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Silver State Scripts Board Meeting

JUNE 23, 2022

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Agenda

Steve Sisolak
Governor

Richard Whitley, MS
Director

DEPARTMENT OF HEALTH AND HUMAN SERVICES

DIVISION OF HEALTH CARE FINANCING AND POLICY

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

Suzanne Bierman, JD MPH
Administrator

NOTICE OF PUBLIC MEETING – SILVER STATE SCRIPTS BOARD

Date of Posting: May 9, 2022

Date of Meeting: Thursday, June 23, 2022, 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
(See final agenda page for full link or employ the shortened link directly below)

OR

https://tinyurl.com/SSSB-JUN-2022

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

Hampton Inn Tropicana
4975 S. Dean Martin Drive
Las Vegas, Nevada, 89118
(702) 948-8100

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: 793 621 411#

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 March 24, 2022.
b. Status Update by DHCFP.

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

a. **For Possible Action:** Discussion and possible adoption of Cardiovascular Agents - Antihypertensive Agents - Beta-Blockers.

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

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

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 Cardiovascular Agents – Antilipemic - Omega-3 Fatty Acids.

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 Neurological Agents – Anticonvulsants.

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 Ophthalmic Agents - Antiglaucoma 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.

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

6. 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 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.

Full Microsoft Teams Link:

https://teams.microsoft.com/l/meetup-join/19%3ameeting_NzQ0M2JjOGItZTFkYi00YjUwLTk5ODMtNWU0YTRhOWY5NjNi%40thread.v2/0?context=%7b%22Tid%22%3a%22db05faca-c82a-4b9d-b9c5-0f64b6755421%22%2c%22Oid%22%3a%222311bd22-e984-4bae-84b9-bedd149b3c85%22%7d

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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

Aditi Singh, MD

Elizabeth Gonzalez, PharmD

Izabela Niezborala, Pharm D

Silver State Scripts Board Meeting scheduled for 2022

Date	Time	South Nevada Location	North Nevada Location
September 22, 2022	1:00 PM	To Be Determined	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

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Current Preferred Drug List

Preferred Products	PA Criteria	Non-Preferred Products
Analgesics		
Analgesic/Miscellaneous		
Neuropathic Pain/Fibromyalgia Agents		
DULOXETINE GABAPENTIN LYRICA® LIDODERM® * 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 * LYRICA® CR HORIZANT® PREGABALIN PREGABALIN ER 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: Form FA-59	AVINZA® QL BUPRENORPHINE PATCH DOLOPHINE® DURAGESIC® PATCHES QL EXALGO® HYDROCODONE BITARTRATE ER KADIAN® QL METHADONE METHADOSE® MS CONTIN® QL OPANA ER® OXYCODONE SR QL OXYMORPHONE SR XARTEMIS XR® QL ZOHYDRO ER® QL
Opiate Agonists - Abuse Deterrent		
XTAMPZA ER®		HYDROCODONE BITARTRATE ER HYSINGLA ER® OXYCONTIN® QL

Preferred Products	PA Criteria	Non-Preferred Products
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) - Oral		
CELECOXIB CAP DICLOFENAC POTASSIUM DICLOFENAC TAB DR 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	CAMBIA® POWDER 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 300mg/5mL		TOBI PODHALER® TOBRAMYCIN NEBULIZER 300mg/4mL

Preferred Products	PA Criteria	Non-Preferred Products
Antivirals		
Alpha Interferons		
PEGASYS® PEGASYS® CONVENIENT PACK		
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	PA Required	CEDAX® CAPS and SUSP CEFDITOREN

	Preferred Products	PA Criteria	Non-Preferred Products
	CEFPODOXIME TABS and SUSP		CEFIXIME CAPS/SUSP OMNICEF® SPECTRACEF® SUPRAX® VANTIN®
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®	Prior authorization is required for all drugs in this class Form FA-61	ENSPRYNG® ILARIS® ENTYVIO® ILUMYA® REMICADE® RINVOQ® SKYRIZI® TREMFYA XELJANZ XR®

Preferred Products	PA Criteria	Non-Preferred Products
OLUMIANT® ORENCIA® OTEZLA® RENFLEXIS® SILIQ® SIMPONI® STELARA® TALTZ® XELJANZ®		
Multiple Sclerosis Agents		
Injectable		
AVONEX® AVONEX® ADMIN PACK BETASERON® COPAXONE® 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® REBIF® QL
Oral		
AUBAGIO® GILENYA® TECFIDERA®	PA required	BAFIERTAM® DIMETHYL FUMARATE MAVENCLAD® MAYZENT® PONVORY® 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®

	Preferred Products	PA Criteria	Non-Preferred Products
			EPROSARTAN HYZAAR® IRBESARTAN MICARDIS® TELMISARTAN TEVETEN®
Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors)			
	BENAZEPRIL BENAZEPRIL HCTZ CAPTOPRIL CAPTOPRIL HCTZ ENALAPRIL ENALAPRIL HCTZ EPANED® £ LISINOPRIL LISINOPRIL HCTZ RAMIPRIL	£ PREFERRED FOR AGES 10 AND UNDER ‡ NONPREFERRED FOR OVER 10 YEARS OLD	ACCURETIC® ENALAPRIL SOLN EPANED® ‡ FOSINOPRIL MAVIK® MOEXIPRIL 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®		EXFORGE® EXFORGE HCT® ISRADIPINE KATERZIA® LOTREL® MATZIM TAB LA

Preferred Products	PA Criteria	Non-Preferred Products
DILTIA XT® DILTIAZEM ER DILTIAZEM HCL FELODIPINE ER NICARDIPINE NIFEDIPINE ER TAZTIA XT® VERAPAMIL VERAPAMIL ER		NISOLDIPINE ER NORVASC® NYMALIZE® SOLN
Vasodilators		
Inhaled		
VENTAVIS® TYVASO®		
Oral		
BOSENTAN ORENITRAM® REVATIO ® TADALAFIL		ADCIRCA® ADEMPAS® ALYQ® AMBRISENTAN LETAIRIS® OPSUMIT® SILDENAFIL TRACLEER® UPTRAVI®
Antilipemics		
Bile Acid Sequestrants		
COLESTIPOL CHOLESTYRAMINE WELCHOL®		COLESEVELAM 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 EZETIMIBE-SIMVASTATIN		ALTOPREV® AMLODIPINE/ATORVASTATIN

	Preferred Products	PA Criteria	Non-Preferred Products
	LOVASTATIN PRAVASTATIN ROSUVASTATIN SIMVASTATIN		CADUET® CRESTOR® QL EZALLOR® FLUVASTATIN FLUVASTATIN XL LESCOL® LESCOL XL® LIPITOR® LIPTRUZET® LIVALO® MEVACOR® PRAVACHOL® SIMCOR® VYTORIN® ZOCOR® ZYPITAMAG®
Niacin Agents			
	NIASPAN® (Brand only) NIACIN ER (ALL GENERICS)		NIACOR®
Omega-3 Fatty Acids			
	OMEGA-3-ACID VASCEPA®		LOVAZA®
PCSK9 Inhibitors			
	PRALUENT® REPATHA®		
Miscellaneous Heart Failure Agents (NEW)			
	CORLANOR® * ENTRESTO® *	* PA required	VERQUVO®
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®		DICLOFENAC (gel/sol) EMLA®

Preferred Products	PA Criteria	Non-Preferred Products
LIDOCAINE LIDOCAINE HC LIDOCAINE VISCOUS LIDOCAINE/PRILOCAINE LIDODERM® QL PENNSAID® VOLTAREN® GEL		LENZAPRO® LICART® LIDOCAINE 5% PATCH 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
Topical Antivirals		
ABREVA® DENAVIR® XERESE® CREAM ZOVIRAX® CREAM ZOVIRAX®, OINTMENT		ACYCLOVIR OINT ACYCLOVIR CREAM
Topical Scabicides		
LINDANE NATROBA® NIX® PERMETHRIN RID® ULESFIA®		EURAX® IVERMECTIN MALATHION OVIDE® SKLICE® SPINOSAD VANALICE® GEL

Preferred Products	PA Criteria	Non-Preferred Products
Topical Anti-inflammatory Agents		
Immunomodulators: Topical		
ELIDEL® QL EUCRISA® PROTOPIC® QL	Prior authorization is required for all drugs in this class	PIMECROLIMUS TACROLIMUS
Topical Antineoplastics		
Topical Retinoids		
DIFFERIN® EPIDUO® RETIN-A TAZORAC® ZIANA®	Payable only for recipients up to age 21.	ARAZLO® ADAPALENE GEL AND CREAM ADAPALENE/BENZOYL PEROXIDE ATRALIN® AVITA® 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®
Potassium Removing Agents (NEW)		
LOKELMA® SODIUM POLYSTYRENE SULFONATE SPS®		VELTASSA®
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

Preferred Products	PA Criteria	Non-Preferred Products
		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 for > 12 years	ACIPHEX® ESOMEPRAZOLE LANSOPRAZOLE NEXIUM® CAPSULES PREVACID® PRILOSEC® PRILOSEC® OTC TABS PROTONIX® RABEPRAZOLE SODIUM
Functional Gastrointestinal Disorder Drugs		
AMITIZA® LINZESS®	PA required	LUBIPROSTONE 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
Gastrointestinal Enzymes		
CREON® PANCREAZE® ZENPEP®		PANCRELIPASE PERTZYE® ULTRESA®

	Preferred Products	PA Criteria	Non-Preferred Products
			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 DETROL® DETROL LA® OXYBUTYNIN TABS/SYRUP/ER SOLIFENACIN TOVIAZ®		DARIFENACIN DITROPAN XL® ENABLEX® FLAVOXATE GELNIQUE® GEMTESA® MYRBETRIQ® OXYTROL® SANCTURA® TOLTERODINE TROSPIUM VESICARE® VESICARE® LS
Hematological Agents			
Anticoagulants			
Oral			
	COUMADIN® ELIQUIS® * JANTOVEN® PRADAXA® * QL WARFARIN XARELTO ® *	* No PA required if approved diagnosis code transmitted on claim	SAVAYSA®*

Preferred Products	PA Criteria	Non-Preferred Products
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: Form FA-72	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® RYBELSUS® TRULICITY® VICTOZA®	No PA required if Dx of Type 2 Diabetes transmitted on claim	ADLYXIN® BYDUREON® BCISE SOLIQUA® TANZEUM® XULTOPHY®
Insulins (Vials, Pens and Inhaled)		
APIDRA® HUMALOG® HUMULIN® 70/30 HUMULIN® U-500 INSULIN ASPART MIX INSULIN LISPRO INJ 100U/ML INSULIN LISPRO MIX LANTUS® LEVEMIR ® NOVOLIN® N NOVOLIN® R NOVOLOG® INSULIN ASPART TOUJEO SOLO® 300 IU/ML TRESIBA FLEX INJ		ADMELOG® AFREZZA® BASAGLAR® FIASP® HUMULIN ® N HUMULIN ® R HUMALOG® U-200 LYUMJEV® NOVOLIN® 70/30 SEMGLEE® LYUMJEV®
Meglitinides		
REPAGLINIDE		NATEGLINIDE PRANDIN® STARLIX®
Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors		
FARXIGA® GLYXAMBI® INVOKANA®		INVOKAMET® XR QTERN® SEGLUROMET®

Preferred Products	PA Criteria	Non-Preferred Products
INVOKAMET® JARDIANCE® SYNJARDY® SYNJARDY® XR XIGDUO XR®		STEGLATRO® STEGLUJAN™ TRIJARDY® XR
Sulfonylureas		
DIABETA® GLIMEPIRIDE (Amaryl®) GLIPIZIDE (Glucotrol®) GLIPIZIDE EXT-REL (Glucotrol XL®) GLYBURIDE MICRONIZED (Glynase®) GLYBURIDE (Diabeta®) METAGLIP®		AMARYL® CHLORPROPAMIDE GLYNASE® GLUCOTROL® GLUCOTROL XL® GLYBURIDE/METFORMIN (Glucovance®) GLUCOVANCE® GLIPIZIDE/METFORMIN (Metaglip®) TOLAZAMIDE TOLBUTAMIDE
Thiazolidinediones		
PIOGLITAZONE		ACTOPLUS MET XR® ACTOPLUS MET® ACTOS® AVANDAMET® AVANDARYL® AVANDIA® DUETACT® PIOGLITAZONE/METFORMIN PIOGLITAZONE/GLIMEPR
Anti-Hypoglycemic Agents		
BAQSIMI® GLUCAGEN® ZEGALOGUE®		GLUCAGON EMERGENCY KIT GVOKE®
Pituitary Hormones		
Growth hormone modifiers		
GENOTROPIN® NORDITROPIN®	PA required for entire class Form FA-67	HUMATROPE® NUTROPIN AQ® OMNITROPE® NUTROPIN® SAIZEN®

Preferred Products	PA Criteria	Non-Preferred Products
		SEROSTIM® SOMAVERT® TEV-TROPIN® ZORBTIVE®
Progestins for Cachexia		
MEGESTROL ACETATE, SUSP		MEGACE ES®
Monoclonal Antibodies for the treatment of Respiratory Conditions		
DUPIXENT® FASENRA® NUCALA® XOLAIR®	PA Required	CINQAIR®
Musculoskeletal Agents		
Antigout Agents		
ALLOPURINOL COLCRYS® TAB FEBUXOSTAT PROBENECID PROBENECID/COLCHICINE		COLCHICINE TAB/CAP MITIGARE® CAP ULORIC® 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		

Preferred Products	PA Criteria	Non-Preferred Products
CHLORZOXAZONE CYCLOBENZAPRINE DANTROLENE METHOCARBAMOL METHOCARBAMOL/ASPIRIN ORPHENADRINE CITRATE ORPHENADRINE COMPOUND TIZANIDINE		
Neurological Agents		
Alzheimers Agents		
DONEPEZIL DONEPEZIL ODT EXELON® PATCH EXELON® SOLN MEMANTINE TABS		ARICEPT® 23mg ARICEPT® GALANTAMINE GALANTAMINE ER MEMANTINE SOL MEMANTINE XR NAMENDA® TABS NAMENDA® XR TABS NAMZARIC® RAZADYNE® RAZADYNE® ER RIVASTIGMINE CAPS RIVASTIGMINE TRANSDERMAL
Anticonvulsants		
CARBAMAZEPINE CARBAMAZEPINE XR CARBATROL ER® CELONTIN® DEPAKENE® DEPAKOTE ER® DEPAKOTE® DIVALPROEX SODIUM DIVALPROEX SODIUM ER EPIDIOLEX® EPITOL® ETHOSUXIMIDE FELBATOL® FINTEPLA® * FYCOMPA® GABAPENTIN	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
			GABITRIL® LAMACTAL ODT® LAMACTAL XR® LAMICTAL® LAMOTRIGINE LEVETIRACETAM LYRICA® NEURONTIN® OXCARBAZEPINE QUDEXY XR® STAVZOR® DR TEGRETOL® TEGRETOL XR® TOPAMAX® TOPIRAGEN® TOPIRAMATE IR 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

Preferred Products	PA Criteria	Non-Preferred Products
Hydantoins		
CEREBYX® DILANTIN® ETHOTOIN FOSPHENYTOIN PEGANONE® PHENYTEK® PHENYTOIN PRODUCTS		
Anti-Migraine Agents		
Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists		
AIMOVIG® AJOVY® EMGALITY® NURTEC® ODT QULIPTA®	PA required for all products	UBRELVY® VYEPTI®
Serotonin-Receptor Agonists		
FROVA® RELPAX® RIZATRIPTAN ODT SUMATRIPTAN TABLET ZOLMITRIPTAN NASAL SPRAY ZOLMITRIPTAN ODT	PA required for exceeding Quantity Limit	ALMOTRIPTAN AMERGE® AXERT® ELETRIPTAN FROVATRIPTAN SUCCINATE IMITREX® MAXALT® TABS MAXALT® MLT NARATRIPTAN ONZETRA XSAIL® REYVOW® RIZATRIPTAN BENZOATE SUMATRIPTAN INJECTION SUMATRIPTAN NASAL SPRAY SUMATRIPTAN/NAPROXEN SUMAVEL® TOSYMRA® TREXIMET® ZEMBRACE SYMTOUCH ZOLMITRIPTAN ZOMIG® SPRAY ZOMIG® TAB ZOMIG® ZMT

Preferred Products	PA Criteria	Non-Preferred Products
Antiparkinsonian Agents		
Dopamine Precursors		
CARBIDOPA/LEVODOPA CARBIDOPA/LEVODOPA ER CARBIDOPA/LEVODOPA ODT CARBIDOPA/LEVODOPA/ ENTACAPONE	*Trial of only one agent is required before moving to a non-preferred agent*	DUOPA™ INBRIJA™ (INH) LODOSYN® TAB RYTARY™ STALEVO®
Non-ergot Dopamine Agonists		
PRAMIPEXOLE ROPINIROLE ROPINIROLE ER		MIRAPEX® MIRAPEX® ER NEUPRO® REQUIP® REQUIP XL®
Movement Disorders (NEW)		
AUSTEDO® * INGREZZA® * TETRABENAZINE	* PA required	XENAZINE®
Ophthalmic Agents		
Antiglaucoma Agents		
ALPHAGAN P® AZOPT® BETAXOLOL BETOPTIC S® CARTEOLOL COMBIGAN® DORZOLAM DORZOLAM / TIMOLOL LATANOPROST LEVOBUNOLOL LUMIGAN® METIPRANOLOL RHOPRESSA® ROCKLATAN® SIMBRINZA® TIMOLOL DROPS/ GEL SOLN TRAVATAN Z® TRAVATAN®		ALPHAGAN® BETAGAN® BETOPTIC ® BIMATOPROST BRIMONIDINE BRINZOLAMIDE COSOPT PF® COSOPT® DORZOL/TIMOL SOL PF OCUPRESS® OPTIPRANOLOL® TIMOPTIC XE® TIMOPTIC® TRAVOPROST BAK Free TRUSOPT® VYZULTA® XALATAN® XELPROS® ZIOPTAN®

Preferred Products	PA Criteria	Non-Preferred Products
Ophthalmic Antihistamines		
AZELASTINE BEPREVE® KETOTIFEN LASTACRAFT® OLOPATADINE (drop/sol) ZADITOR OTC®		ALAWAY® ALOMIDE ALOCRIL ELESTAT® EMADINE® OPTIVAR® PATADAY® PATANOL® PAZEO® 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 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®

Preferred Products	PA Criteria	Non-Preferred Products
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® XIIDRA®		CEQUA® EYSUVIS® RESTASIS® MULTIDOSE
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 ATOMOXETINE CONCERTA® DAYTRANA® DESOXYN® DEXMETHYLPHENIDATE DEXTROAMPHETAMINE SA TAB DEXTROAMPHETAMINE TAB FOCALIN XR® GUANFACINE ER JORNAY PM® METADATE CD® METHYLIN® METHYLPHENIDATE METHYLPHENIDATE ER METHYLPHENIDATE SOL QELBREE®	PA required for entire class Children's Form: Form FA-69 Adult Form:	ADDERALL® ADHANSIA® XR ADZENYS® AMPHETAMINE ER SUSP AMPHETAMINE SALT COMBO XR APTENSIO XR® CLONIDINE HCL ER COTEMPLA XR®-ODT DEXEDRINE® DEXTROAMPHETAMINE SOLUTION DYANAVEL® EVEKEO® EVEKEO® ODT FOCALIN® INTUNIV® METADATE ER® METHYLPHENIDATE TAB ER (RELEXXII) METHYLPHENIDATE CHEW

	Preferred Products	PA Criteria	Non-Preferred Products
	RITALIN LA® STRATTERA® VYVANSE®	Form FA-68	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 EFFEXOR® (ALL FORMS) FETZIMA® FORFIVO XL® KHEDEZLA® TRINTELLIX® VIIBRYD® WELLBUTRIN®
Selective Serotonin Reuptake Inhibitors (SSRIs)			
	CITALOPRAM ESCITALOPRAM FLUOXETINE PAROXETINE PEXEVA® SERTRALINE	PA required for members under 18 years old	CELEXA® FLUVOXAMINE QL LEXAPRO® LUVOX® PAROXETINE ER PAXIL® PROZAC® SARAFEM® ZOLOFT®
Antipsychotics			
Atypical Antipsychotics – Oral/Topical			
	ARIPIPRAZOLE CLOZAPINE FANAPT® GEODON® INVEGA® LATUDA® NUPLAZID®* OLANZAPINE	PA required for Ages under 18 years old PA Forms: Form FA-70A (ages 0-5)	ABILIFY® ABILIFY MYCITE ® ASENAPINE CAPLYTA® CLOZARIL® FAZACLO® LYBALVI® PALIPERIDONE

