated in combination with aliskiren in patients with DM; the combination should also be avoided in patients with renal impairment (glomerular filtration rate [GFR] < 60 mL/min/1.73m^2).
- ACE-I combinations with HCTZ are contraindicated in patients with anuria.
- Due to the verapamil component, trandolapril/verapamil is contraindicated in patients with severe LV dysfunction, hypotension or cardiogenic shock, sick sinus syndrome, second or third degree atrioventricular (AV) block, patients with atrial flutter or fibrillation and an accessory bypass, and patients taking flibanserin.

Warnings and Precautions

- ACE-Is have warnings for anaphylactoid reactions including head and neck angioedema and intestinal angioedema; hypotension; hyperkalemia; and cholestatic jaundice and hepatic failure.
  - Captopril has been shown to cause agranulocytosis and bone marrow depression rarely in patients with uncomplicated HTN, but more frequently in patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Available data from clinical trials are insufficient to show that other ACE-Is do not cause agranulocytosis at similar rates.
- Verapamil has a negative inotropic effect, which is compensated by its afterload reduction (decreased systemic vascular resistance) properties without a net impairment of ventricular performance. However, congestive HF and/or pulmonary

edema have been reported. Verapamil-containing products should be avoided in patients with severe LV dysfunction (eg, ejection fraction < 30%, pulmonary wedge pressure > 20 mm Hg, or severe symptoms of cardiac failure) and in patients with any degree of ventricular dysfunction if they are receiving a β-blocker.
- Perindopril/amlodipine is not recommended in patients with HF. Use caution with amlodipine in patients suffering from aortic or mitral stenosis, or obstructive hypertrophic cardiomyopathy.
- HCTZ may alter glucose tolerance and raise levels of cholesterol, triglycerides, and serum uric acid levels (which may precipitate gout). HCTZ may cause elevations of serum calcium and monitoring is recommended in patients with hypercalcemia.
  - HCTZ is associated with an increased risk of non-melanoma skin cancer.

Adverse Effects
- Common adverse effects of ACE-Is include headache, dizziness, cough, and hypotension.
- ACE-Is may cause electrolyte abnormalities and elevations of blood urea nitrogen (BUN) and creatinine.
- Some combination products contain amlodipine, which may cause peripheral edema.

Important Drug Interactions
- Dual blockade of the RAAS with ARBs, ACE-I, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure), compared to monotherapy.
  - Most patients receiving the combination of 2 RAAS inhibitors do not obtain any additional benefit compared to monotherapy.
- In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, co-administration of non-steroidal anti-inflammatory drugs (NSAIDs) with ACE-Is may result in deterioration of renal function, including acute renal failure. The antihypertensive effect of ACE-Is may be attenuated by NSAIDs.
- Concomitant use of ACE-Is and potassium-sparing diuretics (eg, spironolactone, amiloride, triamterene) can increase the risk of hyperkalemia.
- Patients taking mammalian target of rapamycin (mTOR) inhibitors (eg, temsirolimus, sirolimus, everolimus) or a neprilysin inhibitor may be at increased risk for angioedema with concomitant ACE-I use.
- Verapamil has drug interactions with colchicine, digoxin, immunosuppressants, and several others. Consult the prescribing information for trandolapril/verapamil for the full listing and descriptions.

DOSING AND ADMINISTRATION

- All ACE-I-containing products, with the exception of fosinopril, require dosage adjustment in patients with renal impairment.
- The combination ACE-I products are not recommended for use in patients with severe renal impairment and should be used with caution in patients with hepatic impairment.
- Breastfeeding is not recommended while on ACE-I-containing products.