Preferred Products	PA Criteria	Non-Preferred Products
QUETIAPINE QUETIAPINE XR REXULTI® RISPERIDONE SAPHRIS® VRAYLAR®	Form FA-70B (ages 6-18) *(No PA required Parkinson's related psychosis ICD code on claim)	RISPERDAL® SECUADO® SEROQUEL® SEROQUEL XR® ZIPRASIDONE ZYPREXA®
Atypical Antipsychotics – Long Acting Injectable		
ABILIFY® MAINTENA ARISTADA® ARISTADA® INITIO INVEGA® HAFYERA INVEGA® SUSTENNA INVEGA® TRINZA* RISPERDAL® CONSTA PERSERIS® ZYPREXA® RELPREVV	*PA Required	
Anxiolytics, Sedatives, and Hypnotics		
ESTAZOLAM FLURAZEPAM ROZEREM® TEMAZEPAM TRIAZOLAM ZALEPLON ZOLPIDEM	No PA required if approved diagnosis code transmitted on claim (All agents in this class) PA required for members under 18 years old	AMBIEN® AMBIEN CR® BELSOMRA® DORAL® ESZOPICLONE EDLUAR® HETLIOZ® INTERMEZZO® LUNESTA® SILENOR® SOMNOTE® SONATA® ZOLPIDEM CR ZOLPIMIST®
Psychostimulants		
Narcolepsy Agents		
NUVIGIL® * PROVIGIL® * WAKIX® **	* (No PA required for ICD-10 code G47.4) **PA Required for all ages	ARMODAFINIL * MODAFINIL* SUNOSI®** XYREM® ** XYWAV® **
Respiratory Agents		
Nasal Antihistamines		
AZELASTINE DYMISTA®		ASTEPRO®

Preferred Products	PA Criteria	Non-Preferred Products
OLOPATADINE		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® BREO ELLIPTA® BUDESONIDE NEBS* DULERA® FLOVENT DISKUS® QL FLOVENT HFA® QL INCRUSE ELLIPTA ® PULMICORT FLEXHALER® QVAR® SEREVENT DISKUS® QL SPIRIVA® HANDIHALER SPIRIVA RESPIMAT® STIOLTO RESPIMAT® STRIVERDI RESPIMAT® SYMBICORT®		AEROSPAN HFA® AIRDUO® ALVESCO® ARCAPTA NEOHALER® ARMONAIR® ARNUITY ELLIPTA® ASMANEX® BEVESPI® BREZTRI® BROVANA® BUDESONIDE / FORMOTEROL DUAKLIR® PRESSAIR FLUTICASONE PROPIONATE / SALMETEROL POW LONHALA MAGNAIR® PERFOROMIST NEBULIZER® QVAR® REDIHALER™ SEEBRI NEOHALER®

	Preferred Products	PA Criteria	Non-Preferred Products
	TUDORZA®		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 DIGIHALER® PROAIR RESPICLICK® PROVENTIL® HFA
Toxicology Agents			
Antidotes			
Opiate Antagonists			
	KLOXXADO® NALOXONE NARCAN® NASAL SPRAY		
Substance Abuse Agents			
	BUPRENORPHINE / NALOXONE TAB BUPRENORPHINE SUB TAB SUBLOCADE® SUBOXONE® VIVITROL®		BUNAVAIL® BUPRENORPHINE / NALOXONE FILM ZUBSOLV®

Optum

Meeting Minutes

Silver State Scripts Board

Draft Meeting Minutes

Date of Meeting: Thursday, March 24, 2022, 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 1:14 PM on March 24, 2022. Roll was taken by Chairman Decerbo. Decerbo, Mark, Pharm.D. – Chair: Present ☒ Absent ☐ Adashek, Joseph, MD: Present ☒ Absent ☐ Crumby, Mark, Pharm.D.: Present ☒ Absent ☐ Gonzalez, Elizabeth, Pharm.D.: Present ☒ Absent ☐ Hautekeet, Mike, R.Ph: Present ☒ Absent ☐ Khurana, Sapandeep, MD: Present ☒ Absent ☐ Niezborala, Isabella, Pharm.D.: Present ☒ Absent ☐ Singh, Aditi, MD: Present ☐ Absent ☒ Ward, Kate, Pharm.D.: Present ☒ Absent ☐	**The DHCFP Staff Present were as follows:** Capurro, Antonina, Deputy Administrator 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 Drug classes with proposed changes up for review during the First Quarter 2022 Silver State Scripts Board meeting. Mr. Whittington reminded the board members 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 Dermatological Agents – Acne Agents: Topical, Benzoyl Peroxide, Antibiotics, and Combination Products class, noting the products with proposed changes in PDL status. Mr. Whittington presented the Financial Review of the Neurological Agents – Antiparkinsonian Agents – Non-Ergot Dopamine Agonists 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 Ophthalmic Agents – Ophthalmic Antihistamines class noting the products with proposed changes in PDL status. 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.	**Gainwell Technology Staff Present were as follows**: Leid, Jovanna, Pharm.D. **OptumRx Staff Present were as follows:** Whittington, Kevin, R.Ph. LeCheminant, Jill, Pharm.D Chien, Michael, Pharm.D. Kiriakopoulos, Amanda, Pharm.D. Piccirilli, Annette Medina, Daniel
Open Public Meeting		
1. Call to Order and Roll Call	Chairman Decerbo called the meeting to order at 1:40 PM on March 24, 2022. Roll was taken by Chairman Decerbo.	**The DHCFP Staff Present were as follows:** Capurro, Antonina, Deputy Administrator

Agenda Item	Record			Notes
		Present	Absent	Olsen, David, Social Services Chief III Gudino, Antonio, Social Services Program Specialist III Flowers, Ellen, Program Officer I Lither, Gabriel, SDAG Berntson, Kindra, Social Services Program Specialist II **Gainwell Technology Staff Present were as follows**: Leid, Jovanna, Pharm.D. **OptumRx Staff Present were as follows:** LeCheminant, Jill, Pharm.D. Kiriakopoulos, Amanda, Pharm.D. Whittington, Kevin, R.Ph. Piccirilli, Annette Medina, Daniel Chien, Michael, Pharm.D. **The public attendee list is included as Attachment A.** **Note**: Participants may not have chosen to reveal their identity, and in the absence of a sign-in sheet, the accuracy of the attendee list is not assured.
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	
	Adashek, Joseph, MD	☒	☐	
	Crumby, Mark, Pharm.D.	☒	☐	
	Gonzalez, Elizabeth, Pharm.D.	☒	☐	
	Hautekeet, Mike, R.Ph	☒	☐	
	Khurana, Sapandeep, MD	☒	☐	
	Niezborala, Isabella, Pharm.D.	☒	☐	
	Singh, Aditi, MD	☐	☒	
	Ward, Kate, Pharm.D.	☒	☐	
	A quorum was present.			

Agenda Item	Record	Notes
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 December 9, 2021.	Board Member Khurana corrected the date on the posted slides. Meeting minutes reflected the correct date. The minutes were approved by unanimous consent.	
b. Status Update by the DHCFP.	Chief David Olsen discussed the start date of July 1, 2022, for Magellan Medicaid Administration as Nevada's new Pharmacy Benefit Manager (PBM). He introduced Dr. Tina Hawkins and Dr. James Kim with Magellan. He noted that Dr. Kim would be the new account director with Magellan. Chief Olsen discussed the public hearing to be held on March 29, 2022, at 10:00 AM regarding the Medicaid Pooling Initiative. Chief Olsen mentioned Senate Bill 325, which enables pharmacists to prescribe HIV preventative therapy and dispense oral contraceptive therapy without a prescription. He noted this rule does require certain continuing education (CE) training for pharmacists. Chief Olsen stated that provider enrollment was not expected to begin until June 2022. Chief Olsen introduced two new members to the Board, Elizabeth Gonzalez and Isabella Niezborala. With the introduction of new members, Chief Olsen reminded the Board of the Board's role and the bylaws regarding maintaining the PDL. He stated that the Board reviews efficacy, safety, and outcomes of drug therapy. If all of these are considered equal, then cost is considered.	

Agenda Item	Record	Notes
	Antonio Gudino reminded the Board to remain on camera during the meeting and when voting. He asked public members to stay off camera unless speaking during public comment.	
4. Established Drug Classes Being Reviewed Due to the Release of New Drugs		
a. For Possible Action: Discussion and possible adoption of Dermatological Agents – Acne Agents: Topical, Benzoyl Peroxide, Antibiotics, and Combination Products.		
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. Jill LeCheminant discussed Winlevi, the new product within this drug class. She presented the generic availability within the drug class and noted the indication, mechanism of action, and efficacy studies. 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 Adashek 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. ☐ Adashek, Joseph, MD: Yes ☒ No ☐ Abst. ☐	

Agenda Item	Record				Notes
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Gonzalez, Elizabeth, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Niezborala, Isabella, Pharm.D.	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended adding Winlevi to non-preferred on the PDL. She recommended moving Aczone to non-preferred, and Benzaclin 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 proposed changes. Board Member Crumby seconded the motion. A vote was held:				
		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
	Adashek, Joseph, MD	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Gonzalez, Elizabeth, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Niezborala, Isabella, Pharm.D.	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
b. For Possible Action: Discussion and possible adoption of Neurological Agents – Antiparkinsonian Agents – Non-Ergot Dopamine Agonists					

Agenda Item		Record	Notes
i.	Public comment.	Telephonic and web comment was called for, and the phone lines were opened. Comment was provided by Brian Wensel with Sunovion Pharmaceuticals regarding Kynmobi. He provided information regarding Parkinson's treatments, Kynmobi's indication, available formulations, dosing, clinical efficacy data, and adverse events. He asked that Kynmobi be added to preferred.	
ii.	Drug class review presentation by OptumRx.	Dr. LeCheminant discussed the two apomorphine products, Kynmobi and Apokyn, and provided the current generic availability She noted the indication of off-episodes, clinical trial information, current guideline recommendations, and available formulations. She stated that Apokyn requires first dose administration by a medical professional. 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 Adashek moved to accept the list is clinically and therapeutically equivalent. Board Member Khurana seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Adashek, Joseph, MD: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Gonzalez, Elizabeth, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Niezborala, Isabella, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	

Agenda Item	Record	Notes
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended the Board add Apokyn and Kynmobi to non-preferred. She recommended moving Mirapex ER to preferred and pramipexole ER to non-preferred.	
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Chairman Decerbo inquired if any of the agents in this class had prior authorization criteria. Dr. LeCheminant stated that they currently did not. She noted that management occurred through preference status on the PDL. Board Member Ward asked if the DUR Board would address prior authorization criteria for the apomorphine agents if maintained as non-preferred. Board Member Khurana agreed that criteria for appropriate use might be warranted. Chairman Decerbo commented that criteria could ensure the drugs were used in the correct patients. Even though utilization was currently low, he would want it to be managed appropriately. Chairman Decerbo moved to accept the proposed updates as presented with the added recommendation to have the DUR Board assess prior authorization criteria for the apomorphine agents. Board Member Ward seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Adashek, Joseph, MD: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Gonzalez, Elizabeth, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Niezborala, Isabella, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
c. For Possible Action: Discussion and possible		

Agenda Item		Record	Notes
	adoption of Psychotropic Agents – ADHD Agents		
i.	Public comment.	Telephonic and web comment was called for, and the phone lines were opened. Comment was provided by Lance Lewis, in Field Medical Affairs with Corium regarding Azstarys. He noted the unique characteristics of Azstarys, indication, dosage forms, dosing, and administration. He commented that Azstarys is a Schedule II product that has an early onset of action with extended duration. He provided clinical efficacy studies and safety information. He noted that complete prescribing information could be found in the package insert. Comment was provided by Patrick Harvey from Supernus for Qelbree. He informed the board he was available for any questions. No questions were asked. Dr. LeCheminant stated that a written comment was provided to the Board for Qelbree.	
ii.	Drug class review presentation by OptumRx.	Dr. LeCheminant discussed Azstarys clinical efficacy information and dosing. She noted multiple generic formulations 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.	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. ☐ Adashek, Joseph, MD: Yes ☒ No ☐ Abst. ☐	

Agenda Item	Record				Notes
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Gonzalez, Elizabeth, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Niezborala, Isabella, Pharm.D.	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended Azstarys to be added to the PDL as non-preferred and Desoxyn to move 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 Adashek seconded the motion. A vote was held:				
		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
	Adashek, Joseph, MD	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Gonzalez, Elizabeth, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Niezborala, Isabella, Pharm.D.	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
5. Established Drug Classes Being Reviewed Due to the Release of New Generics					
a. For Possible Action: Discussion and possible					

Agenda Item	Record	Notes
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 discussed available generics. 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 Adashek seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Adashek, Joseph, MD: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Gonzalez, Elizabeth, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Niezborala, Isabella, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended adding bepotastine as non-preferred.	

Agenda Item	Record	Notes
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 Khurana seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: ☒ Yes ☐ No ☐ Abst. Adashek, Joseph, MD: ☒ Yes ☐ No ☐ Abst. Crumby, Mark, Pharm.D.: ☒ Yes ☐ No ☐ Abst. Gonzalez, Elizabeth, Pharm.D.: ☒ Yes ☐ No ☐ Abst. Hautekeet, Mike, R.Ph: ☒ Yes ☐ No ☐ Abst. Khurana, Sapandeep, MD: ☒ Yes ☐ No ☐ Abst. Niezborala, Isabella, Pharm.D.: ☒ Yes ☐ No ☐ Abst. Ward, Kate, Pharm.D.: ☒ Yes ☐ No ☐ Abst.	
6. Established Drug Classes		
a. For Possible Action: Discussion and possible adoption of Biologic Response Modifiers – Multiple Sclerosis Agents, oral		
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened. Comment was provided by KayOnda Bayo from Bristol Myers Squibb regarding Zeposia. She noted indications, clinical studies, and adverse events of Zeposia. She requested that Zeposia be moved to preferred on the PDL. Comment was provided by Melissa Sommers from Novartis regarding Mayzent. She stated that Mayzent was the only agent to have efficacy in	

Agenda Item	Record	Notes
	clinical trials for secondary progressive multiple sclerosis. She asked that Mayzent be moved to preferred on the PDL.	
ii. Drug class review presentation by OptumRx.	Dr. LeCheminant discussed available generics. 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 Adashek moved to accept the class as clinically and therapeutically equivalent. Board Member Ward seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: ☒ Yes ☐ No ☐ Abst. Adashek, Joseph, MD: ☒ Yes ☐ No ☐ Abst. Crumby, Mark, Pharm.D.: ☒ Yes ☐ No ☐ Abst. Gonzalez, Elizabeth, Pharm.D.: ☒ Yes ☐ No ☐ Abst. Hautekeet, Mike, R.Ph: ☒ Yes ☐ No ☐ Abst. Khurana, Sapandeep, MD: ☒ Yes ☐ No ☐ Abst. Niezborala, Isabella, Pharm.D.: ☒ Yes ☐ No ☐ Abst. Ward, Kate, Pharm.D.: ☒ Yes ☐ No ☐ Abst.	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended dimethyl fumarate move to preferred on the PDL and Tecfidera move 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 Adashek seconded the motion. A vote was held:	

Agenda Item	Record				Notes
		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
	Adashek, Joseph, MD	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Gonzalez, Elizabeth, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Niezborala, Isabella, Pharm.D.	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
7. OptumRx Reports: New Drugs to Market and New Line Extensions	Dr. LeCheminant reviewed dextromethorphan/bupropion, bimekizumab, tapinarof, and tirzepatide.				
8. Closing Discussion					
a. Public comments on any subject.	Telephonic and web comment was called for, and the phone lines were opened. Comment was provided by Dr. Dana Trippi, a Board-Certified Physician that specializes in the treatment of obesity. Dr. Trippi discussed the treatment of obesity and the need for medication therapy. She commented that she needs all the tools available to be able to treat her patients effectively. She requested that agents used in the treatment of obesity be covered. Dr. Trippi commented that other states are covering obesity agents. Chairman Decerbo thanked Dr. Trippi for her feedback and noted that he had received this feedback in the past. He inquired why these agents were not currently covered. Dr. LeCheminant stated that they are excluded in Chapter 1200 and that further discussion with DHCFP would need to take place prior to review. Chief Olsen said that it would be reviewed internally and that a fiscal impact would likely need to be reviewed. Board Member Khurana expressed the need of treatment for obesity and metabolic disease. Board Member Ward asked if the Board should make a motion to have these items reviewed. Gabriel Lither, SDAG, stated that this was out of				

	the Board's purview and that the Office would review. Chief Olsen committed to review.	
b. Date and location of the next meeting.	Chairman Decerbo confirmed that the next meeting is scheduled for June 23, 2022, at the Hampton Inn Tropicana.	
c. Adjournment.	Chairman Decerbo adjourned the meeting at 2:44 PM.	

Attachment A – Members of the Public in Attendance

Ashton, Elisa, JNJ
Asokan, Vimal, Anthem
Bala, Kayson, Biogen
Balen, Valerie, Belz & Case
Bayo, KayOnda, BMS
Block, David, Corium
Bogard, Lisa, Anthem
Bott, Jason, Lily
Capen, Maribeth, Anthem
Colabianchi, Jeana
Cowan, Sarah, NV Health
Delgado, Jonathan, Novo Nordisk
Diebes, Tressa, Takeda
Eletreby, Iman, Anthem
Germain, Joe, Biogen
Patrick, Harvey, Supernus
Hawkins, Tina, Magellan
Henry, Lawrence, Fidelis
Hertzberg, Susan, Gene
Kim, James, Magellan
Levin, Amy, Anthem
Lawrence, Henry, Fidelis
Lewis, Lance, Corium
Lim, Luke, Anthem
McKenna, Brian, Oyster Point
Mendez, Natasha, BMS
Miller, Temyka, Anthem
Nguyen, Bao, JNJ
Ou, Karen, Gilead
Overman, Julia, Corium
Roa, Ryan, Merck
Santarone, Christopher, BMS
Sebastian, Paul, Optum
Selm-Keck, Emma, DK Pierce
Sommers, Melissa, Novartis
Tran, Jimmy, Molina
Trippi, Dr. Dana
Walter, Lindsey, Novartis
Wensel, Brian, Sunvion
White, Rianna, Fidelis
William, Paul
Zagrob, Michael

Attachment B – Submitted Written Comment

Qelbree_1 pager Nevada Medicaid Testimony

Secuado_Medicaid_Summary

Optum

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

Therapeutic Class Overview
Beta-adrenergic Blocking Agents

INTRODUCTION

- Approximately 126.9 million American adults have at least 1 type of cardiovascular (CV) disease according to the American Heart Association (AHA) Heart Disease and Stroke Statistics 2021 update. The age-adjusted prevalence of all types of heart disease was 11.2% in 2018. Cardiovascular disease deaths were most often caused by coronary heart disease (42.1%), followed by stroke (17.0%), high blood pressure (BP; 11%), heart failure (HF; 9.6%), diseases of the arteries (2.9%), and other minor causes (17.4%) *(Virani et al 2021)*.
- Beta-adrenergic blocking agents (beta-blockers) are a group of drugs that block the sympathomimetic effects of catecholamines on beta receptors. This results in negative inotropic and chronotropic effects and relaxation of smooth muscle.
- Beta-blockers have varied pharmacologic properties.
  - Cardioselective beta-blockers preferentially interact with $beta_1$-receptors, which are predominantly found in the heart. Non-cardioselective beta-blockers also interact with $beta_2$-receptors found on smooth muscle in the lungs, blood vessels, and other tissues. The cardioselectivity of beta-blockers is dose-dependent; therefore, $beta_2$ blockade can occur at higher doses with certain cardioselective agents.
  - Some beta-blockers (acebutolol and pindolol) have intrinsic sympathomimetic activity (ISA), which may result in a lower incidence of bradycardia and bronchoconstriction *(Lexicomp 2021)*. In addition, some beta-blockers (nebivolol and propranolol) have higher lipophilicity, which may increase the risk for central nervous system-related adverse events *(Lexicomp 2021)*.
  - Carvedilol and labetalol also block alpha-adrenergic receptors and may reduce peripheral resistance more than other beta-blockers *(Clinical Pharmacology 2021)*.
- Specific indications for the beta-blockers vary by product. Most beta-blockers (all except sotalol) are approved to treat hypertension (HTN). The 2017 American College of Cardiology (ACC)/AHA clinical practice guideline defines HTN as BP ≥ 130/80 mm Hg (*Whelton et al 2017).* Nearly half of American adults (46%) have HTN based on this definition. Other indications for 1 or more beta-blockers include, but are not limited to: angina pectoris, arrhythmias, myocardial infarction (MI), HF, left ventricular dysfunction following MI, treatment of essential tremor, and migraine prophylaxis.
- Most of the beta-blockers are available generically. Brand Hemangeol is an oral solution of propranolol in a strength of 4.28 mg/mL (equivalent to 3.75 mg); however, generic oral solutions of propranolol are available in strengths of 4 and 8 mg/mL.
- There has been extensive experience with beta-blockers in clinical practice, and clinical trials do not consistently demonstrate a clinical advantage of one agent over another for most Food and Drug Administration (FDA)-approved indications. In general, treatment guidelines do not recommend the use of one beta-blocker over the other, as recommendations regarding the use of these agents are made for the class as a whole. There are some exceptions, however. Guidelines do recognize the role of 3 beta-blockers (carvedilol, bisoprolol, and extended release metoprolol) for the reduction of mortality and hospitalization in patients with HF *(Yancy et al 2013, Yancy et al 2017, Maddox et al 2021)*. Also, sotalol has some unique properties and is considered separately from the other beta-blockers, as this agent is not indicated to treat HTN and is instead used to treat certain ventricular arrhythmias or for the maintenance of normal sinus rhythm in patients with symptomatic atrial fibrillation/atrial flutter.
- Although some single-ingredient beta-blockers have several indications, the beta-blocker/diuretic combination products are FDA-approved only for the treatment of HTN. Patients with HTN frequently require the use of 2 or more agents from different therapeutic classes in order to adequately reduce BP, and the dose of each product should be titrated to its desired effect. Thus, the place in therapy for the beta-blocker/diuretic combinations is for patients who require both agents at doses for which a combination product is available. Several of the combination products (all except for Dutoprol and Ziac) contain specific wording in their prescribing information stating that the product is not approved for initial therapy *(Gradman 2012)*.
- Both beta-blockers and diuretics are well established in the management of HTN. The choice of antihypertensive agent(s) for a particular patient will depend on the patient's comorbidities.

- All of the beta-blockers contained within the combination products are also available generically as single-entity agents. The diuretics hydrochlorothiazide (HCTZ) and chlorthalidone are available generically as single-entity agents. All of the combination products except for Dutoprol (metoprolol succinate extended release/HCTZ) are available generically.
- Little guidance on the use of fixed-dose combination products is available within treatment guidelines; however, they are recognized as having the ability to simplify treatment regimens and to improve adherence to therapy (*Williams et al 2018)*.
- This class includes the orally-administered beta-blockers, as well as the orally-administered alpha/beta-blocking agents, carvedilol and labetalol, and the beta-blocker/diuretic combination products. Several beta-blockers are also available in intravenous (IV) forms for in-hospital use; however, the IV formulations are not included within the scope of this review.
- Medispan drug class: Beta Blockers - Beta Blockers Non-Selective; Beta Blockers Cardio-Selective; Alpha-Beta Blockers; Antihypertensive Combinations - Beta Blocker & Diuretic Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single-Entity Beta-blockers	
acebutolol	✔
Betapace, Betapace AF, Sorine, Sotylize (sotalol)	✔ *
betaxolol	✔
bisoprolol	✔
Bystolic (nebivolol)	✔
Coreg, Coreg CR (carvedilol)	✔
Corgard (nadolol)	✔
Hemangeol, Inderal LA, Inderal XL, Innopran XL (propranolol)	✔ ‡
Toprol XL, Kapspargo Sprinkle (metoprolol succinate extended release)	✔ †
labetalol	✔
Lopressor (metoprolol tartrate)	✔
pindolol	✔
Tenormin (atenolol)	✔
timolol	✔
Beta-blocker/Diuretic Combinations	
Dutoprol (metoprolol succinate extended release/HCTZ)	-
Lopressor HCT (metoprolol tartrate/HCTZ)	✔
Tenoretic (atenolol/chlorthalidone)	✔
Ziac (bisoprolol/HCTZ)	✔

*Sotylize (sotalol oral solution) is brand-name only.
† Kapspargo Sprinkle (metoprolol succinate extended release capsule) is brand-name only.
‡ Hemangeol (propranolol oral solution), Inderal XL, and Innopran XL are brand-name only.

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications for Single-Entity Beta-blockers

Generic Name	Hypertension	Angina pectoris	Cardiac arrhythmias*	Myocardial infarction	Heart failure	Pheochromocytoma	Migraine prophylaxis	Hypertrophic subaortic stenosis	Proliferating infantile hemangioma requiring systemic therapy	Essential tremor	Left ventricular dysfunction following myocardial infarction
acebutolol	✔ †		✔								
atenolol	✔ †	✔ ‡		✔ §							
betaxolol	✔ †										
bisoprolol	✔ ‖										
carvedilol	✔ †¶				✔ #						✔ **
labetalol	✔ ††										
metoprolol	✔ §§	✔ ‖‖		✔ ¶¶	✔ ##						
nadolol	✔ †	✔ ***									
nebivolol	✔ ‖										
pindolol	✔ †										
propranolol	✔ †,†††	✔ ‡‡‡	✔	✔ §§§		✔ ‖‖‖	✔	✔ ¶¶¶	✔ ††††	✔ ###	
sotalol			✔								
timolol	✔ †			✔ ****			✔				

* See Table 3 for the specific cardiac arrhythmias for which these agents are indicated.
† May be used alone or in combination with other antihypertensive agents, especially thiazide-type diuretics.
‡ Indicated for the long term management of patients with angina pectoris due to coronary atherosclerosis.
§ Indicated for the management of hemodynamically stable patients with definite or suspected acute MI to reduce CV mortality.
‖ May be used alone or in combination with other antihypertensive agents.
¶ Indicated for the management of essential HTN.
# Indicated for the treatment of mild to severe chronic HF of ischemic or cardiomyopathic origin, usually in addition to diuretics, angiotensin converting enzyme inhibitors and digitalis to increase survival, and also to reduce the risk of hospitalization.
** Indicated to reduce CV mortality in clinically stable patients who survived the acute phase of an MI and have a left ventricular ejection fraction ≤ 40% (with or without symptomatic HF).
†† Labetalol tablets may be used alone or in combination with other antihypertensive agents, especially thiazide and loop diuretics.
§§ Metoprolol succinate extended release tablets and capsules and metoprolol tartrate tablets may be used alone or in combination with other antihypertensive agents.
‖‖ Metoprolol succinate extended release tablets and capsules and metoprolol tartrate tablets are indicated in the long term treatment of angina pectoris.
¶¶ Metoprolol tartrate tablets are indicated in the treatment of hemodynamically stable patients with definite or suspected acute MI to reduce CV mortality when used alone or in conjunction with IV metoprolol tartrate. Oral therapy can be initiated after IV therapy or, alternatively, oral treatment can begin within 3 to 10 days of the acute event.
Metoprolol succinate extended release tablets are indicated for the treatment of stable, symptomatic (New York Heart Association Class II or III) HF of ischemic, hypertensive or cardiomyopathic origin. Metoprolol succinate extended release capsules are indicated for the treatment of patients with HF to reduce the risk of CV mortality and HF-related hospitalization.
*** Indicated for the long term management of patients with angina pectoris.
††† Inderal XL and Innopran XL are indicated for the treatment of HTN only.
‡‡‡ Indicated to decrease angina frequency and increase exercise tolerance in patients with angina pectoris due to coronary atherosclerosis.
§§§ Propranolol tablets and oral solution are indicated to reduce CV mortality in patients who have survived the acute phase of an MI and are clinically stable.
‖‖‖ Propranolol tablets and oral solution are indicated as an adjunct to alpha-adrenergic blockade to control BP and reduce symptoms of catecholamine-secreting tumors.
¶¶¶ Improves New York Heart Association functional class in symptomatic patients with hypertrophic subaortic stenosis.
Propranolol tablets and oral solution are indicated for the management of familial or hereditary essential tremor.
**** Indicated in patients who have survived the acute phase of an MI, and are clinically stable, to reduce CV mortality and the risk of reinfarction.

†††† Only approved for Hemangeol oral solution. Hemangeol is not FDA-approved for any other indication.

(Prescribing information: acebutolol 2017, Betapace and Betapace AF 2021, betaxolol 2020, bisoprolol 2021, Bystolic 2019, Coreg 2017, Coreg CR 2020, Corgard 2019, Hemangeol 2021, Inderal LA 2019, Inderal XL 2021, Innopran XL 2021, Kapspargo 2020, labetalol 2021, Lopressor 2017, pindolol 2019, propranolol solution 2017, propranolol tablets 2021, Sorine 2021, Sotylize 2015, Tenormin 2021, timolol 2020, Toprol XL 2016)

Table 3. FDA-Approved Cardiac Arrhythmia Indications

Indication	acebutolol	propranolol	sotalol
Control ventricular rate in patients with atrial fibrillation and a rapid ventricular response		✔ (oral solution, tablet)	
Maintenance of normal sinus rhythm (delay in time to recurrence of atrial fibrillation/atrial flutter [AFIB/AFL]) in patients with symptomatic AFIB/AFL who are currently in sinus rhythm*			✔
Management of ventricular premature beats	✔		
Treatment of documented life-threatening ventricular arrhythmias, such as sustained ventricular tachycardia**			✔

* Limitations of use: Because sotalol can cause life-threatening ventricular arrhythmias, reserve it for patients in whom AFIB/AFL is highly symptomatic. Patients with paroxysmal AFIB whose AFIB/AFL that is easily reversed (by Valsalva maneuver, for example) should usually not be given sotalol.
** Limitations of use: Sotalol may not enhance survival in patients with ventricular arrhythmias. Because of the proarrhythmic effects of Sorine and Sotylize, including a 1.5 to 2% rate of Torsade de Pointes (TdP) or new ventricular tachycardia/fibrillation (VT/VF) in patients with either non-sustained ventricular tachycardia (NSVT) or supraventricular arrhythmias (SVT), its use in patients with less severe arrhythmias, even if the patients are symptomatic, is generally not recommended. Avoid treatment of patients with asymptomatic ventricular premature contractions.

(Prescribing information: acebutolol 2017, propranolol solution 2017, propranolol tablets 2021, Betapace and Betapace AF 2021, Sorine 2021, Sotylize 2015)

Table 4. FDA-Approved Indications for Beta-blocker/Diuretic Combinations

Drug	HTN
Dutoprol (metoprolol succinate extended release/HCTZ)	✔
Lopressor HCT (metoprolol tartrate/HCTZ)	✔*
Tenoretic (atenolol/chlorthalidone)	✔*
Ziac (bisoprolol/HCTZ)	✔

*The fixed-dose combination product is not indicated for initial therapy of HTN. If the fixed combination represents the dose titrated to the individual patient's needs, it may be more convenient than the separate components.

(Prescribing information: Dutoprol 2020, Lopressor HCT 2020, Tenoretic 2021, Ziac 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

- Clinical trials demonstrating the safety and efficacy of beta-blockers for their FDA-approved indications have demonstrated that beta-blockers are superior to placebo and efficacious compared to active comparators for these varied indications, including:
  - HTN (*Dahlöf et al 1991, Davidov et al 1988, Dhakam et al 2008, Dietz et al 2008, Fogari et al 1997, Giles et al 2014, Greathouse 2010, Materson et al 1990, Neutel et al 2010, Stoschitzky et al 2006, Van Bortel et al 2005, Veterans Administration Cooperative Study Group on Antihypertensive Agents 1977, Wald et al 2008*)
  - Angina (*Pandhi et al 1985, van der Does et al 1999, Weiss et al 1998*)
  - Arrhythmia (*Lui et al 1983, Seidl et al 1998*)
  - Heart failure (*Bristow et al 1996, CIBIS Investigators and Committees 1994, CIBIS-II Investigators and Committees 1999, Dargie et al 2001, Di Lenarda et al 1999, Flather et al 2005, Goldstein et al 2001, Krum et al 1995, MERIT-HF Study Group 1999, Metra et al 2000, Packer et al 1996, Packer et al 2001[b], Packer et al 2002, Poole-Wilson et al 2003, Ruwald et al 2013, Waagstein et al 1993*)
  - Infantile hemangiomas (*Bauman et al 2014, Novoa et al 2018*)

  - Essential tremor (*Calzetti et al 1981, Gironell et al 1999, Yetimalar et al 2005*)
  - Migraine prophylaxis (*Ashtari et al 2008, Chowdhury et al 2021, Domingues et al 2009, Jackson et al 2019, Rao et al 2000, Schellenberg et al 2008, Tfelt-Hansen et al 1984*)
- Head-to-head trials have demonstrated that no one beta-blocker is consistently superior compared to the others for the treatment of HTN *(Czuriga et al 2003, Davidov et al 1988, Dhakam et al 2008, Fogari et al 1997, Seleme et 2021)*.
- Trials have demonstrated CV advantages with beta-blocker use in patients with prior MI; however, post-hoc analyses examining the use of beta-blockers have been mixed *(Bangalore et al 2014, Dahl Aarvik et al 2019, Freemantle et al 1999, Gottlieb et al 2001, Jonsson et al 2005, Olsson et al 1992, Safi et al 2021)*.
- A meta-analysis (MA) of 6 observational studies showed that beta-blockers did not reduce major adverse cardiovascular events compared to no beta-blocker therapy in patients with stable coronary artery disease without prior MI or left ventricular dysfunction (*Arero et al 2021*).
- For the treatment of HF, a survival benefit has been demonstrated with bisoprolol, carvedilol, and sustained release metoprolol succinate; however, only carvedilol and metoprolol succinate extended release are FDA-approved for the treatment of HF. Carvedilol has demonstrated superiority to other beta-blockers in certain populations. Beta-blockers that have been shown to reduce mortality in patients with systolic dysfunction include carvedilol, bisoprolol, and long-acting metoprolol *(Bristow et al 1996, CIBIS-II Investigators and Committees 1999, Dargie 2001, Di Lenarda et al 1999, Goldstein et al 2001, Hamaad et al 2007, Maack et al 2001, MERIT-HF Study Group 1999, Metra et al 2000, Packer et al 1996, Packer et al 2001[b], Packer et al 2002, Poole-Wilson et al 2003, Ruwald et al 2013, Sanderson et al 1999)*. In elderly patients with HF, nebivolol demonstrated a significant improvement in a composite measure of death or CV hospitalization; however, differences for the individual components of the composite measure did not reach statistical significance *(Flather et al 2005)*.
  - Head-to-head trials have compared metoprolol to carvedilol in patients with HF; however, available trials used the immediate release formulation of metoprolol rather than the extended release formulation that has FDA approval for this indication *(Di Lenarda et al 1999, Maack et al 2001, Metra et al 2000, Poole-Wilson et al 2003, Sanderson et al 1999)*. Most of the comparative trials have been small and have evaluated outcomes other than mortality *(Di Lenarda et al 1999, Maack et al 2001, Metra et al 2000, Sanderson et al 1999)*. One larger trial, COMET (N = 3029), demonstrated that all-cause mortality was significantly lower in patients treated with carvedilol compared to patients treated with metoprolol tartrate (hazard ratio [HR], 0.83; 95% confidence interval [CI], 0.74 to 0.93; p = 0.0017). However, questions have been raised about the choice of metoprolol formulation and its dosing for this trial, so definitive conclusions could not be made *(Kveiborg et al 2007)*.
  - A MA that included trials that evaluated immediate and sustained release metoprolol revealed that treatment with carvedilol improved mean left ventricular ejection fraction significantly more than treatment with metoprolol *(Packer et al 2001[a])*.
  - Another MA found that carvedilol significantly reduced the incidence of post-operative atrial fibrillation when compared to metoprolol in patients following a coronary artery bypass grafting (CABG) procedure *(DiNicolantonio et al 2014)*.
  - Several meta-analyses have confirmed the mortality benefit of beta-blockers for the treatment of HF *(Brophy et al 2001, Chatterjee et al 2013, Lechat et al 1998, Whorlow et al 2000)*.
- For the treatment of infantile hemangiomas, a systematic review (SR) and MA of 28 trials concluded that oral propranolol probably improves clinician-assessed clearance vs placebo (risk ratio, 16.61; 95% CI, 4.22 to 65.34) and provides a clinician-assessed reduction in mean hemangioma volume by 45.9% (95% CI, 11.60 to 80.20) *(Novoa et al 2018)*. Compared with topical timolol, oral propranolol was not significantly different in the proportion of patients with clinician-assessed reductions of 50% or greater in hemangioma size. Another SR of 9 trials supports the efficacy of oral atenolol for the treatment of infantile hemangioma based on a response rate of 0.90 (95% CI, 0.85 to 0.93) and an overall rate of adverse events of 0.26 (95% CI, 0.12 to 0.47) (*Wang et al 2018*). A trial published in 2021 of infants with problematic infantile hemangiomas found that oral atenolol had similar efficacy and a lower rate of adverse events compared to oral propranolol (*Ji et al 2021*).

Combination products

- Most trials compared the combination product to placebo or to 1 or both of the individual product components. Results demonstrate that:
  - The combination products are superior to placebo (*de Leeuw et al 1997, Lewin et al 1993, Nissinen et al 1980*).

- Additional BP lowering is achieved when the combination therapy is compared to 1 or both of the individual drug components administered as monotherapy *(Dafgard et al 1981, Fogari et al 1984, Frishman et al 1994, Frishman et al 1995, Hansson et al 1999, Leonetti et al 1986, Liedholm et al 1981, Smilde et al 1983, Stevens et al 1982)*.
- The CAPPP study compared an angiotensin converting enzyme (ACE) inhibitor to treatment with a diuretic and/or beta-blockers. For both diabetic and non-diabetic patients, both regimens were equally effective in preventing the composite of fatal and non-fatal MI, stroke, and CV deaths *(Hansson et al 1999)*. A sub-analysis of diabetic patients within the CAPPP trial found that in hypertensive diabetic patients, captopril (ACE inhibitor) was superior to a diuretic and/or beta-blocker antihypertensive treatment regimen in preventing CV events, especially in those with metabolic decompensation *(Niskanen et al 2001)*. Further studies should be performed to validate beta-blockers in combination with a diuretic and their place in therapy with diabetic patients.

CLINICAL GUIDELINES

- Hypertension:
  - The 2017 ACC/AHA guideline for the prevention, detection, evaluation, and management of high BP in adults *(Whelton et al 2017)* offers classifications of HTN and goals of treatment (Table 5).

Table 5. Classification of BP measurements

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

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, calcium channel blockers (CCBs), and ACE inhibitors or angiotensin II receptor blockers (ARBs).
    - Diuretics, ACE inhibitors, ARBs, CCBs, and beta-blockers have been shown to prevent CV disease compared with placebo.
      - Beta-blockers are not recommended as first-line agents unless the patient has ischemic heart disease (IHD) or HF.
      - Cardioselective beta-blockers (atenolol, betaxolol, bisoprolol, metoprolol tartrate and succinate) are preferred in patients with bronchospastic airway disease requiring a beta-blocker.
      - Non-cardioselective beta-blockers (ie, nadolol, propranolol) should be avoided in patients with reactive airways disease.

    - Bisoprolol, carvedilol, and metoprolol succinate are preferred in patients with HF with reduced ejection fraction (HFrEF).
    - In general, beta-blockers with ISA (ie, acebutolol, penbutolol, pindolol) should be avoided, especially in patients with IHD or HF.
  - Most HTN guidelines recommend a thiazide-type diuretic, an ACE inhibitor, an ARB, or a CCB as first-line therapy *(Go et al 2014, James et al 2014, Unger et al 2020, Whelton et al 2017, Williams et al 2018)*.
  - In the treatment of severe HTN in pregnancy, labetalol is outlined as an option with consideration of maternal and fetal side effects *(American Diabetes Association 2021, Bushnell et al 2014, de Boer et al 2017, Unger et al 2020)*.
  - Beta-blockers have strong clinical outcome benefits in hypertensive patients with a history of MI, HF, acute coronary syndrome, and in the management of angina pectoris. Some guidelines endorse beta-blockers for first-line therapy in these populations *(Arnett et al 2019, Go et al 2014, Rosendorff et al 2015, Unger et al 2020, Williams et al 2018)*.
  - Patients with resistant HTN (defined as above-goal elevated BP despite concurrent use of 3 drug classes) may require additional treatment *(Carey et al 2018)*. Guidelines from the AHA/ACC for the treatment of resistant HTN suggest beta-blockers may be helpful in patients with obstructive sleep apnea, coarctation of the aorta, and patients without bradycardia who have failed multiple other antihypertensives. No specific beta-blocker is preferred by this guideline.
- The beta-blockers are also a mainstay of HF treatment, as evidenced by recommendations within treatment guidelines *(Yancy et al 2013, Yancy et al 2017, Maddox et al 2021)*. Of note, carvedilol and metoprolol succinate extended release are the only 2 beta-blockers that are FDA-approved for the treatment of HF, but a mortality benefit has also been shown for bisoprolol in clinical trials, and all 3 are recognized as appropriate options in clinical guidelines *(CIBIS Investigators and Committees 1994, CIBIS-II Investigators and Committees 1999, MERIT-HF Study Group 1999, Waagstein et al 1993, Yancy et al 2013, Yancy et al 2017, Maddox et al 2021)*.
  - Conclusive data on the medical management of HF in patients with a systemic right ventricle (RV) are lacking, despite the high incidence of late clinical HF and sudden death in this population. Use of conventional HF medications may be problematic because of preexisting sinus node dysfunction, heart block, baffle stenosis, nondistensible atria, and restrictive RV physiology. Beta-blockade may exacerbate bradyarrhythmias, whereas vasodilation could be counterproductive in patients with nondistensible atria or restrictive physiology *(Stout et al 2016)*.
- Guidelines also support the use of beta-blockers for additional CV diseases including stable IHD, unstable angina, MI (acute and long-term after MI), rate control in atrial fibrillation and atrial flutter, maintenance of normal sinus rhythm in atrial fibrillation (sotalol), non-ST-segment elevation acute coronary syndromes, select ventricular and supraventricular arrhythmias, complications following CABG, valvular heart disease, and hypertrophic cardiomyopathy *(Amsterdam et al 2014[a,b], Arnett et al 2019, Brugada et al 2019, Collet et al 2021, Fihn et al 2012, Fihn et al 2014, Ibanez et al 2018, January et al 2014[a,b], January et al 2019, Jneid et al 2012, Knuuti et al 2019, Montalescot et al 2013, Neumann et al 2018, O'Gara et al 2013, Otto et al 2021, Page et al 2016, Ommen et al 2021, Priori et al 2015, Rosendorff et al 2015)*.
- In the treatment of HTN in chronic kidney disease, a beta-blocker is a fourth-line therapy option if blood pressure is not adequately controlled with the combination of a renin angiotensin system inhibitor, CCB, and diuretic at recommended doses (*Cheung et al 2021, KDIGO 2021)*. Beta-blockers may be incorporated earlier in the treatment regimen if there is an appropriate compelling indication (*Cheung et al 2021*).
- Metoprolol, propranolol, and timolol are established as effective for migraine prevention *(Silberstein et al 2012, Snow et al 2002, American Headache Society 2019, Oskoui 2019)*.
- Propranolol is the only beta-blocker that is FDA-approved for the treatment of essential tremor. Guidelines recommend propranolol, long-acting propranolol, or primidone for limb tremor in essential tremor, depending on concurrent medical conditions and potential side effects *(Zesiewicz et al 2011)*.
- A 2019 treatment guideline on infantile hemangioma was published by the American Academy of Pediatrics. If pharmacologic therapy is needed, oral propranolol should be used as a first-line agent. No other systemic beta-blockers are recommended due to a lack of high-quality data (*Krowchuk et al 2019*).