Table 5. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single-Entity ACE-Is				
benazepril	Tablets	Oral	HTN: Once or twice daily	FDA-approved for use in children ≥ 6 years.
captopril	Tablets	Oral	Diabetic nephropathy, HF, LV dysfunction after MI: Three times daily HTN: Twice to 3 times daily	Take 1 hour before meals.
enalapril	Tablets, 1 mg/mL oral solution	Oral	Asymptomatic LV dysfunction, HF:	FDA-approved for use in children aged ≥ 1 month.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Twice daily HTN: Daily in 1 or 2 divided doses	
enalaprilat	Injection	IV	HTN: Every 6 hours	Administer as a slow IV infusion or as an IV bolus over 5 minutes.
fosinopril	Tablets	Oral	HF: Once daily HTN: Daily in 1 or 2 divided doses	FDA-approved for use in children ≥ 6 years weighing more than 50 kg.
lisinopril	Tablets, 1 mg/mL solution	Oral	AMI to improve survival, HF, HTN: Once daily	FDA-approved for use in children ≥ 6 years.
moexipril	Tablets	Oral	HTN: Daily in 1 or 2 divided doses	Take 1 hour before meals.
perindopril	Tablets	Oral	HTN: Daily in 1 or 2 divided doses Stable CAD: Once daily	Bioavailability of perindopril is higher with hepatic impairment. Dosage adjustment in elderly patients is required.
quinapril	Tablets	Oral	HF: Twice daily HTN: Daily in 1 or 2 divided doses	Dosage adjustment in elderly patients is required.
ramipril	Capsules	Oral	HF after MI: Twice daily HTN: Daily in 1 or 2 divided doses Reduce risk of MI, stroke, and death from CV causes: Once daily	Capsules should be swallowed whole; capsule contents can be sprinkled on applesauce or mixed in 120 mL of water or apple juice.
trandolapril	Tablets	Oral	HF or LV dysfunction after MI: Once daily HTN: Once to twice daily	Dosage adjustment with hepatic cirrhosis is required.
ACE-I/HCTZ Combinations*				
benazepril/HCTZ	Tablets	Oral	HTN: Once daily	
captopril/HCTZ	Tablets	Oral	HTN: Once daily	Take 1 hour before a meal.
enalapril/HCTZ	Tablets	Oral	HTN: Once daily	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
fosinopril/HCTZ	Tablets	Oral	HTN: Once daily	
lisinopril/HCTZ	Tablets	Oral	HTN: Once daily	
quinapril/HCTZ	Tablets	Oral	HTN: Once daily	
ACE-I/CCB Combinations*				
benazepril/amlodipine	Capsules	Oral	HTN: Once daily	Exposure is increased in elderly patients and in hepatic dysfunction; a lower dosage should be considered.
perindopril/amlodipine	Tablets	Oral	HTN: Once daily	Exposure is increased in elderly patients and in hepatic dysfunction; a lower maximum dosage should be considered in elderly patients.
trandolapril/verapamil	Tablets, extended-release	Oral	HTN: Once daily	Administer with food.

Abbrv: ACE-I=angiotensin converting enzyme inhibitor, AMI=acute myocardial infarction, CAD=coronary artery disease, CCB=calcium channel blocker, CV=cardiovascular, FDA=Food and Drug Administration, HCTZ=hydrochlorothiazide, HF=heart failure, HTN=hypertension, IV=intravenous, LV=left ventricular, MI=myocardial infarction

*Captopril/HCTZ and perindopril/amlodipine are the only combination ACE-Is that are FDA-approved for use as initial HTN therapy. All other agents are recommended for use after the patient has failed to achieve the desired antihypertensive effect and/or experienced unacceptable side effects on monotherapy with one of the principal components. Combination therapy may be initiated after failure on monotherapy or substituted for the titrated individual components.

See the current prescribing information for full details.

CONCLUSION

- The single-entity and combination ACE-I products are FDA-approved for the treatment of HTN, and most are generically available. Most single-entity ACE-Is are also approved for the treatment of HF. With the exception of captopril/HCTZ and perindopril/amlodipine, the combination ACE-Is are not approved for use as initial HTN therapy.
- Evidence-based guidelines recognize the important role ACE-Is play in the treatment of HTN and other CV and renal diseases. There is no consensus on BP goals for certain populations such as older patients and patients with DM. The current ACC/AHA guidelines *(Whelton et al 2018)* recommend a BP goal of < 130/80 mm Hg for most patients.
- ACE-Is have demonstrated efficacy in the treatment of HTN, for protection against progressive nephropathy in patients with DM, for reducing mortality associated with HF, and for reducing the risk of CV mortality, MI, and stroke in patients with CAD.
  - ACE-Is have generally demonstrated comparable efficacy to ARBs across indications.
- Studies have demonstrated that the combination of 2 RAAS inhibitors, including an ACE-I with an ARB, provide no renal or CV benefits and may increase risk of adverse events, including hyperkalemia, hypotension, and renal dysfunction. All agents in this class have safety warnings against combined use.
- All ACE-Is have a boxed warning for use in pregnancy and are contraindicated in patients with a history of angioedema. Other warnings include anaphylactoid reactions including head and neck angioedema, hypotension, hyperkalemia, and cholestatic jaundice and hepatic failure.
- Common adverse effects of ACE-Is include headache, dizziness, cough, and hypotension. ACE-Is may cause electrolyte abnormalities and increases in BUN and creatinine.
- Current guidelines recommend ACE-Is as a first-line therapy for patients with HTN, DM with microalbuminuria, stable CAD with HTN, HF, and post-MI *(ADA 2021, Amsterdam et al 2014, Arnett et al 2019, Arnold et al 2020, de Boer et al 2017, Go et al 2014, Rosendorff et al 2015, Unger et al 2020, Whelton et al 2018, Yancy et al 2017).*
  - Due to differences in the activity of the RAAS, ACE-Is are often less effective as HTN monotherapy in black patients; CCBs and thiazide diuretics should be used as first-line options in these patients.

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Established Drug Classes

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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