SAFETY SUMMARY

- Beta-blockers have a number of contraindications related to their pharmacologic properties. They should be avoided in patients with sinus bradycardia and second- or third-degree heart block. They also should not be initiated in patients with uncontrolled HF or cardiogenic shock. Based on their ability to block $beta_2$ receptors in the lung, beta-blockers should generally not be used (or used with caution) in patients with asthma and/or chronic obstructive pulmonary disease. This

is particularly a concern with non-selective beta-blockers. Other contraindications vary based on the specific drug and the clinical use.

- A boxed warning exists for atenolol, metoprolol (non-boxed warning for metoprolol succinate extended release capsules), nadolol, and timolol: worsening angina, MI, and arrhythmias have been reported in patients with angina following the abrupt discontinuation of therapy with beta-blockers. When discontinuing a chronically administered beta-blocker, particularly in patients with IHD, the dosage should be gradually reduced over a period of 1 to 2 weeks, and the patient should be carefully monitored. Sotalol also carries a boxed warning, noting that patients initiated or reinitiated on sotalol or sotalol AF should be placed for a minimum of 3 days (on their maintenance dose) in a facility that can provide cardiac resuscitation and continuous electrocardiographic monitoring. Creatinine clearance (CrCL) should be calculated prior to dosing.
- Hemangeol has specific contraindications for use in premature infants with corrected age < 5 weeks, infants weighing < 2 kg, BP < 50/30 mm Hg, and pheochromocytoma.
- Key additional warnings and precautions include:
  - Beta-blockers can precipitate or aggravate symptoms of arterial insufficiency in peripheral vascular disease.
  - Patients with a history of severe anaphylactic reaction to a variety of allergens may be more reactive to repeated challenge when taking a beta-blocker. Such patients may also be unresponsive to the usual doses of epinephrine used to treat allergic reactions.
  - Beta-blocker therapy should not be routinely withdrawn prior to major surgery; however, the impaired ability of the heart to respond to reflex adrenergic stimuli may augment the risks of general anesthesia and surgical procedures.
  - Some beta-blockers may potentiate insulin-induced hypoglycemia and mask some of its manifestations (eg, tachycardia). Propranolol has been associated with hypoglycemia regardless of a history of diabetes. Hemangeol can cause hypoglycemia at any time during therapy, especially during fasting or with increased glucose demands. The dose of Hemangeol should be withheld under these conditions or discontinued if hypoglycemia develops.
  - Beta-blockers should not be given to patients with untreated pheochromocytoma. In patients with this condition, a beta-blocker should be given only after an alpha-blocker has been initiated.
  - Bradycardia and/or hypotension may occur.
  - Sotalol can provoke new or worsened ventricular arrhythmias in some patients. This may include Torsades de Pointes, the risk of which increases with increasing prolongation of the QT interval. Use with particular caution if the QTc is > 500 milliseconds. Use is contraindicated in patients with congenital or acquired long QT syndrome or if serum potassium < 4 mEq/L.
  - The value of using betaxolol in psoriatic patients should be carefully weighed since it has been reported to cause an aggravation in psoriasis.
  - Hemangeol has demonstrated an increased risk of stroke in PHACE syndrome patients with severe cerebrovascular anomalies. Infants with large facial infantile hemangioma should be investigated for potential arteriopathy associated with PHACE syndrome prior to therapy.
- Common adverse reactions (occurring in > 10% of patients for at least 1 medication) include: bradycardia, chest pain, hypotension, palpitations, dizziness, drowsiness, fatigue, headache, insomnia, lightheadedness, hyperglycemia, diarrhea, nausea, weight gain, decreased sexual ability, weakness, and dyspnea.

Combination products

- Based on the beta-blocker component, the beta-blocker/diuretic combinations are contraindicated in patients with sinus bradycardia, second-or third-degree heart block, cardiogenic shock, and overt cardiac failure.
- Based on the diuretic component, the beta-blocker/diuretic combinations are contraindicated in patients with anuria, hypersensitivity to the ingredients, or hypersensitivity to sulfonamide-derived drugs.
  - Lopressor HCT and Dutoprol are contraindicated in patients with sick sinus syndrome, which includes patients with sinus bradycardia and patients with sinus pauses or arrest.
  - Lopressor HCT is contraindicated in those with severe peripheral arterial circulatory disorders.
- A precaution is included in some package inserts (Dutoprol, Lopressor HCT, and Ziac) related to the diuretic component of HCTZ-containing products regarding the risk for non-melanoma skin cancer. Patients taking HCTZ should protect skin from the sun and undergo regular skin cancer screening.
- Boxed warning for Dutoprol and Lopressor HCT: Do not discontinue abruptly; withdraw gradually with appropriate monitoring to avoid potential exacerbation of IHD. This is also a warning for Tenoretic and Ziac (although not boxed).
- Avoid in overt HF; use with caution in patients with controlled HF.

- Avoid in patients with bronchospastic disease. Low doses of beta$_1$ selective agents may be used in patients with bronchospastic disease when no acceptable alternative exists.
- Dutoprol has a warning for bradycardia, particularly in patients with first-degree atrioventricular block, sinus node dysfunction, or conduction disorders. Concomitant use of beta adrenergic blockers, non-dihydropyridine CCB, digoxin, or clonidine increases the risk. The drug also has additional warnings for an increased risk of acute renal failure in patients with chronic kidney disease, severe HF, or volume depletion; and reduced effectiveness of epinephrine when treating anaphylaxis.
- Some beta-blockers may cause hypoglycemia or potentiate insulin-induced hypoglycemia and mask some of its manifestations (eg, tachycardia).
- Thyrotoxicosis: Beta blockade may mask certain clinical signs of thyrotoxicosis (eg, tachycardia). Abrupt withdrawal of beta blockade may precipitate a thyroid storm.
- Thiazides should be used with caution in severe renal disease, as they may precipitate azotemia in this setting.
- Thiazides should be used with caution in patients with impaired hepatic function because minor alterations of fluid/electrolyte balance may precipitate hepatic coma.
- Adverse reactions reported in > 5% of patients in clinical trials for Lopressor HCT include bradycardia, dizziness/vertigo, drowsiness/somnolence, fatigue/lethargy, and headache.
- Adverse reactions which occurred greater than 1% more frequently in patients treated with Dutoprol than placebo include nasopharyngitis and fatigue.
- Adverse reactions reported in > 2% of patients in clinical trials for Ziac include cough, upper respiratory tract infection, fatigue, dizziness, headache, myalgia, and diarrhea.
- Adverse reaction rates for Tenoretic are not specifically listed in the prescribing information; however, adverse reactions are known based on experience with the individual components. Notable adverse reactions include HF, intensification of atrioventricular block, bradycardia, peripheral vascular insufficiency, heart rhythm/conduction disturbance, depression, nausea, vomiting, diarrhea, constipation, orthostatic hypotension, dizziness, fatigue, vertigo, headache, hypersensitivity, hyperglycemia, hyperuricemia, and bronchospasm.

DOSING AND ADMINISTRATION

Table 6. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single-Entity Beta-blockers				
acebutolol	Capsules	Oral	Cardiac arrhythmias (ventricular): Twice daily HTN: Once to twice daily	Dosage adjustment in renal impairment is required. Older patients have an approximately 2-fold increase in bioavailability and may require lower maintenance doses; avoid doses above 800 mg.
atenolol	Tablets	Oral	Angina pectoris: Once daily HTN: Once daily Acute MI*: After initial IV dosing in the acute setting, 50 mg should be initiated 10 minutes after the last IV dose followed by another 50 mg oral dose 12 hours later. Thereafter, once or twice daily for a further 6 to 9 days or until discharge.	Dosage adjustment in renal impairment is required.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
betaxolol	Tablets	Oral	HTN: Once daily	Dosage adjustment in renal impairment is required. Consideration should be given to reducing the starting dose to 5 mg in elderly patients.
bisoprolol	Tablets	Oral	HTN: Once daily	Dosage adjustment in renal and hepatic impairment is required.
carvedilol	ER capsules (Coreg CR), tablets (Coreg)	Oral	HF: ER capsule: Once daily; Tablet: Twice daily HTN: ER capsule: Once daily; Tablet: Twice daily Left ventricular dysfunction following MI: ER capsule: Once daily; Tablet: Twice daily	Patients controlled with immediate release (IR) tablets may be switched to ER capsules (see prescribing information for details). When switching from the higher doses of IR carvedilol to ER, a lower starting dose is recommended for the elderly. Contraindicated in severe hepatic dysfunction. ER capsule: Take once daily in the morning with food. Should be swallowed as a whole capsule or may alternatively be opened, and the beads sprinkled over a spoonful of applesauce. Tablet: Take with food.
labetalol	Tablets	Oral	HTN: Twice daily	Dose adjustment is required in the elderly. Use with caution in hepatic dysfunction; metabolism of the drug may be diminished.
metoprolol	ER tablets (succinate; Toprol XL), ER capsules (succinate; Kapspargo), tablets (tartrate)	Oral	Angina pectoris: ER tablet or ER capsule: once daily; Tablet: daily in 2 divided doses HF: ER tablet (NYHA Class II): once daily [start with 25 mg/day]; ER tablet (severe HF): once daily [start with 12.5 mg/day]; ER capsule: once daily [start with 25 mg/day] HTN: ER tablet or ER capsule: once daily; Tablet: daily in single or divided doses	Hepatic dosage adjustment may be necessary; initiate at low doses with cautious gradual titration. ER tablet or ER capsule: Dosing recommendations are available for pediatric hypertensive patients ≥ 6 years of age; product is not recommended in patients < 6 years. ER tablet: Take with or immediately after meals. ER tablets are scored and can be divided, but not crushed or chewed.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			MI: Tablet: After initial IV dosing in the acute setting, initiate tablets at 50 mg every 6 hours 15 minutes after the last IV dose and continue for 48 hours; thereafter, the maintenance dose is 100 mg twice daily	ER capsule: swallow whole or sprinkle capsule contents over soft food; mix contents with water for nasogastric tube administration ER capsule: 1 to 1 dose conversion with ER tablet Tablet: Take with or immediately after meals. Do not chew.
nadolol	Tablets	Oral	Angina pectoris: Once daily HTN: Once daily	Dosage adjustment in renal impairment is required.
nebivolol	Tablets	Oral	HTN: Once daily	Dosage adjustment in renal and hepatic impairment is required.
pindolol	Tablets	Oral	HTN: Twice daily	Poor hepatic function may cause blood levels to increase substantially; use with caution.
propranolol	ER capsules (Inderal LA), ER beads capsules (Inderal XL, Innopran XL), oral solution (Hemangeol), oral solution (generic), tablets (generic)	Oral	Angina pectoris: ER capsule (Inderal LA): Once daily; Oral solution, tablet: Daily in 2, 3 or 4 divided doses Cardiac arrhythmias (atrial fibrillation): Oral solution, tablet: Three to 4 times daily before meals and at bedtime Essential tremor: Oral solution, tablet: Twice daily HTN: ER capsules (all): Once daily; Oral solution, tablet: Twice daily; if control is not adequate, a larger dose, or 3 times daily therapy may achieve better control Hypertrophic subaortic stenosis: Oral solution, tablet: Three to 4 times daily before meals and at bedtime; ER capsule (Inderal LA): Once daily Infantile hemangioma: Oral solution (Hemangeol): Twice daily Migraine prophylaxis: Oral solution, tablet: Daily in divided	Propranolol is not indicated for the treatment of hypertensive emergencies. With propranolol, hepatic insufficiency increases plasma concentration and prolongs the half-life; use with caution. Hemangeol is not intended for pregnant or nursing women. Hemangeol should be initiated at ages 5 weeks to 5 months. Administer doses at least 9 hours apart and during or after feeding. Monitor heart rate and BP for 2 hours after first dose or increasing dose. Of 460 infants (aged 5 weeks to 5 months), 60% had complete or near complete resolution of hemangioma at week 24. Inderal XL and Innopran XL should be administered once daily at bedtime and should be taken consistently either on an empty stomach or with food.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			doses; ER capsule (Inderal LA): Once daily MI: Oral solution, tablet: Twice or 3 times daily Pheochromocytoma: Oral solution, tablet (operable tumors): Daily in divided doses for 3 days preoperatively as adjunct to alpha-adrenergic blockade; Oral solution, tablet (inoperable tumors): Daily in divided doses as adjunct to alpha-adrenergic blockade	
sotalol	Tablets (Betapace, Betapace AF, Sorine), oral solution (Sotylize)	Oral	Cardiac arrhythmias (maintenance of normal sinus rhythm in patients with symptomatic atrial fibrillation/atrial flutter): Tablet (Betapace, Betapace AF, Sorine): Twice daily; Oral solution (Sotylize): Once or twice daily based on renal function Cardiac arrhythmias (ventricular): Tablet (Betapace, Betapace AF, Sorine): Twice daily; Oral solution (Sotylize): Once or twice daily based on renal function	Pediatric dosing is available for the treatment of cardiac arrhythmias (ventricular and symptomatic atrial fibrillation/atrial flutter). Dosage adjustment in renal impairment is required. For treatment of atrial fibrillation or flutter, use is contraindicated if CrCL is < 40 mL/min. See the Betapace or Sorine prescribing information for instructions on compounding an oral solution from the tablets.
timolol	Tablets	Oral	HTN: Twice daily Migraine prophylaxis: Twice daily MI: Twice daily	During maintenance therapy for migraine prophylaxis, doses of 10 mg or 20 mg may be given once daily. Dosage reductions may be necessary in kidney and hepatic dysfunction as timolol is substantially excreted by the kidney (ie, risk of toxic reactions may be increased) and is partially metabolized in the liver.
Beta-blocker/Diuretic Combinations				
Dutoprol (metoprolol succinate extended release/HCTZ)	Tablets	Oral	Once daily	Safety and effectiveness in severe renal impairment (CrCL ≤ 30 mL/min) have not been established; no dose adjustment necessary in

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				patients with moderate renal impairment. Minor alterations of fluid and electrolyte balance may precipitate hepatic coma in patients with impaired hepatic function or progressive liver disease.
Lopressor HCT (metoprolol tartrate/ HCTZ)	Tablets	Oral	Daily in single or divided doses	While once-daily dosing is effective and can maintain a reduction in BP throughout the day, lower doses may not maintain a full effect at the end of the 24-hour period; larger or more frequent doses may be required. Should be taken with or immediately following meals.
Tenoretic (atenolol/ chlorthalidone)	Tablets	Oral	Once daily	Dosage adjustment in renal impairment is required.
Ziac (bisoprolol/ HCTZ)	Tablets	Oral	Once daily	Use with caution when dosing/titrating patients with renal and hepatic impairment; discontinue use with progressive renal impairment.

See the current prescribing information for full details.
Abbrv: BP = blood pressure, CrCL = creatinine clearance, ER = extended release, HCTZ = hydrochlorothiazide, HTN = hypertension, IV = intravenous, MI = myocardial infarction, NYHA = New York Heart Association
* Dosing from the package insert is summarized for completeness, but an IV formulation of atenolol is no longer marketed.

CONCLUSION

- Beta-blockers are a group of drugs that block the effects of catecholamines on beta receptors.
- Beta-blockers have a range of FDA-approved indications as the agents within the class differ in pharmacologic and pharmacokinetic properties. Such differences may include adrenergic-receptor blocking activity, ISA, and lipophilicity.
- There are several national and international evidence-based antihypertensive guidelines that provide recommendations regarding the use of beta-blockers. All of the agents within the class, with the exception of sotalol, are FDA-approved for the treatment of HTN. Most guidelines recommend that the selection of an antihypertensive agent be based on compelling indications for use; the 2017 ACC/AHA guideline for the prevention, detection, evaluation, and management of high BP in adults recommends the use of beta-blockers as secondary agents after thiazide diuretics, ACE inhibitors, ARBs, and CCBs *(Whelton et al 2017)*.
- The choice of a beta-blocker for a specific patient will depend on several factors. In addition to considering the clinical trial data and FDA-approved indications, patient diagnoses and comorbidities should be considered when selecting a product; for example:
  - Beta-blockers are best avoided in patients with asthma and chronic obstructive pulmonary disease; however, if no suitable alternatives exist, a $beta_1$-selective agent is preferred.
  - For patients with HF, bisoprolol, carvedilol, or metoprolol extended release should be considered as these have demonstrated a reduction in mortality; some guidelines recommend nebivolol as an option in certain HF patients *(Rosendorff et al 2015)*.
  - For patients with hepatic or renal disease, drugs that are not hepatically or renally eliminated, respectively, are preferred.

  - For patients receiving concomitant therapy with a cytochrome (CYP) 2D6 inhibitor, beta-blockers that are not CYP2D6 substrates are preferred *(Clinical Pharmacology 2021)*.
  - For patients with HTN and acute coronary syndrome, initial therapy should include a short-acting beta$_1$-selective beta-blocker without ISA (metoprolol tartrate or bisoprolol) *(Rosendorff et al 2015)*.
- Most beta-blockers are available generically, including those that are recognized as effective for providing a mortality benefit in patients with HF *(Drugs@FDA 2021, Yancy et al 2013, Yancy et al 2017, Maddox et al 2021)*. Available generic products will provide ample options for the majority of patients and clinical situations.
- The beta-blocker/diuretic combination products are FDA-approved for the treatment of HTN and are well-established for this indication.
- The beta-blocker/diuretic combinations are more effective compared to placebo and compared to the individual components given alone. There are currently no head-to-head trials comparing the various combination products to one another or any trials to demonstrate differences in clinical outcomes when the drug components are administered as separate agents concurrently versus the fixed-dose combination products.
- Many patients with HTN require more than 1 antihypertensive medication to achieve BP goals. Little guidance on the use of fixed-dose combination products is available within treatment guidelines; however, they are recognized as having the ability to simplify treatment regimens and to improve adherence (*Williams et al 2018*).
- HTN guidelines recommend combination therapy as a treatment option in patients who have BP that is not at goal with monotherapy *(James et al 2014, Unger et al 2020)*.
- Most guidelines agree that beta-blockers are of particular value for hypertensive patients with certain co-morbid diseases, such as HF, post-MI, angina pectoris, coronary artery disease, and ventricular dysfunction *(*Arnett *et al 2019, Go et al 2014, Rosendorff et al 2015, Unger et al 2020)*. Other guidelines recommend beta-blockers for atrial fibrillation and diabetes *(Go et al 2014)*. Diuretics also offer benefits in terms of diseases associated with edema, such as HF *(Go et al 2014, Unger et al 2020)*. However, caution should be exercised as some guidelines do not recommend the use of beta-blockers in combination with a diuretic in patients at risk for diabetes as they have adverse effects associated with glucose metabolism.

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Publication Date: January 3, 2022

Therapeutic Class Overview
Pulmonary Arterial Hypertension Agents

INTRODUCTION

- Pulmonary arterial hypertension (PAH), a subtype of pulmonary hypertension (PH), is a chronic, life-threatening disease that is characterized by increased resistance in the pulmonary circulation caused by progressive pulmonary artery remodeling and constriction of the pulmonary vasculature (*Buckley et al 2013, Wu et al 2013*).
  - PH is defined as a mean pulmonary arterial pressure (mPAP) of ≥ 20 mmHg at rest. In the past, PH was hemodynamically defined by an mPAP ≥ 25 mmHg; however, this cutoff was somewhat arbitrary and targeted at avoiding the over-detection of PH (*Rubin and Hopkins 2021*).
  - Additionally, for patients with PAH, the diagnosis requires a pulmonary vascular resistance (PVR) ≥ 3 Wood units (*Rubin and Hopkins 2021*).
  - PAH often manifests with clinical symptoms such as shortness of breath and decreased functional capacity, and eventually leads to right heart failure and death (*Gomberg-Maitland et al 2011*).
- Early recognition of PAH is essential and the gold standard for the clinical diagnosis of PAH is right heart catheterization (*Buckley et al 2013*).
- According to the 6th World Symposium on PH, the condition is classified into 5 World Health Organization (WHO) groups (*Simonneau et al 2019*):
  - Group 1 – PAH
  - Group 2 – PH secondary to left heart disease
  - Group 3 – PH secondary to lung diseases and/or hypoxia
  - Group 4 – PH due to pulmonary artery obstructions
  - Group 5 – PH with unclear and/or multifactorial mechanisms
- Group I encompasses PAH, including idiopathic PAH, heritable PAH, drug- and toxin-induced PAH, and PAH associated with other disorders such as connective tissue disease, portal hypertension, human immunodeficiency virus infection, congenital heart disease, and schistosomiasis (*Simonneau et al 2019*).
- In addition to the diagnostic classification, patients may be stratified according to their WHO functional capacity, which was adapted from the New York Heart Association (NYHA) classification of left heart failure. A brief description of these functional classes (FC) is as follows (*Stringham et al 2010*):
  - Class I: No limitation of physical activity
  - Class II: Slight limitation of physical activity
  - Class III: Marked limitation of physical activity
  - Class IV: Inability to carry out any physical activity without symptoms
- The prevalence of WHO Group 1 PAH has been estimated at 7 to 26 cases per million adults (*Pogue et al 2016*). The disease has a poor prognosis and an approximate mortality rate of 15% within 1 year on therapy (*McLaughlin et al 2009*). The median survival in the 1980s was 2.8 years; this had improved to 7 years in the late 2000s (*Pogue et al 2016*).
- Pulmonary artery obstruction (Group 4), including chronic thromboembolic PH (CTEPH), is a leading cause of severe PH that results from thrombus formation leading to fibrous stenosis or complete obliteration of pulmonary arteries.
  - The incidence of CTEPH is uncertain, but in a 2017 meta-analysis, the overall pooled incidence after pulmonary embolism was 2.3% (*Ende-Verhaar et al 2017*).
- Specific agents to treat PAH primarily target 3 pathways critical to its pathobiology: the prostacyclin, endothelin, and nitric oxide pathways (*Wu et al 2013*). There are currently 10 molecular entities within 5 therapeutic classes that are Food and Drug Administration (FDA)-approved for the treatment of PAH (*Lexicomp 2021*).
  - Drugs active within the prostacyclin pathway are the prostacyclin analogues (PCAs) or prostanoids (intravenous [IV] epoprostenol; inhaled iloprost; and IV, subcutaneous [SC], inhaled, and oral treprostinil) and a prostacyclin receptor agonist (oral and IV selexipag).
  - Drugs active within the endothelin pathway are the endothelin receptor antagonists (ERAs) (oral ambrisentan, oral bosentan, and oral macitentan).

  - Drugs active within the nitric oxide pathway are the phosphodiesterase-type-5 (PDE-5) inhibitors (IV and oral sildenafil and oral tadalafil) and a soluble guanylate cyclase (sGC) stimulator (oral riociguat).
- The goals of treatment include improvement in the patient's symptoms, quality of life (QOL), and survival. The optimal therapy for a patient should be individualized, taking into account many factors including severity of illness, route of administration, side effects, comorbid illness, treatment goals, and clinician preference (*McLaughlin et al 2009*).
- Initial management of PAH includes the use of warfarin, diuretics, and/or oxygen depending on the patient's diagnosis and symptoms. Prior to the initiation of advanced therapy, patients with PAH should undergo a vasoreactivity test. Oral calcium channel blockers (CCBs) are indicated only for patients who have a positive acute vasodilator response to testing (*Galiè et al 2015[b], Klinger et al 2019, McLaughlin et al 2009*).
- For patients who do not have a positive acute vasodilator response to testing and are considered at risk (NYHA Class II or III) based on clinical assessment, combination therapy with certain agents is preferred initially but monotherapy can be considered if combination therapy is not an option. Agents that can be used include ERAs, PDE-5 inhibitors, an sGC stimulator, and a prostacyclin receptor (IP) agonist. In patients with high-risk disease, continuous treatment with an IV PCA therapy (epoprostenol or treprostinil) would be recommended. Add-on therapy may be considered if patients do not respond adequately to initial therapy (*Barst, 2009, Galiè et al 2015[b], Klinger et al 2019, McLaughlin et al 2009*).
- The PAH agents are FDA-approved for the treatment of patients with WHO Group I PAH; however, there are differences in the study populations for which their FDA-approvals were based (*McLaughlin et al 2009*).
- Adempas (riociguat) is a first-in-class sGC stimulator with a dual mode of action involving endogenous nitric oxide that leads to increased generation of cyclic guanosine monophosphate (cGMP) with subsequent vasodilation. This agent is also FDA-approved for treating adults with persistent/recurrent CTEPH after surgical treatment or inoperable CTEPH. Adempas is the first and only drug to be FDA-approved in the treatment of CTEPH. Pulmonary endarterectomy is curative for CTEPH, but it is technically demanding which may limit access to its use as a treatment (*Archer 2013*).
- In PAH, prostacyclin synthase is reduced, resulting in inadequate production of prostacyclin I_2, a potent vasodilator with antiproliferative effects and an inhibitor of platelet aggregation (*McLaughlin et al 2009*). The PCAs, iloprost and treprostinil, were developed as chemically stable alternatives to epoprostenol, which requires continuous IV infusion due to its lack of stability (*Asaki et al 2015*). Orenitram (treprostinil) is the first FDA-approved oral PCA. It may represent a more convenient dosage form than the other treprostinil formulations (Remodulin and Tyvaso). However, patients with more severe PAH are likely to receive infused PCA rather than oral therapy (*McLaughlin et al 2009*). Among these agents, epoprostenol IV is the only agent that has demonstrated improved patient survival in high-risk PAH patients (*Galiè et al 2015[bj]*). Uptravi (selexipag) works at the same pathway as the PCAs, but activates the IP receptor, also known as the prostacyclin receptor. Orenitram and Uptravi are the only orally administered agents that work within the prostacyclin pathway (*Asaki et al 2015*).
  - In 2021, Tyvaso gained approval for use in PH associated with interstitial lung disease (WHO Group 3), making it the only approved agent for this disease state (*Tyvaso prescribing information 2021, United Therapeutics 2021*).
- Endothelial dysfunction in PAH causes increased production of endothelin-1 resulting in vasoconstriction, which is mediated by the endothelin receptors, ET_A and ET_B. Stimulation of ET_A causes vasoconstriction and cell proliferation, while stimulation of ET_B results in vasodilatation, antiproliferation and endothelin-1 clearance. The ERAs (Letairis [ambrisentan], Opsumit [macitentan], and Tracleer [bosentan]) competitively bind to both receptors with different affinities. Letairis and Opsumit are highly selective for the ET_A receptor, while Tracleer is slightly selective for the ET_A receptor over the ET_B receptor. In addition, Opsumit has a pharmacologically active metabolite and is considered "tissue-targeting" because it displays high affinity and sustained occupancy at the ET receptors in human pulmonary arterial smooth muscles. However, the clinical significance of receptor affinities of the ERAs has not been established (*McLaughlin et al 2009*). Of the ERAs, Letairis is approved to be used in conjunction with Adcirca to reduce the risks of disease progression and hospitalization for worsening PAH and to improve exercise ability (*Klinger et al 2019, Letairis prescribing information 2019*). In addition to treatment of PAH (WHO Group I) in adults, Tracleer is approved for use in children 3 years and older with idiopathic or congenital PAH to improve pulmonary vascular resistance (*Tracleer prescribing information 2021*).
- In patients with PAH, there is also an impaired release of nitric oxide by the vascular endothelium, thereby reducing cGMP concentrations. The PDE-5 enzyme is the predominant phosphodiesterase in the pulmonary vasculature and is responsible for the degradation of cGMP. The PDE-5 inhibitors, Revatio (sildenafil) and Adcirca (tadalafil), increase the concentrations of cGMP resulting in relaxation of the pulmonary vascular bed.

- Medispan class: Cardiovascular Agents, Miscellaneous – Prostaglandin Vasodilators; Pulmonary Hypertension: Endothelin Receptor Antagonists, Phosphodiesterase Inhibitors, Prostacyclin Receptor Agonist, and Soluble Guanylate Cyclase Stimulator.

Table 1. Medications Included Within Class Review

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

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

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

INDICATIONS

Table 2. FDA-approved Indications

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

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

Abbreviations: CTEPH=chronic thromboembolic pulmonary hypertension; FC=functional class; NYHA=New York Heart Association, PAH=pulmonary arterial hypertension, PH=pulmonary hypertension, WHO=World Health Organization.
*Studies establishing effectiveness included predominantly patients with WHO FC II to III symptoms and etiologies of idiopathic or heritable PAH (60%) or PAH associated with connective tissue diseases (34%).
§The delay in clinical worsening was demonstrated when Revatio was added to background epoprostenol therapy. Studies establishing effectiveness were short-term (12 to 16 weeks) and included predominately patients with NYHA FC II to III symptoms and idiopathic etiology (71%) or associated with connective tissue disease (25%).
†Studies establishing effectiveness included predominately patients with WHO FC II to IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%).
¶Studies establishing effectiveness included predominately patients with NYHA FC II to III symptoms and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (23%).
≠Studies included predominately patients with NYHA FC III to IV symptoms and etiologies of idiopathic or heritable PAH (49%) or PAH associated with connective tissue diseases (51%).
¶¶The studies that established effectiveness included predominantly patients with WHO FC II to III symptoms and etiologies of idiopathic or heritable PAH (66%) or PAH associated with connective tissue disease (26%).
ƨStudies establishing effectiveness included predominately patients with NYHA FC II to IV symptoms and etiologies of idiopathic or heritable PAH (58%), PAH associated with congenital systemic-to-pulmonary shunts (23%), and PAH associated with connective tissue diseases (19%).
ΩStudies establishing effectiveness included predominately patients with NYHA FC III symptoms and etiologies of idiopathic or heritable PAH (56%) or PAH associated with connective tissue diseases (33%).
₳Studies establishing effectiveness included predominately patients with NYHA FC III to IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.
**Effectiveness was established in a long-term study in PAH patients with predominantly WHO FC II to III symptoms treated for an average of 2 years. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).
‖Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominately patients with WHO FC II to III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%).
¥Studies establishing effectiveness included predominately patients with NYHA FC III to IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with connective tissue diseases (23%).
‡Effectiveness was established in a long-term study in PAH patients with WHO FC II to III symptoms. Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue diseases (29%), and PAH associated with congenital heart disease with repaired shunts (10%).
†† Study establishing effectiveness predominately included patients with etiologies of idiopathic interstitial pneumonia (45%) inclusive of idiopathic pulmonary fibrosis, combined pulmonary fibrosis and emphysema (25%), and WHO Group 3 connective tissue disease (22%).

(*Prescribing information: Adcirca 2020, Adempas 2021, Flolan 2021, Letairis 2019, Opsumit 2021, Orenitram 2021, Remodulin 2021, Revatio 2020, Tracleer 2021, Tyvaso 2021, Uptravi 2021, Veletri 2021, Ventavis 2021*)

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

CLINICAL EFFICACY SUMMARY

Adcirca (tadalafil)

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

Adempas (riociguat)

- The efficacy and safety of Adempas were evaluated in CHEST-1, a multinational, multicenter, double-blind,16-week trial in 261 adult patients with CTEPH. The majority of patients were WHO FC II (31%) or class III (64%). The primary endpoint of CHEST-1 was change from baseline in 6MWD after 16 weeks. Secondary endpoints included changes from baseline in pulmonary vascular resistance (PVR), N-terminal pro-brain natriuretic peptide (NT-proBNP) level, WHO FC, time to clinical worsening, Borg dyspnea score, QOL variables, and safety. Improvements in walking distance occurred beginning at week 2. At week 16, the placebo adjusted mean increase in 6MWD within the Adempas group was 46 m (95% confidence interval [CI], 25 m to 67 m; p < 0.001) (*Ghofrani et al 2013[a]*).
  - An open-label, non-comparative, extension study (CHEST-2) included 237 patients who completed CHEST-1. CHEST-2 consisted of an 8-week, double-blind dose-adjustment phase, followed by an open-label study phase that

continued until Adempas received official approval and became commercially available. At the March 2013 cut-off date, 211 patients (89%) were receiving ongoing treatment, and 179 (76%) had received over 1 year of treatment. The safety profile of Adempas in CHEST-2 was similar to CHEST-1, with no new safety signals. Improvements in 6MWD and WHO FC observed in CHEST-1 persisted for up to 1 year in CHEST-2. In the observed population at 1 year, mean±standard deviation (SD) 6MWD had changed by 51±62 m (n = 172) versus CHEST-1 baseline (n = 237), and WHO FC had improved, stabilized, or worsened in 47, 50, or 3% of patients (n = 176) versus CHEST-1 baseline (n = 236). Of patients treated for 1 year in CHEST-2, 145 (92%) out of 157 were continuing to receive monotherapy, and 12 (8%) patients were receiving additional PH-specific medication (8 [5%] were receiving ERAs and 4 [3%] were receiving prostanoids). No patient required additional treatment with both an ERA and prostanoid at 1 year (Simmoneau et al 2015). An exploratory analysis noted a significant association with overall survival for 6MWD and NT-proBNP concentration at baseline (p = 0.0199, and 0.0183, respectively), and at follow-up (p = 0.0385, and 0.0068, respectively). Additionally, short-term improvements were associated with long-term survival and worsening-free survival. At 2 years, the overall survival rate was 93% (95% CI, 89 to 96%) and the rate of clinical worsening-free survival was 82% (95% CI, 77 to 87%) (*Simonneau et al 2016*). Due to lack of a control group and because certain outcomes were considered exploratory, data from this study must be interpreted cautiously.

- The efficacy and safety of Adempas were also evaluated in PATENT-1, a multinational, multicenter, double-blind, 12-week trial in 443 adult patients with PAH as defined by PVR > 300 dyn*sec*cm^{-5} and a PAP_{mean} > 25 mmHg. In this study, 50% of the patients were treatment-naïve with respect to PAH therapy, 44% were pre-treated with an ERA, and 6% were pretreated with a PCA (inhaled, oral, or SC). Patients were randomized to 1 of 3 treatment groups: placebo (n = 126), an exploratory capped titration arm of Adempas 1.5 mg 3 times daily (n = 63), or a capped maximum dose of Adempas 2.5 mg 3 times daily (n = 254). The primary endpoint of PATENT-1 was change from baseline in 6MWD after 12 weeks in the Adempas 2.5 mg group compared to placebo. Secondary endpoints included changes from baseline in PVR, NT-proBNP level, WHO FC, time to clinical worsening, Borg dyspnea score, QOL variables, and safety. At week 12, the placebo-adjusted mean increase in 6MWD within the Adempas 2.5 mg treatment group was 36 m (95% CI, 20 m to 52 m, p < 0.001). The group receiving the capped dose at 1.5 mg was excluded from the efficacy analysis (*Ghofrani et al 2013[b]*).
  - An open-label, non-comparative, extension study (PATENT-2) included 396 patients who completed PATENT-1. PATENT-2 consisted of an 8-week, double-blind dose-adjustment phase, followed by an open-label study phase that continues until all patients have transitioned to the commercially available drug. A total of 197 patients received Adempas monotherapy and 199 received Adempas in combination with an ERA or prostanoid, or both. The primary objective of the study was to assess the safety and tolerability of long-term Adempas treatment. Assessments took place at entry to PATENT-2, at weeks 2, 4, 6, 8, and 12, and every 3 months thereafter. At the March 2013 data cut-off, 324 patients (82%) were receiving ongoing treatment and 84% had received 1 year or more of treatment. Mean treatment duration was 95 weeks (median 91 weeks), and cumulative treatment exposure was 718 patient-years (Rubin et al 2015). An exploratory analysis concluded that there was a significant association between overall survival and 6MWD, NT-proBNP concentration, and WHO FC at baseline (p = 0.0006, 0.0225, and 0.0191, respectively), and at follow-up (p = 0.021, 0.0056, and 0.0048, respectively). Additionally, short-term improvements were associated with long-term survival and worsening-free survival. The estimated survival rate was 97% (95% CI, 95 to 98%) and rate of clinical worsening-free survival was 88% (95% CI, 85 to 91%) at 1 year and 79% (95% CI, 74 to 82%) at 2 years (*Ghofrani et al 2016*). Certain outcomes were considered exploratory, so data from this study must be interpreted cautiously.
- The REPLACE trial was an open-label, randomized trial that evaluated efficacy and safety of switching from PDE-5 inhibitor therapy to Adempas. Patients with symptomatic PAH at intermediate risk of 1-year mortality were randomized to remain on their current PDE-5 inhibitor treatment (Revatio ≥ 60 mg/day or Adcirca 20 to 40 mg/day; n = 115) or switch to Adempas (up to 2.5 mg 3 times daily; n = 111). The primary endpoint, clinical improvement by week 24, was defined as the absence of clinical worsening and improvement in at least 2 of the following: 6MWD, WHO FC, or NT-proBNP. The primary endpoint was met in more patients who switched to Adempas (41% vs 20%; p = 0.0007) (*Hoeper et al 2021*).

Flolan (epoprostenol)

- The safety and efficacy of chronically-infused Flolan were evaluated in 2 similar, open-label, randomized trials of 8 to 12 weeks' duration comparing Flolan plus conventional therapy (eg, anticoagulants, oral vasodilators, diuretics, digoxin, oxygen) with conventional therapy alone in idiopathic or heritable PAH (NYHA Class II to IV) patients (n = 106). The average Flolan dose was 9.2 ng/kg/min at the trials' end. A statistically significant improvement was observed in the 6MWD in patients receiving Flolan plus conventional therapy for 8 to 12 weeks compared with those receiving

conventional therapy alone. Improvements were noted as early as week 1. Increases in exercise capacity were accompanied by statistically significant improvement in dyspnea and fatigue, as measured by the Chronic Heart Failure Questionnaire and the Dyspnea Fatigue Index, respectively.

- The efficacy of chronically-infused Flolan in PAH and scleroderma spectrum of diseases (NYHA Class II to IV) was evaluated in an open-label, randomized, 12-week trial (n = 111) comparing Flolan plus conventional therapy with conventional therapy alone. The mean Flolan dose was 11.2 ng/kg/min at the end of week 12. Statistically significant improvement was observed in the 6MWD in patients receiving continuous Flolan plus conventional therapy for 12 weeks compared to those receiving conventional therapy alone. Increases in exercise capacity were accompanied by statistically significant improvements in dyspnea and fatigue, as measured by Borg Dyspnea Index and Dyspnea Fatigue Index. At week 12, the NYHA FC improved in 41% of patients treated with Flolan plus conventional therapy compared to none of the patients treated with conventional therapy alone. However, the majority of patients in both treatment groups showed no change in FC, with 4% of the Flolan plus conventional therapy group and 27% of the conventional therapy group alone worsening.

Letairis (ambrisentan)

- The safety and efficacy of Letairis in the treatment of PAH were established in the ARIES trials. ARIES-1 and ARIES-2 were 12-week, randomized, double-blind, placebo-controlled trials that compared Letairis to placebo in 394 patients. Compared to placebo, treatment with Letairis resulted in a significant increase in exercise capacity as measured by 6MWD (*Galiè et al 2008[a]*). ARIES-E was the open-label extension study for ARIES-1 and ARIES-2. After 1 year of treatment, there was an improvement in 6MWD in the 2.5, 5 and 10 mg Letairis groups (25, 28 and 37 m, respectively). After 2 years of treatment, the improvement was sustained in the 5 and 10 mg groups (23 and 28 m), but not the 2.5 mg group (7 m) (*Oudiz et al 2009*).
- ARIES-3 was a long-term, open-label, single-arm, safety, and efficacy study of Letairis in patients with PH receiving Letairis 5 mg once daily for 24 weeks. The primary endpoint was change from baseline in 6MWD at week 24. Secondary efficacy endpoints included change in plasma NT-proBNP, Borg Dyspnea Index, WHO FC, time to clinical worsening of PAH, survival and adverse events (AEs). A total of 224 patients with PH due to idiopathic and familial PAH (31%), connective tissue disease (18%), chronic hypoxemia (22%), chronic thromboembolic disease (13%), or other etiologies (16%) were enrolled, and 53% of patients received stable background PAH therapies. After 24 weeks of therapy, there was an increase in 6MWD of 21 m (95% CI, 12 to 29), and a decrease in NT-proBNP of -26% (95% CI, -34 to -16%) observed in the overall population compared to baseline. However, increases in 6MWD were not observed in several non-Group 1 PH subpopulations. Peripheral edema, headache, and dyspnea were the most common AEs (*Badesch et al 2012*).
- The AMBITION trial (n = 610) was a double-blind, randomized, Phase 3/4 trial, which compared combination treatment with Letairis plus Adcirca to monotherapy with each in patients with WHO FC II or III symptoms. The study protocol was amended during the trial resulting in 17% of the initial protocol patients being excluded from the analysis, and treatment was administered significantly longer in the combination group vs monotherapy groups (p = 0.03). Results demonstrated that patients receiving combination therapy had significantly fewer clinical failure events (defined as death, hospitalization for worsening PAH, disease progression, or unsatisfactory long-term clinical response) compared to patients receiving individual monotherapy (combination vs pooled-monotherapy group, hazard ratio [HR] 0.5; 95% CI, 0.35 to 0.72; p < 0.001). Primary event outcomes were primarily driven by hospitalization. No significant differences were observed in terms of change in FC or all-cause death. The most common AEs that occurred more often with combination treatment included peripheral edema, headache, nasal congestion, anemia, and bronchitis (*Galiè et al 2015[a]*). Based on results from the AMBITION trial, the FDA-approved Letairis in combination with Adcirca to reduce the risks of disease progression and hospitalization for worsening PAH, and to improve exercise ability (*Letairis prescribing information 2019).*

Opsumit (macitentan)

- The efficacy and safety of Opsumit on progression of PAH were demonstrated in a multicenter, Phase 3, event-driven, placebo-controlled trial (SERAPHIN) in 742 patients with symptomatic PAH (WHO FC II, III, or IV) with or without concomitant use of oral PDE-5 inhibitors, oral or inhaled PCAs, CCBs, or L-arginine for the 3 month period prior to randomization. Patients were randomized to placebo (n = 250), Opsumit 3 mg once daily (n = 250), or Opsumit 10 mg once daily (n = 242). The mean treatment durations were 85.3, 99.5, and 103.9 weeks in the placebo, Opsumit 3 mg, and Opsumit 10 mg groups, respectively. The primary study endpoint was time to the first occurrence of death, a

significant morbidity event (defined as atrial septostomy, lung transplantation, initiation of IV or SC PCAs), or other worsening of PAH (defined as a sustained ≥ 15% decrease from baseline in 6MWD, worsening of PAH symptoms as determined by worsening of WHO FC, and need for additional treatment of PAH) during the double-blind treatment plus 7 days. Pre-specified secondary endpoints included change from baseline to month 6 in the 6MWD and percentage of patients with improvement in WHO FC. Other critical pre-specified secondary endpoints were time to PAH death or PAH hospitalization. The primary endpoint occurred in 46.4%, 38%, and 31.4% of the patients in the placebo, Opsumit 3 mg, and Opsumit 10 mg groups, respectively. Opsumit 10 mg once-daily therapy resulted in a 45% reduction compared to placebo (HR, 0.55; 97.5% CI, 0.39 to 0.76; p < 0.001) in the occurrence of the primary endpoint to the end of the double-blind treatment. The beneficial effect of Opsumit 10 mg was primarily due to its reduction in clinical worsening (*Pulido et al 2013*).
    - In a sub-group analysis of the effect of Opsumit on hospitalizations, there were 117 (46.8%), 104 (41.6%), and 90 (37.2%) patients in the placebo, Opsumit 3 mg and 10 mg groups, respectively, who were hospitalized for any cause at least once during double-blind treatment, and they experienced a total of 171, 159, and 135 all-cause hospitalizations, respectively. Compared with that of placebo, the risk of all-cause hospitalization with Opsumit 3 mg was reduced by 18.9% (HR, 0.811; 95% CI, 0.623 to 1.057; p = 0.1208) and with Opsumit 10 mg by 32.3% (HR, 0.677; 95% CI, 0.514 to 0.891; p = 0.0051). Compared with placebo, the rate of PAH-related hospitalization was reduced by 44.5% in the Opsumit 3 mg group (p = 0.0004) and by 49.8% in the Opsumit 10 mg group (p < 0.0001). The mean number of annual hospital days for PAH-related hospitalizations was reduced by 53.3% in the Opsumit 3 mg arm (p = 0.0001) and by 52.3% in the Opsumit 10 mg arm (p = 0.0003). Due to the exploratory nature of this endpoint and small population, data from this study must be interpreted cautiously (*Channick et al 2015*).

Remodulin (treprostinil)

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

Orenitram (treprostinil)

- The efficacy and safety of Orenitram were evaluated in 3 multicenter, randomized, placebo-controlled, double-blind trials in 349 patients (FREEDOM-M), 350 patients (FREEDOM-C), and 310 patients (FREEDOM-C2).
    - FREEDOM-M compared twice daily administration of Orenitram with placebo in patients newly diagnosed with PAH and not receiving any background PAH treatment. The dose titration was based on patient's clinical response and tolerability. The primary endpoint was change in 6MWD over 12 weeks. The Orenitram group showed a significant improvement in 6MWD of 23 m (p = 0.0125). More than 50% of patients had an improvement of ≥ 20 m, and over 30% of patients had an improvement of > 50 m (*Jing et al 2013*). Orenitram demonstrated AEs typical of prostacyclin treatments (*Waxman 2013*).
    - FREEDOM-C and FREEDOM-C2 failed to meet the primary endpoint of improved 6MWD (*Tapson et al 2012, Tapson et al 2013*).
- The multicenter, randomized, double-blind FREEDOM-EV trial compared 3 times daily Orenitram to placebo in 690 patients who had recently started background therapy with sildenafil, tadalafil, bosentan, ambrisentan, macitentan, or riociguat. The primary endpoint was time to first adjudicated clinical worsening event. Patients receiving Orenitram were less likely to experience a clinical worsening event (HR, 0.74; 95% CI, 0.56 to 0.97; p = 0.028) (*White et al 2020*).

Revatio (sildenafil)

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

blind, placebo-controlled trial consisting of 267 patients receiving epoprostenol with predominantly WHO FC II or III symptoms. Revatio added to epoprostenol improved exercise capacity, hemodynamic measurements and time to clinical worsening more than epoprostenol plus placebo (*Simonneau et al 2008*).

Tracleer (bosentan)

- Tracleer was originally FDA-approved in PAH patients with WHO FC III and IV symptoms based on the results from 2 randomized, double-blind, placebo-controlled trials in 32 (Study 351) and 213 (BREATHE-1) patients treated for 16 and 12 weeks, respectively. In both studies, significant increases in the 6MWD were observed in all Tracleer groups compared to placebo. Tracleer was also associated with a significant reduction in dyspnea during walk tests and a significant improvement in WHO FC symptoms (*Channick et al 2001, Rubin et al 2002*). The FDA-approved indication was subsequently expanded to include patients with WHO FC II symptoms based on the results of the EARLY study consisting of 168 patients. In this 26-week study, treatment with Tracleer resulted in an increase in the 6MWD of 11.2 m compared to a decrease of 7.9 m in the placebo group; however, the difference was not statistically significant. The study did show a significant delay in clinical worsening and a lower incidence of worsening FC symptoms in the Tracleer group compared to placebo (*Galiè et al 2008[b], McLaughlin et al 2006*).
  - The results of an open-label extension phase of the EARLY trial suggested that the majority of patients exposed to long-term Tracleer therapy maintained or improved their FC. Approximately 20% of patients discontinued treatment because of AEs, which were most commonly PAH worsening (defined as death or initiation of IV or SC PCAs) and elevated liver enzymes. Due to lack of a control group, data from this study must be interpreted cautiously (*Simmoneau et al 2014*).
- The COMPASS-2 trial (n = 334) was a prospective, double-blind, randomized controlled trial consisting of symptomatic PAH patients ranging from WHO FC II to IV who were taking stable Revatio doses (mean dose, 60 mg) for ≥ 3 months. Patients were randomized to Tracleer 125 mg twice daily plus Revatio or placebo plus Revatio for 16 weeks. There was no difference in the primary endpoint, time to the first morbidity/mortality event (defined as time to all-cause death, hospitalization for worsening PAH, initiation of IV prostanoid, atrial septostomy, lung transplant, or worsening PAH). There were also no significant differences in the individual measures of the primary endpoint; however, observed benefits were seen in terms of the mean 6MWD test. A high drop-out rate was observed during the trial; therefore, study power was reduced (*McLaughlin et al 2015*).

Tyvaso (treprostinil)

- The safety and efficacy of Tyvaso were evaluated in TRIUMPH I, a 12-week, multicenter, randomized, placebo-controlled, double-blind trial in WHO Group I PAH (98% NYHA Class III) patients who were receiving either Tracleer or Revatio (n = 235) for at least 3 months prior to study initiation. Patients received either placebo or Tyvaso in 4 daily treatments with a target dose of 9 breaths (54 mcg) per session. The primary endpoint, 6MWD, was measured at peak exposure (10 to 60 minutes post dose) and 3 to 5 hours after Tracleer or 30 to 120 minutes after Revatio. Patients receiving Tyvaso had a placebo-corrected median change from baseline in peak 6MWD of 20 meters (m) at week 12 ($p < 0.001$). The 6MWD measured at trough exposure (measured 4 hours after dosing) improved by 14 m.
- In a long-term follow-up of patients who were treated with Tyvaso in the pivotal study and the open-label extension (n = 206), Kaplan-Meier estimates of survival at 1, 2, and 3 years were 97%, 91%, and 82%, respectively. Of note, these observations were uncontrolled and therefore cannot be compared to the control group to determine the long-term effect of Tyvaso on mortality.
- The safety and efficacy of Tyvaso for PH associated with interstitial lung disease (WHO Group 3) were evaluated in INCREASE, a 16-week, multicenter, randomized, placebo-controlled, double-blind trial. Patients were assigned to receive placebo (n = 163) or Tyvaso up to 72 mcg (12 breaths) 4 times daily (target dose, 9 breaths or 54 mcg 4 times daily; n = 163). The primary endpoint, change in peak 6MWD from baseline to week 16, was significantly greater with Tyvaso (difference in change from baseline between Tyvaso and placebo, 31.12 m; $p < 0.001$). There was a reduction of 15% in NT-proBNP levels from baseline with Tyvaso as compared with an increase of 46% with placebo (treatment ratio, 0.58; $p < 0.001$). Clinical worsening was more common in the placebo group (33.1% vs 22.7%; $p = 0.04$) (*Waxman et al 2021*).

Uptravi (selexipag)

- The safety and efficacy of Uptravi were evaluated in the GRIPHON study (n = 1,156), a randomized, double-blind, placebo-controlled trial consisting of patients with predominantly idiopathic PAH, and WHO FC II or III symptoms. The

median duration of treatment varied from 1.2 to 1.4 years for placebo and Uptravi, respectively, and treatment end was defined as 7 days after the last day of treatment intake. Compared to placebo, Uptravi significantly reduced the composite endpoint signifying the time to progression of PAH, defined as all-cause death or a PAH complication (27% vs 41.6%; HR, 0.6; 99% CI, 0.46 to 0.78; p < 0.001); however, there were no differences in mortality between groups. The reduction in PAH complications was primarily driven by a reduction in disease progression (17.2% vs 6.6%) and PAH-related hospitalization (18.7% vs 13.6%). The safety of Uptravi compared to other agents in class is not clear. The GRIPHON pre-specified sub-group analysis did not stratify AEs by background treatment, but the study allowed stable doses of PDE-5 inhibitors and/or an ERA which accounted for approximately 80% of patients within the placebo baseline group. Those AEs that occurred significantly more often with Uptravi treatment included headache, diarrhea, jaw pain, nausea, myalgia, vomiting, extremity pain, flushing (p < 0.001 for all AEs), anemia (p = 0.05), and hyperthyroidism (p = 0.004) (*Sitbon et al 2015*).
    - In long-term follow-up of patients who were treated with Uptravi in the pivotal study and the open-label extension (N = 574), Kaplan-Meier estimates of survival at 1, 3, 5 and 7 years were 92%, 79.3%, 71.2%, and 63%, respectively. The median exposure to Uptravi was 31.7 months. Due to lack of a control group and because certain outcomes were considered exploratory, data from this study must be interpreted cautiously (*Galie et al 2021*).
- Frost and colleagues demonstrated that transitioning patients from inhaled treprostinil to Uptravi was effective and safe (*Frost et al 2018*). Of 34 enrolled patients, 32 (94.1%) stopped inhaled treprostinil and were receiving Uptravi, with 28 patients (82.4%) meeting all criteria for sustained treatment transition. In general, patients remained clinically stable throughout therapy and reported improved outcomes.
- Temporary switching between oral and IV Uptravi was evaluated in an open-label, single-sequence, crossover study, which enrolled 20 patients with PAH who were stable on oral Uptravi doses (*Klose et al 2021*). The safety profile with IV Uptravi was consistent with previous studies and the switch between the 2 formulations was well-tolerated. Pharmacokinetic analyses demonstrated similar exposure to the active metabolite of Uptravi with oral and IV administration.

Veletri (epoprostenol)
- Please refer to the clinical efficacy summary for Flolan above.

Ventavis (iloprost)
- The efficacy of Ventavis was evaluated in a 12-week, randomized, multicenter, double-blind, placebo-controlled trial consisting of 203 patients with NYHA Class III PAH (majority), Class IV PAH, or CTEPH. Patients received 2.5 or 5 mcg of Ventavis 6 to 9 times daily during waking hours. The difference in the primary composite endpoint (10% increase in 6MWD 30 minutes after dose, improvement by at least one NYHA class compared to baseline, and no death or deterioration of PH) was statistically significant (19% vs 4% placebo, p = 0.0033). The results for the CTEPH patients were not included in the aforementioned results, since there was inadequate evidence of benefit in this patient population. The placebo-corrected difference in the 6MWD in Ventavis patients at 12 weeks was 40 m (p < 0.01).
- The safety of Ventavis was evaluated in a prospective, 2 year, open-label study with 63 PAH patients. Patients received Ventavis 2 to 4 mcg 6 to 9 times daily. Thirty-six patients completed at least 630 days of therapy, 19 patients dropped out prematurely, and 8 patients died. AEs were mild to moderate, the most common of which were cough and flushing. Two-year survival was found to be 87% [95% CI, 76% to 98%] (*Olschewski et al 2010*).

Meta-analyses and systematic reviews
- The results of a meta-analysis of 18 randomized controlled trials (n = 4,363) suggested that all oral PAH therapies confer a therapeutic benefit. More specifically, the findings showed:
    - PDE-5 inhibitors were associated with a statically significant reduction in mortality (relative risk [RR], 0.22; 95% CI, 0.07 to 0.71; p = 0.011), while other drugs only showed a trend toward reducing mortality.
    - Compared with placebo, ERAs, PDE-5 inhibitors, and riociguat significantly reduced clinical worsening, ameliorated WHO function class, and increased 6MWD. Oral prostanoids only showed a mild effect on 6MWD (19.88 m; 95% CI, 10.12 to 29.64, p = 0), and did not have any effect on reducing mortality and clinical worsening. Additionally, oral prostanoids significantly increased the incidence of treatment discontinuation due to AEs (RR, 3.41; 95% CI, 2.06 to 5.63; p = 0) (*Zheng et al 2014[a]*).
- A meta-analysis of 14 randomized controlled trials (n = 2,244) that evaluated the improvement in overall survival with use of oral, SC, IV, and inhaled PCAs, suggested the following:

- Only IV PCAs showed a survival benefit (RR, 0.36; 95% CI, 0.16 to 0.79; p = 0.011), while oral (RR, 0.73; 95% CI, 0.32 to 1.66; p = 0.446), inhaled (RR, 0.28; 95% CI, 0.05 to 1.67; p = 0.162), and SC administration (RR, 0.91; 95% CI, 0.38 to 2.20; p = 0.837) did not show a benefit.
- Overall mortality in the 14 studies was 3.30% (74 of 2,244 patients) with 2.52% (30 of 1,189 patients) mortality in the PCA-treated group and 4.17% (44 of 1,055 patients) mortality in the placebo group. The cumulative RR estimate of death showed a significant reduction of 44% (RR, 0.56; 95% CI, 0.35 to 0.88; p = 0.01), and no heterogeneity (I^2 = 0.0%; p = 0.84) was detected among studies (*Zheng et al 2014[b]*).

- A 2019 meta-analysis of 17 randomized controlled trials evaluated the efficacy of PCAs (15 studies), including the prostacyclin receptor agonist Uptravi (2 studies), and demonstrated the following:
  - WHO FC was improved with prostanoids (OR, 2.39; 95% CI, 1.72 to 3.32), largely due to improvements after IV and inhaled therapy but not after oral therapy.
  - IV prostanoid therapy improved 6MWD (19.5 m; 95% CI, 14.82 to 24.19).
  - Mortality was reduced with IV prostanoid administration (OR, 0.29; 95% CI, 0.12 to 0.69) but not after administration by other routes.
  - Compared to placebo, Uptravi improved 6MWD (12.62 m; 95% CI, 1.90 to 23.34) and clinical worsening (OR, 0.47; 95% CI, 0.37 to 0.60), but no difference in mortality was observed (risk difference, 0.02; 95% CI, 0.00 to 0.04) (*Barnes et al 2019[b]*).
- The results of a meta-analysis of 21 randomized controlled trials (n = 5,105) suggested that there was a reduction in the number of combined clinical worsening events (defined as all-cause mortality, lung or heart-lung transplant, hospitalization for PAH, and escalation of treatment) in patients with PAH with oral treatments, but showed less favorable effects on life expectancy in the short-term follow-up. Results demonstrated:
  - All classes reduced clinical worsening compared to placebo, including oral prostanoids (odds ratio [OR], 0.616; 95% CI, 0.419 to 0.906; p = 0.014), ERAs (OR, 0.504; 95% CI, 0.409 to 0.621; p < 0.001), PDE-5 inhibitors (OR, 0.468; 95% CI, 0.329 to 0.664; p < 0.001), and Adempas (OR, 0.277; 95% CI, 0.098 to 0.782; p = 0.015).
  - There were no significant reductions in mortality with any class versus placebo (*Zhang et al 2015*).
- A meta-analysis of 5 randomized controlled trials (n = 962) of < 16 weeks duration in adults and children treated with an sGC stimulator determined the following (all comparisons are vs placebo):
  - sGC stimulators improve PAP in patients with PAH (who are treatment naïve or receiving a prostanoid or ERA) or those with recurrent or inoperable CTEPH.
  - Pooled analysis showed a mean difference in 6MWD of 30.13 m (95% CI, 5.29 to 54.96; I^2 = 64%). On subgroup analysis, for PAH, there was no effect on 6MWD (11.91 m; 95% CI, -44.92 to 68.75; I^2 = 77%), and for CTEPH, sGC stimulators improved 6MWD by a mean difference of 45 m (95% CI, 23.87 to 66.13; I^2 = 0%).
  - The secondary outcome of mortality showed no change on pooled analysis.
  - Although pooled results demonstrated an increase (improvement) in WHO FC (OR, 1.53; 95% CI, 0.87 to 2.72; I^2 = 49%), the results did not reach statistical significance. Also, there was no effect on clinical worsening (OR, 0.45; 95% CI, 0.17 to 1.14; I^2 = 54%) or a reduction in MAP (−2.77 mmHg; 95% CI, −4.96 to −0.58; I^2 = 49%). The pooled analysis did not show any significant difference in serious AEs (OR, 1.12; 95% CI, 0.66 to 1.90; I^2 = 39%).
  - sGC stimulators should not be taken by people also receiving PDE-5 inhibitors or nitrates due to the risks of hypotension, and there is currently no evidence supporting their use in pulmonary hypertension associated with left heart disease (*Wardle et al 2016*).
- Several additional meta-analyses have been conducted evaluating ERAs, PDE-5 inhibitors, and PCAs. Notable observations in meta-analyses include the following:
  - Survival benefit was seen more with IV PCAs, especially in patients with more severe disease, compared with other routes such as oral and inhalation (*Ryerson et al 2010*).
  - ERAs (Letairis and Tracleer) may have a somewhat lower effect on exercise tolerance in patients with connective tissue diseases, whereas PDE-5 inhibitors (Revatio and Adcirca) and the PCA epoprostenol showed consistent effects regardless of the presence or absence of connective tissue diseases (*Kuwana et al 2013*).
  - Combination therapy appears to improve exercise capacity and reduce the risk of clinical worsening in PAH patients compared with monotherapy (*Zhu et al 2012*).
  - A network meta-analysis of 16 randomized controlled trials concluded that add-on therapy with Adcirca or Tyvaso improved 6MWD compared to ERAs alone, add-on therapy with Opsumit or Tracleer improved 6MWD compared to PDE-5 inhibitors alone, and add-on therapy with PDE-5 inhibitors improved 6MWD compared to epoprostenol alone. However, differences in all-cause mortality were not significant (*Petrovic et al 2020*).

- Favorable effects on clinical events were not predicted by changes in the 6MWD (*Savarese et al 2012*). In addition, pulmonary hemodynamics correlated with exercise capacity, but not with clinical events (*Savarese et al 2013*).
- According to an Agency for Healthcare Research and Quality meta-analysis, prostacyclin analogues showed a statistically significant improvement in mortality. In addition, all drug classes improved 6MWD, but comparisons between agents were inconclusive. Combination therapy also improved 6MWD compared with monotherapy, but comparisons between specific regimens were inconclusive. Patients taking ERAs and PDE-5 inhibitors had a lower risk of hospitalization than those taking placebo, while the reduction in patients taking PCAs compared with placebo was similar, but not statistically significant (*McCrory et al 2013*).
- A meta-analysis including 15 RCTs comparing combination and monotherapy for the treatment of PAH found that the absolute risk reduction of clinical worsening was relatively constant beyond a 6 to 12-month treatment duration, and cast doubt on the need for trials of longer duration for measuring treatment efficacy in this population (*Lajoie et al 2018*).
- A Cochrane review of PDE-5 inhibitors for pulmonary hypertension concluded that these agents have clear beneficial effects in Group 1 PAH (*Barnes et al 2019[a]*). For Group 2 PAH, there appears to be some benefit; however, it is unclear which type of left heart disease stands to benefit from therapy. Additionally, there is no clear benefit for PDE-5 inhibitors in PAH secondary to lung disease or CTEPH.
- A Cochrane review evaluating the efficacy and safety of ERAs for PAH has been published, which included 17 randomized trials and a total of 3322 participants (*Liu et al 2021*).
  - Compared to placebo, ERAs demonstrated benefits on exercise capacity (increase in 6MWD of approximately 25 m) and improvement in WHO FC (OR, 1.41 [95% CI, 1.16 to 1.70), as well as lowering the odds of WHO FC deterioration (OR, 0.43 [95% CI, 0.26 to 0.72]). It was reported that ERAs may lead to a decrease in mortality (OR, 0.78 [95% CI, 0.58 to 1.07), and may improve cardiopulmonary hemodynamics and Borg dyspnea score in symptomatic patients.
  - Little comparative evidence is available; only 2 trials included comparisons of ERAs to PDE5 inhibitors. In the larger of these 2 trials (AMBITION), no difference was demonstrated between the Letairis and Adcirca monotherapy groups for 6MWD improvement or WHO FC improvement or deterioration.
  - Although further study is needed, the combination of ERAs plus PDE-5 inhibitors may provide additional benefit in patients with PAH.
- A Bayesian meta-analysis with 50 RCTs (N = 10,996) evaluated differences in clinical outcomes among PAH-targeted drugs. For 6MWD, Tracleer combined with Revatio, Revatio, Tracleer combined with Ventavis, and Tracleer combined with Adcirca were rated as the best treatment options based on surface under the cumulative ranking curves. For reducing clinical worsening, Tracleer combined with Adcirca and Tracleer combined with Ventavis were rated as the best treatment options. Only Letairis and treprostinil significantly reduced the risk of all-cause death compared to placebo (*Fu et al 2021*).

CLINICAL GUIDELINES

- Several published clinical guidelines on PAH are available.
  - The Chest Guideline and Expert Panel Report 2019 update on pharmacologic therapy for PAH recommends initial combination therapy rather than monotherapy, which is a change from the 2014 guideline (*Klinger et al 2019*).
    - Initial therapy: For patients in WHO FC II or III, combination therapy with Letairis and Adcirca is recommended to improve 6MWD. For patients unwilling or unable to take combination therapy, monotherapy with an ERA, PDE-5 inhibitor or sGC is recommended. For WHO FC III patients with evidence of rapid progression or markers of poor prognosis, a parenteral PCA should be considered. For patients in WHO FC IV, a parenteral PCA is recommended; however, if patients are unable or unwilling to manage a parenteral product, an alternative is an inhaled PCA combined with an ERA and an oral PDE-5 inhibitor.
    - Subsequent therapy: For patients in WHO FC III who have evidence of progression or markers of poor prognosis despite treatment with one or two classes of oral agents, addition of an inhaled or parenteral prostanoid should be considered. In patients in WHO FC III or IV, if clinical status is unacceptable, a second (and if needed, a third) class of PAH therapy can be added.
    - Due to limited evidence, the guideline does not provide recommendations for or against the use of Orenitram or Uptravi.
  - The European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines for the diagnosis and treatment of PH (*Galiè et al 2015[b]*) provide several options for both monotherapy and combination therapy of PAH.

- Monotherapy: For patients in WHO FC II, recommendations include an ERA, a PDE-5 inhibitor, an sGC stimulator, or a prostacyclin receptor agonist. For patients in WHO FC III, the same medications may be used, and another option is a PCA. PCAs (eg, epoprostenol) are generally preferred for patients in WHO FC IV.
- Initial drug combination therapy: Only the combination of Adcirca and Letairis has a category I recommendation for patients in WHO FC II and III; this combination also has a category IIb recommendation for patients in WHO FC IV. Other double- and triple-therapy combinations are also options, including other ERA and PDE-5 inhibitor combinations (WHO FC II, III, and IV) and some combinations of oral therapies with parenteral PCAs (WHO FC III and IV).
- Sequential drug combination therapy: Several options are provided for sequential combination therapy. Oral combinations are commonly recommended for patients in WHO FC II and III, including Opsumit added to Revatio, Adempas added to Tracleer, and Uptravi added to an ERA and/or a PDE-5 inhibitor. Other oral combinations and combinations of oral therapies with inhaled or parenteral agents may also be used in patients in WHO FC II, III, and/or IV, but in most cases these recommendations are not as strong.

- A 2018 scientific statement on the evaluation and management of right-sided heart failure from the American Heart Association (AHA) summarizes data for the use of prostacyclin analogs, PDE-5 inhibitors, and endothelin receptor agonists in patients with PAH (*Konstam et al 2018*). However, specific recommendations concerning the use of these agents in the PAH population are not provided in this document.
- Reputable society groups agree that evidence supporting pediatric treatment is lacking. The AHA and American Thoracic Society (ATS) published a guideline on pediatric PH. This guideline states that in pediatric patients with lower-risk PAH, oral therapy with either a PDE-5 inhibitor or an ERA is recommended, and in pediatric patients with higher-risk PAH, IV or SC PCAs should be initiated without delay (*Abman et al 2015*). An expert consensus statement from the European Pediatric Pulmonary Vascular Disease Network (endorsed by the Association for European Pediatric and Congenital Cardiology, the European Society for Pediatric Research, and the International Society of Heart and Lung Transplantation) recommends a PDE-5 inhibitor, ERA, or oral/inhaled prostacyclin agonist therapy for pediatric patients with low- or intermediate-risk PAH. Initial combination therapy with a PDE-5 inhibitor and an ERA may be considered for patients who are at intermediate risk. Higher-risk patients should be treated with intravenous epoprostenol or intravenous or subcutaneous treprostinil; early combination therapy with a PDE-5 inhibitor, an ERA, and a PCA may also be considered in these patients (*Hansmann et al 2019*).

SAFETY SUMMARY

- sGC Stimulator
  - Adempas has a boxed warning due to embryo-fetal toxicity. It is contraindicated in pregnancy because it may cause fetal harm when administered to pregnant women.
  - Females can only receive Adempas through the Adempas REMS Program, a restricted distribution program that requires enrollment and certification of prescribers, patients, and pharmacies. The program also requires females of reproductive potential to comply with pregnancy testing and contraception requirements.
  - Adempas is contraindicated in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias.
  - Additional contraindications for Adempas include co-administration with nitrates or nitric oxide donors, PDE-inhibitors (specific and non-specific), and other sGC stimulators.
  - Warnings and precautions for Adempas include symptomatic hypotension, bleeding, and pulmonary edema in patients with veno-occlusive disease (if confirmed, treatment should be discontinued).
  - The most common AEs associated with Adempas include headache, dyspepsia and gastritis, dizziness, nausea, diarrhea, hypotension, vomiting, anemia, gastroesophageal reflux disease, and constipation.
- ERAs
  - The ERAs (Letairis, Opsumit, and Tracleer) have boxed warnings for embryo-fetal toxicity and/or risks of teratogenicity due to the potential for fetal harm when administered to women who are or may become pregnant.
  - The Ambrisentan and Macitentan REMS programs, respectively, are designed in the same manner as the Adempas REMS program described above.
  - The Bosentan REMS program requires healthcare professionals who prescribe or dispense this product to enroll and comply with requirements, which include monthly reviews of pregnancy tests in women of reproductive potential and liver enzymes and bilirubin in all patients. All patients must understand the risks and complete an enrollment form.
    - Letairis has an additional contraindication for idiopathic pulmonary fibrosis (IPF).

- Tracleer has additional contraindications for use with cyclosporine A or with glyburide.
- Tracleer has an additional boxed warning for risks of hepatotoxicity and birth defects. Throughout treatment and for 1 month after stopping Tracleer, females of reproductive potential must use 2 reliable methods of contraception unless the patient has had a tubal sterilization or had an intrauterine device (IUD) inserted.
- Drug Reaction with Eosinophilia and Systematic Symptoms (DRESS), anaphylaxis, rash, and angioedema have been reported with Tracleer.
- Pulmonary edema/fluid retention has been reported during postmarketing surveillance of Letairis, Opsumit, and Tracleer. Fluid retention may occur within weeks after starting Letairis or Opsumit, and is more common when Letairis is used in combination with Adcirca than with Letairis or Adcirca alone.
- Tracleer should be avoided in patients taking certain combinations of CYP2C9 and CYP3A inhibitors. Opsumit should be avoided in patients taking strong CYP3A4 inducers or inhibitors, as well as in patients taking moderate dual CYP3A4 and CYP2C9 inhibitors or combined CYP3A4 and CYP2C9 inhibitors.
- Decreases in sperm count, decreased hemoglobin and hematocrit levels, and pulmonary edema (associated with pulmonary veno-occlusive disease (PVOD) have been observed in patients taking ERAs.

- PDE-5 Inhibitors
  - All PDE-5 inhibitor products have a contraindication for use in patients on nitrates as well as a warning with concomitant alpha blocker use due to resulting hypotension. The patient should allow 48 hours to elapse between the last dose of Adcirca and taking nitrates. Additionally, Revatio and Adcirca are contraindicated for concomitant use with the sGC stimulator, Adempas.
  - In August 2012, the prescribing information for Revatio was updated with a warning stating that the use of Revatio in pediatric patients is not recommended due to increased mortality associated with higher doses and noted that lower doses are not effective in improving exercise capacity. The FDA clarified the warning related to pediatric use of Revatio in March 2014, stating it was not intended to suggest that Revatio never be used in children. The FDA acknowledged there may be situations in which the benefit-to-risk profile may be acceptable in individual children, for example, when other treatment options are limited, in which case Revatio can be used with close monitoring (*FDA Drug Safety Communication 2012; FDA Drug Safety Communication 2014).*
  - Warnings and precautions for Adcirca and Revatio include prolonged erection (for more than 4 hours), hearing loss, and vision loss (in 1 or both eyes), all of which require immediate medical attention
  - Co-administration of Revatio with potent CYP3A inhibitors is not recommended. Co-administration of Adcirca with potent CYP3A inhibitors or inducers is not recommended.
  - Blood pressure lowering effects are increased when Adcirca is taken with alcohol.
  - Revatio and Adcirca are generally well tolerated with headaches, myalgia, flushing, and dyspepsia being the most common AEs reported for both products.
  - Stevens-Johnson syndrome and exfoliative dermatitis have been reported with Adcirca, and anaphylactic reaction, anaphylactic shock and anaphylactoid reaction have been reported with Revatio.
  - Vision loss, including permanent vision loss because of non-arteritic anterior ischemic optic neuropathy has been reported with the use of PDE-5 inhibitors.
- Prostacyclin Receptor Agonist
  - Uptravi is contraindicated with strong CYP2C8 inhibitors.
  - Uptravi has a warning/precaution to consider PVOD if acute pulmonary edema develops.
  - Uptravi is not recommended in patients with severe hepatic impairment (Child-Pugh Class C) and has not been studied in dialysis patients (or with eGFR < 15 mL/min/1.73m^2).
  - Concomitant administration of Uptravi with strong inhibitors of CYP2C8 (eg, gemfibrozil) is contraindicated.
  - The most common AEs reported with Uptravi are headache, diarrhea, jaw pain, nausea, myalgia, vomiting, pain in extremity, and flushing. These AEs are more frequent during the dose titration phase.
- PCAs
  - Orenitram is contraindicated for use in patients with severe hepatic impairment (Child-Pugh Class C).
  - Flolan and Veletri are contraindicated in patients with heart failure due to severe left ventricular dysfunction. Additionally, Veletri is contraindicated in patients with pulmonary edema, stating that the development of pulmonary edema during dose initiation may be associated with pulmonary veno-occlusive disease.
  - Tyvaso carries a warning/precaution related to an increased risk of bleeding, particularly in patients receiving anticoagulants. Remodulin inhibits platelet aggregation and thereby can increase the risk of bleeding. Additional warnings and precautions for Tyvaso include symptomatic hypotension, possible Tyvaso dose changes when inhibitors or inducers of CYP2C8 are added or withdrawn, and a possible increase in exposure or a decrease in

tolerability with hepatic or renal impairment. Orenitram carries a warning that in patients with diverticulosis/blind-end pouches, the tablet shell can become lodged within a diverticulum.
- The safety of Tyvaso and Ventavis has not been established in patients with significant underlying lung disease (eg, asthma, chronic obstructive pulmonary disease, acute pulmonary infections). Patients with acute pulmonary infections who are taking Tyvaso should be carefully monitored to detect any worsening of lung disease and loss of drug effect. Ventavis can induce bronchospasm.
- Hypotension leading to syncope has been observed with Ventavis. It should not be administered in patients with a systolic blood pressure below 85 mmHg. Remodulin can cause symptomatic hypotension.
- Flolan and Ventavis carry additional warnings and precautions regarding pulmonary edema. If signs of pulmonary edema occur, treatment should be stopped because this could be a sign of pulmonary venous hypertension or pulmonary veno-occlusive disease.
- With Flolan, Orenitram, Remodulin, and Veletri, abrupt withdrawal (including interruptions in drug delivery) or sudden large reductions in the dose can worsen PAH symptoms (or cause rebound PH in patients taking Flolan).
- Flolan carries additional warnings and precautions that include vasodilation reactions and an increased risk of bleeding.
- Flolan, Remodulin, and Veletri are administered via an indwelling central venous catheter. This route of administration is associated with blood stream infections (BSI) and sepsis, which may be fatal. During long-term follow-up, sepsis was reported at a rate of 0.3 infections per patient per year in patients treated with Flolan. In an open-label study of IV Remodulin using an external infusion pump (n = 47), there were 7 catheter-related line infections during approximately 35 patient years, or about one BSI event per 5 years of use. A Centers for Disease Control and Prevention survey of 7 sites that used IV Remodulin for the treatment of PAH found approximately one BSI event per 3 years of use. In an open-label study of an implantable pump (n = 60), there were 2 BSIs related to the implant procedure during approximately 265 patient-years. Continuous SC infusion (undiluted) is the preferred mode of administration of Remodulin. Veletri was associated with chills/fever/sepsis/flu-like symptoms in 25% of patients in controlled trials for idiopathic or heritable PAH.
- Ventavis solution should not be allowed to come into contact with skin or eyes, and ingestion should be avoided.
- Remodulin and Tyvaso exposure may increase or decrease when administered with strong inhibitors or inducers of CYP2C8.
- AEs reported with Tyvaso include cough, headache, throat irritation/pharyngolaryngeal pain, nausea, flushing, and syncope. AEs with Remodulin include infusion site pain, infusion site reaction, headache, diarrhea, nausea, rash, jaw pain, vasodilation, dizziness, edema, pruritus, and hypotension. The most common AEs reported with Orenitram include headache, diarrhea, nausea/vomiting, and flushing.
- AEs associated with Ventavis include vasodilation (flushing), increased cough, headache, trismus, insomnia, nausea, hypotension, vomiting, increased alkaline phosphatase, flu syndrome, back pain, tongue pain, palpitations, syncope, increased gamma-glutamyl transpeptidase, muscle cramps, hemoptysis, and pneumonia.
- The most common AEs reported with Flolan and Veletri include dizziness, jaw pain, nausea, vomiting, headache, hypotension, flushing, and musculoskeletal pain.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Adcirca (tadalafil)	Tablet: 20 mg	Oral	Daily	Dividing the dose over the course of the day is not recommended.
Adempas (riociguat)	Tablet: 0.5, 1, 1.5, 2, and 2.5 mg	Oral	Three times daily	Patients who smoke may tolerate higher doses. If they stop smoking, dose decreases may be required. Lower starting doses should be considered in patients unable to tolerate the hypotensive effects and patients

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				receiving strong CYP and P-gp/BCRP inhibitors. Adempas may be crushed and mixed with water or soft foods immediately before administration. Discontinue at least 24 hours prior to administering a PDE-5 inhibitor. Pregnancy test required prior to treatment initiation, monthly during treatment, and one month after stopping treatment.
Flolan (epoprostenol)	Powder for injection: 0.5 and 1.5 mg	IV	Continuous infusion; Initiate infusion through a central venous catheter at 2 ng/kg/min; increase in increments of 1 to 2 ng/kg/min at intervals of at least 15 minutes based on clinical response	Abrupt withdrawal or sudden large reductions in infusion rates should be avoided. Continuous chronic infusion is administered through a central venous catheter. Temporary peripheral IV infusion may be used until central access is established.
Letairis (ambrisentan)	Tablet: 5 and 10 mg	Oral	Once daily (with or without tadalafil daily); titrate at 4-week intervals	Doses > 10 mg once daily have not been studied. Tablets should not be split, crushed, or chewed. Pregnancy test required prior to treatment initiation, monthly during treatment, and one month after stopping treatment.
Opsumit (macitentan)	Tablet: 10 mg	Oral	Once daily	Doses > 10 mg once daily are not recommended. Pregnancy test required prior to treatment initiation, monthly during treatment, and one month after stopping treatment.
Orenitram (treprostinil)	Extended-release tablet: 0.125, 0.25, 1, 2.5, and 5 mg	Oral	Twice or 3 times daily; maximum dose is determined by tolerability; titrate not more than every 3 to 4 days as tolerated	Should be taken with food. Tablets should be swallowed whole. Coadministration with CYP2C8 inhibitors (eg, gemfibrozil) and the presence of mild hepatic impairment require a lower starting dose. Avoid use in moderate hepatic impairment; contraindicated in severe hepatic impairment.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Remodulin (treprostinil)	Multi-dose vials for injection: 1, 2.5, 5, 10, 20 mg/mL	SC, IV	Continuous infusion; initial dose for patients new to therapy: 1.25 ng/kg/min; increase in increments of 1.25 to 2.5 ng/kg/min at weekly intervals, depending on clinical response	SC is preferred, although administration via a central IV line can be performed if SC administration is not tolerated. An implantable IV infusion pump has been approved for use with Remodulin (Implantable System for Remodulin or ISR). Refer to the pump manufacturer's manual for specific instructions for use. Use a lower starting dose in patients with mild or moderate hepatic impairment.
Revatio (sildenafil)	Tablet: 20 mg Powder for oral suspension: 10 mg/mL Solution for injection: 10 mg/12.5 mL	Oral, IV	Oral: 3 times daily approximately 4 to 6 hours apart Injection: IV bolus 3 times daily	Doses above 20 mg 3 times daily are not recommended. Revatio 10 mg injection dose is predicted to be the equivalent of a 20 mg oral dose. Revatio injection is for continued treatment of patients who are temporarily unable to take oral treatment. Oral suspension expires within 60 days of reconstitution.
Tracleer (bosentan)	Tablet: 62.5 and 125 mg Tablet for oral suspension: 32 mg	Oral	Twice daily (age and weight based dosing) Concurrent ritonavir: Once daily or every other day in patients who have been receiving ritonavir for ≥ 10 days; discontinue Tracleer at least 36 hours prior to initiation of ritonavir; resume Tracleer 10 days following ritonavir initiation	Tablets for oral suspension should be dispersed in a minimal amount of water immediately before administration. Pregnancy test required prior to treatment initiation, monthly during treatment, and one month after stopping treatment. Initiation should be avoided in patients with aminotransferases > 3x ULN. Doses > 125 mg twice daily do not have additional benefit sufficient to offset the increased risk of hepatotoxicity.
Tyvaso (treprostinil)	Inhalation solution (solution, refill, and starter solution): 0.6 mg/mL (1.74 mg per 2.9 mL)	Inhale	3 breaths per treatment session, 4 times a day (4 hours apart); titrate by an additional 3 breaths per session at 1 to 2 week intervals; target dose: 9 to 12 breaths per session	Inhalation system consists of an ultrasonic, pulsed delivery device and its accessories.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Uptravi (selexipag)	Tablet: 200, 400, 600, 800, 1000, 1200, 1400, and 1600 mcg Titration pack: 200/800 mcg Powder for injection: 1800 mcg	Oral, IV	Oral: twice daily; increase in increments of 200 mcg twice daily at weekly intervals; maximum: 1600 mcg twice daily Injection: IV infusion administered twice daily	Swallow tablets whole. Food may improve tolerability. Use a once-daily starting dose in patients with moderate hepatic impairment, and reduce dosing to once daily in patients taking concomitant moderate CYP2C8 inhibitors. Uptravi injection is for continued treatment of patients who are temporarily unable to take oral treatment.
Veletri (epoprostenol)	Powder for injection: 0.5 and 1.5 mg	IV	Continuous infusion; Initiate infusion at 2 ng/kg/min; increase in increments of 2 ng/kg/min at intervals of at least 15 minutes based on clinical response If symptoms persist or recur after improving, increase in increments of 1 to 2 ng/kg/min at intervals of at least 15 minutes	Abrupt withdrawal or sudden large reductions in infusion rates should be avoided. Continuous chronic infusion is administered through a central venous catheter. Temporary peripheral IV infusion may be used until central access is established.
Ventavis (Iloprost)	Inhalation solution: 10 and 20 mcg/mL	Inhale	Administered 6 to 9 times per day (no more than once every 2 hours); maximum: 9 times daily	Ventavis is intended to be inhaled using the I-neb Adaptive Aerosol Delivery System. The 20 mcg/mL concentration is for patients who are maintained at the 5 mcg dose and who have repeatedly experienced extended treatment times, which could result in incomplete dosing. Vital signs should be monitored while initiating Ventavis. Consider increasing (lengthening) the dosing interval in patients with Child-Pugh Class B or C hepatic impairment.

Abbreviations: CYP = cytochrome P450; IV = intravenous; PDE-5 = phosphodiesterase-type-5; P-gp/BCRP = P-glycoprotein/breast cancer resistance protein; SC = subcutaneous; ULN = upper limit of normal.

CONCLUSION

- PAH is a life-threatening disorder that is associated with a poor prognosis.
- There are 5 classes of drugs that are used in the management of PAH, including ERAs, PDE-5 inhibitors, PCAs, a prostacyclin receptor agonist, and an sGC stimulator.

- All of the PAH agents have shown improved pulmonary hemodynamics and exercise capacity in PAH patients as compared to placebo. Meta-analyses have suggested statistically significant reductions in mortality with PDE-5 inhibitors and IV prostanoids (*Barnes et al 2019[b], Zheng et al 2014[a], Zheng et al 2014[b]*).
- Most trials for PAH have been relatively short-term trials (12 to 18 weeks) that evaluated changes in exercise capacity using the 6-minute walk distance (6MWD) as a primary endpoint. However, recently there has been a preference toward longer, event-driven trials that evaluate composite clinical worsening events (*LeVarge et al 2015*). Published event-driven trials include SERAPHIN, GRIPHON, AMBITION, and COMPASS-2 (*Galiè et al 2015[a], McLaughlin et al 2015, Pulido et al 2013, Sitbon et al 2015*).
- Clinical trials have demonstrated the safety and efficacy of the individual PAH agents, and some data are available on the use of combination therapy. Two trials evaluating combination therapy include the AMBITION and COMPASS-2 trials. The AMBITION trial demonstrated that combination treatment with Letairis and Adcirca resulted in reduced disease progression and hospitalization in mainly FC II and III PAH patients compared to monotherapy (*Galiè et al 2015[a]*). Results of this study are the primary driver of the change in the CHEST guidelines that recommend initial combination treatment with Letairis and Adcirca (*Klinger et al 2019*). However, the COMPASS-2 trial demonstrated no difference between Tracleer plus Revatio versus Revatio monotherapy for most endpoints with the exception of the mean 6MWD test (*McLaughlin et al 2015*).
- The 2019 update to the 2014 CHEST Guideline and Expert Panel Report recommends initial combination therapy with Letairis plus Adcirca for treatment-naïve symptomatic patients with WHO class II and III PAH. Alternatives include monotherapy with PDE-5 inhibitors, ERAs, and the sGC stimulator. Intravenous PCAs are recommended as initial or add-on treatment for patients with rapid progression and/or poor prognosis or for patients with WHO class IV PAH. Inhaled PCA is recommended as an add-on therapy for patients who remain symptomatic despite oral treatment. The update does not provide recommendations for or against the use of Orenitram or Uptravi (*Klinger et al 2019*).
- The 2015 European Society of Cardiology/European Respiratory Society (ESC/ERS) guideline stratifies PAH treatment by low-, intermediate-, or high-risk patients. In adult patients with low or intermediate risk (FC II to III), initial monotherapy or initial oral combination therapy is recommended. Based on the AMBITION trial, guidelines state that initial combination treatment with Letairis plus Adcirca has proven to be superior to initial monotherapy with either drug in delaying clinical failure. In adult patients with high risk (FC IV), initial combination therapy including IV PCAs is recommended, with epoprostenol IV considered first-line due to the mortality benefits in trials (*Galiè et al 2015[b]*).
- The 2015 American Heart Association and American Thoracic Society guidelines recommend oral therapy with either a PDE-5 inhibitor or an ERA in lower-risk PAH pediatric patients. In pediatric patients with higher-risk PAH, IV and SC PCAs should be initiated immediately with a goal to transition patients to oral or inhaled therapy after the patient is asymptomatic and stable (*Abman et al 2015*). The 2015 ESC/ERS guidelines recommend that pediatric treatment follows adult guidelines, taking risks into account (*Galiè et al 2015[b]*). A 2019 expert consensus statement from the European Pediatric Pulmonary Vascular Disease Network (endorsed by the Association for European Pediatric and Congenital Cardiology, the European Society for Pediatric Research, and the International Society of Heart and Lung Transplantation) recommends a PDE-5 inhibitor, ERA, or oral/inhaled prostacyclin agonist therapy for pediatric patients with low- or intermediate-risk PAH. Initial combination therapy with a PDE-5 inhibitor and an ERA may be considered for patients who are at intermediate risk. Higher-risk patients should be treated with intravenous epoprostenol or intravenous or subcutaneous treprostinil; early combination therapy with a PDE-5 inhibitor, an ERA, and a prostacyclin agonist may also be considered in these patients (*Hansmann et al 2019*).
- A 2018 scientific statement on the evaluation and management of right-sided heart failure from the AHA summarizes data for the use of PCAs, PDE-5 inhibitors, and ERAs in patients with PAH (*Konstam et al 2018*). However, specific recommendations concerning the use of these agents in the PAH population are not provided in the document.
- Adempas is the first and only drug to be FDA-approved in the treatment of CTEPH. Pulmonary endarterectomy can be curative for CTEPH, but it is technically demanding which may limit access to its use as a treatment. Adempas is dosed 3 times daily, which is more frequent than several other oral treatments for PAH.
- Tyvaso is the first and only FDA-approved treatment for PH associated with interstitial lung disease (WHO Group 3) (*Tyvaso prescribing information 2021, United Therapeutics 2021*).

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Publication Date: December 16, 2021

Therapeutic Class Overview
Omega-3 Fatty Acids (FA)

INTRODUCTION

- The independent relationship of triglycerides (TGs) to the risk of future cardiovascular disease (CVD) events has long been controversial. With regard to omega-3 fatty acids (FA) and TGs, the controversy is in part due to variations in doses and components of omega-3 FA evaluated (*Mach et al 2020, Miller et al 2011, Virani et al 2021*).
- Rich sources of omega-3-FA come from fatty fish and plant sources, and fish oil contains eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).
  - It is estimated that doses of omega-3 FA of 4 g/day are associated with TG lowering of ≥ 30% in those with very high TG (>500 mg/dL) and between 20% to 30% in patients with TG levels between 200 to 499 mg/dL (*Skulas-Ray et al 2019*).
  - Select clinical trials suggest that relatively high doses of omega-3-FA, in the form of fish, fish oils, or high-linolenic acid oils, reduce the risk for major coronary events in persons with established coronary heart disease (CHD); however, the overall body of literature offers conflicting evidence that fish oil supplements are beneficial for preventing CVD or improving outcomes (*Abdelhamid et al 2020, Manson et al 2019, Smith et al 2011, Virani et al 2021*).
  - A 2018 large-scale randomized controlled trial (RCT) with Vascepa (icosapent ethyl), REDUCE-IT, demonstrated a significant reduction in cardiovascular events when added to statin therapy in patients with elevated TG levels despite maximally tolerated statin therapy (*Bhatt et al 2019*).
- The scope of this review will focus on Lovaza (omega-3-acid ethyl esters) and Vascepa (icosapent ethyl), which are prescription omega-3 FA Food and Drug Administration (FDA)-approved as adjunct therapy to diet to reduce TGs in adults with severe (≥ 500 mg/dL) hypertriglyceridemia.
  - Lovaza (omega-3-acid ethyl esters) is available as a 1 gram soft-gelatin capsule, containing approximately 375 mg and 465 mg of DHA and EPA, respectively.
  - Vascepa (icosapent ethyl) is available as a soft-gelatin capsule, containing icosapent ethyl, an esterified formulation of EPA. Vascepa contains ≥ 96% EPA (*LexiComp 2021*).
  - Epanova, Omtryg, and Triklo (omega-3-acid ethyl esters) have been discontinued (*Drugs@FDA.gov*).
  - Of note, there are several products containing omega-3 FA that are marketed as nutritional supplements. These products do not have FDA-approved indications and may not contain the same amount of the active ingredient (*LexiComp 2021*).
- The 2018 American College of Cardiology/American Heart Association (ACC/AHA) guideline on the management of blood cholesterol provides recommendations based on a patient's overall atherosclerotic CVD (ASCVD) risk to guide appropriate treatment. Primary therapies in reducing ASCVD risk are adherence to a heart-healthy lifestyle and statin therapy. Omega-3 FA and fibrates are recommended in patients with TGs ≥ 500 mg/dL, but neither agent is considered a low-density lipoprotein cholesterol (LDL-C)-lowering drug (*Grundy et al 2019*). ACC/AHA recommendations on non-statin use do not consider the use of omega-3 FA as the authors did not include therapies for severe hypertriglyceridemia (*Lloyd-Jones et al 2016, Lloyd-Jones et al 2017*). However, the 2021 ACC expert consensus decision pathway recommends the use of icosapent ethyl in certain patient management groups for reducing ASCVD risk (*Virani et al 2021*).
- The National Lipid Association (NLA) recommends omega-3 FA, fibric acid derivatives, or niacin as first-line agents for patients with TG levels ≤ 1000 mg/dL. These agents may also be considered for patients with contraindications or intolerance to statin therapy (*Jacobson et al 2015*). The NLA recently released a position statement on the use of icosapent ethyl in high- and very high-risk patients based on new data from the REDUCE-IT trial (*Orringer et al 2019*). For patients ≥ 45 years of age with clinical ASCVD, or ≥ 50 years of age with Type 2 diabetes and ≥ 1 additional risk factor, icosapent ethyl is recommended for additional ASCVD reduction if the patient is already on a maximally tolerated statin and has TG levels between 135 to 499 mg/dL.
- Several diabetes guidelines recommend the use of icosapent ethyl to reduce cardiovascular risk in patients with ASCVD or ASCVD risk factors (*American Diabetes Association [ADA] 2021, Arnold et al 2020, and Garber et al 2020, Virani et al 2021)*. Both, the ADA standards of care and the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) guidelines recommend the addition of icosapent ethyl for patients with TG levels between 135 to 499 mg/dL on maximally tolerated statin therapy. The AHA recommends icosapent ethyl as first-

line therapy in patients with coronary artery disease (CAD) and TG level > 135 mg/dL, despite a maximally tolerated statin.
- Medi-Span Class: Antihyperlipidemics – Misc.

Table 1. Medications Included Within Class Review

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

Omtryg and Triklo (omega-3-acid ethyl esters) and Epanova (omega-3-carboxylic acid) are no longer marketed.
*Lovaza was initially marketed in the United States as Omacor.

(*Drugs@FDA.gov 2021; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2021; Reliant Pharmaceuticals 2007*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Lovaza (omega-3-acid ethyl esters)	Vascepa (icosapent ethyl)
Adjunctive treatment to diet to reduce TG levels in adult patients with severe (≥ 500 mg/dL) hypertriglyceridemia	✔	✔
Adjunct to maximally tolerated statin therapy to reduce the risk of myocardial infarction, stroke, coronary revascularization, and unstable angina requiring hospitalization in adult patients with elevated TG levels (≥ 150 mg/dL) and established CVD or diabetes mellitus and 2 or more additional risk factors for CVD	--	✔
Limitations of use		
Effect on the risk for pancreatitis has not been determined	✔	✔
Effect on cardiovascular mortality and morbidity has not been determined	✔	--

(*Prescribing information: Lovaza 2021, Vascepa 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

- There are currently no head-to-head efficacy trials comparing Lovaza (omega-3-acid ethyl esters) and Vascepa (icosapent ethyl).
- One study compared the effects of an acylglycerol omega-3 formulation, which is often available in non-prescription omega-3 supplements, to Lovaza. In this double-blind (DB) trial in patients with TG concentrations of 150 to 500 mg/dL, 120 patients were randomized to 5563 mg acylglycerol omega-3 daily, Lovaza 4 g daily, or placebo (olive oil). Both omega-3 groups had decreased TG concentrations compared with placebo ($p < 0.001$), but no difference was found between active treatments (28% reduction with acylglycerol omega-3 and 22% with Lovaza; $p = 0.785$). Because patients included in this study had mild to moderate elevations in TG levels at baseline, it is unclear if the acylglycerol omega-3 formulation would have similar results in patients with severe hypertriglyceridemia (*Hedengran et al 2015*).
- Lovaza (omega-3-acid ethyl esters) and Vascepa (icosapent ethyl) were consistently associated with decreases in TG levels from baseline compared to placebo in studies of hypertriglyceridemia (*Ballantyne et al 2012, Bays et al 2011, Bays et al 2010[a], Bays et al 2010[b], Calabresi et al 2000, Calabresi et al 2004, Davidson et al 2007, Durrington et al*

2001, Eritsland et al 1996, GISSI-Prevenzione Investigators 1999, Johansen et al 1999, Koh et al 2012, Macchia et al 2013, Maki et al 2008, Maki et al 2010, McKeone et al 1997, Nilsen et al 2001, Nordoy et al 1998, Peters et al 2012, Pownall et al 1999, Risk and Prevention Study Collaborative Group et al 2013, Roth et al 2009, Stalenhoef et al 2000, Van Dam et al 2001).

- In select placebo-controlled trials, Lovaza (omega-3-acid ethyl esters) was associated with an increase in LDL-C levels from baseline compared to placebo (*Bays et al 2010[a], Calabresi et al 2000, Calabresi et al 2004, Koh et al 2012, Maki et al 2010, Pownall et al 1999, Roth et al 2009, Stalenhoef et al 2000*).
- Lovaza (omega-3-acid ethyl esters) was generally associated with an additive decrease in TGs and total cholesterol (TC) levels when added to a regimen containing a statin or a fibric acid derivative (*Bays et al 2010[a], Bays et al 2010[b], Davidson et al 2007, Durrington et al 2001, Maki et al 2008, Maki et al 2010, Nordoy et al 1998, Peters et al 2012, Roth et al 2009*).
- When compared in head-to-head trials, Lovaza (omega-3-acid ethyl esters) was associated with similar decreases in cholesterol parameters from baseline compared to fenofibrate. When compared to gemfibrozil, 1 DB RCT demonstrated similar significant decreases in TGs and an increase in HDL-C and LDL-C concentrations. However, a second RCT demonstrated that Lovaza (omega-3-acid ethyl esters) was associated with a significantly smaller decrease in TG levels from baseline (–28.9% vs –51.2%, respectively; p = 0.007). TC was decreased 10.2% with Lovaza, and 13.0% with gemfibrozil (p = 0.51) (*Koh et al 2012, Stalenhoef et al 2000, Van Dam et al 2001*).
- In placebo-controlled trials, Vascepa (icosapent ethyl) was not associated with an increase in LDL-C levels from baseline compared to placebo (*Ballantyne et al 2012, Bays et al 2011*).
- The omega-3 FA have been studied in several cardiovascular outcomes trials with inconsistent findings (*Bhatt et al 2019, Bonds et al 2014, Bosch et al 2012, Galan et al 2010, GISSI-Prevenzione 1999, Manson et al 2019, Marchioli et al 2009, Rauch et al 2010, Risk and Prevention Study Collaborative Group 2013, The ASCEND Study Group 2018, Yokoyama et al 2007*). To date, 4 cardiovascular outcomes trials have found a reduction in cardiovascular endpoints; these 4 trials include GISSI-P with omega-3 acid ethyl esters, GISSI-HF with omega-3 FA, JELIS with Epadel (Japanese product not available in the U.S.), and REDUCE-IT with Vascepa (icosapent ethyl).
  - The GISSI-Prevenzione trial demonstrated the beneficial effects of omega-3 acid ethyl esters in patients who have experienced a recent myocardial infarction (MI); omega-3-acid ethyl esters significantly reduced the risk of death, nonfatal MI, and nonfatal stroke compared to vitamin E. Treatment with omega-3 poly unsaturated FA (PUFA), but not vitamin E, significantly lowered the risk of the composite of death, nonfatal MI, and nonfatal stroke (relative risk [RR], 0.10; 95% confidence interval [CI], 0.01 to 0.18; p = 0.048 by 2-way analysis and RR, 0.15; 95% CI, 0.20 to 0.25; p = 0.023 by 4-way analysis) (*GISSI-Prevenzione Investigators 1999*).
  - In the DB, placebo-controlled, randomized GISSI-HF study, omega-3 FA and rosuvastatin were evaluated in patients with heart failure (*Marchioli et al 2009*). Over a median of 3.9 years, 6975 patients received omega-3 FA 1 g/d or placebo. Approximately one-half of the patients were on statins including rosuvastatin 10 mg daily. For all-cause death, 27% of the omega-3 FA group and 29% of the placebo group died (adjusted hazard ratio [HR], 0.91; 95% CI, 0.833 to 0.998; p = 0.041). For all-cause death or cardiovascular-related hospitalization, 57% of the omega-3 FA group and 59% of the placebo group met the endpoint (adjusted HR, 0.92; 95% CI, 0.849 to 0.999; p = 0.009). For the rosuvastatin study with 4574 patients, no benefit with rosuvastatin was observed for all-cause death (adjusted HR, 1.00; 95% CI, 0.989 to 1.122; p = 0.943) or for the combined endpoint of all-cause death or cardiovascular-related hospitalization (adjusted HR, 1.01; 99% CI, 0.908 to 1.112; p = 0.903).
  - The multicenter, randomized, DB, placebo-controlled REDUCE-IT trial (n = 8179) evaluated the effect of Vascepa (icosapent ethyl) on ischemic events in patients with elevated TGs despite statin therapy and established CVD (70.7%) or other risk factors (eg, diabetes). The primary endpoint was a composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina. After a median follow-up of 4.9 years, a primary endpoint event was observed in 17.2% of patients in the Vascepa (icosapent ethyl) group vs 22.0% of patients in the placebo group (HR, 0.75; 95% CI, 0.68 to 0.83; p < 0.001). The number needed to treat to avoid 1 primary endpoint event was 21 (95% CI, 15 to 33). Vascepa (icosapent ethyl) was also associated with a significant reduction in the key secondary endpoint (composite of cardiovascular death, nonfatal MI, or nonfatal stroke; HR, 0.74; 95% CI, 0.65 to 0.83; p < 0.001) (*Bhatt et al 2019*).
- Additionally, a formulation of EPA has been marketed in Japan since 1994 under the trade name Epadel (ethyl-eicosapentaenoic acid, the active metabolite of icosapent ethyl). Published studies have evaluated this formulation as an adjunctive therapy with estriol and statins in the cardiovascular outcomes of this agent.

- In a prospective, observational, 48-week trial, Epadel (ethyl-eicosapentaenoic acid) 1800 mg daily added to estriol 2 mg daily was compared to estriol 2 mg daily alone. TC decreased significantly from baseline in both groups. Serum levels of TGs decreased significantly from 194.5 to 141.5 mg/dL (-27.2%; p = 0.001) in the study group but increased slightly from 192.9 to 207.4 mg/dL (+7.5%) in the control group at week 48 in the women whose level of TGs was not < 150 mg/dL (*Kurabayashi et al 2000*).
- In an open-label (OL) trial, 900 to 1800 mg/day of Epadel (ethyl-eicosapentaenoic acid) was administered to patients with hyperlipidemia who had been treated with statins for an average of 30 months. Serum TC and TG concentrations were significantly decreased 3 months after the administration of Epadel (ethyl-eicosapentaenoic acid) (from 5.63 to 5.02 mmol/L, p < 0.05; from 2.07 to 1.08 mmol/L; p < 0.01, respectively) (*Nakamura et al 1999*).
- In the Japan Eicosapentaenoic Acid Lipid Intervention Study (JELIS), a prospective, OL, blinded endpoint trial, 18,645 patients were randomly assigned to receive either 1800 mg of Epadel (ethyl-eicosapentaenoic acid) daily with a statin or statin therapy alone. The primary endpoint was any major coronary event, including sudden cardiac death, fatal and non-fatal MI, and other non-fatal events including unstable angina pectoris, angioplasty, stenting, or coronary artery bypass grafting. At a mean follow-up of 4.6 years, the primary endpoint occurred less frequently in the Epadel (ethyl-eicosapentaenoic acid) group compared to the control group (262 [2.8%] vs 324 [3.5%], respectively; RR, 0.19; p = 0.011) (*Yokoyama et al 2007*).
  - Seven sub-analyses have been published of the JELIS study.
    - The reduction in cardiovascular risk was greater in the Epadel (ethyl-eicosapentaenoic acid) group compared to the control group in patients unable to attain LDL-C and/or HDL-C goals (-38% reduced risk; p = 0.007), those with peripheral artery disease (HR, 0.44; 95% CI, 0.19 to 0.97; p = 0.041), those with preexisting CAD and a TC ≥ 250 mg/dL (8.7% vs 10.7%, respectively; HR, 0.77, 95% CI, 0.63 to 0.96; p = 0.017) and regardless of the number of cardiovascular risk factors (hypercholesterolemia, obesity, high TG or low HDL-C, diabetes, and hypertension) (p < 0.05 for all comparisons) (*Ishikawa et al 2010, Matsuzaki et al 2009, Saito et al 2008, Sasaki et al 2012*).
    - The use of Epadel (ethyl-eicosapentaenoic acid) was associated with a significantly greater decrease in CAD compared to the control group in patients with impaired glucose metabolism, but not normoglycemic patients (p = 0.048 and p = 0.062, respectively) (*Oikawa et al 2009*).
    - Adherence to ≥ 80% of the medication regimen was associated with a decreased incidence of cardiovascular endpoints compared to those exhibiting < 80% adherence to study medications (p = 0.041) (*Origasa et al 2010*).
    - The incidence of secondary stroke was lower in the Epadel (ethyl-eicosapentaenoic acid) group compared to the control group (6.8 vs 10.5%, respectively; HR, 0.80; 95% CI, 0.64 to 0.997; p = 0.047); however, there was no difference between groups in the incidence of primary stroke (1.5 vs 1.3%, respectively; HR, 1.08; 95% CI, 0.95 to 1.22; p = 0.244) (*Tanaka et al 2008*).

- The STRENGTH trial was a DB, MC, RCT study (N = 13,078) that evaluated the efficacy of Epanova (omega-3 carboxylic acid [CA] formulation of omega-3 FA) 4 g/day vs corn oil in statin treated patients with high cardiovascular risk, hypertriglyceridemia, and low levels of HDL-C. The primary efficacy endpoint was composite of cardiovascular death, nonfatal MI, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization. The study was terminated early when 1384 patients (of 1600 planned) had experienced a primary endpoint; at a median follow up of 41 months, 1580 patients experienced a primary endpoint event (785 omega-3 CA [12%] vs 795 with corn oil [12.2%]) demonstrating no significant difference in composite outcome of major adverse cardiovascular events (HR, 0.99; 95% CI, 0.90 to 1.09; p = 0.84) (*Nicholls et al 2020*).
- An RCT comparing Lovaza (omega-3-acid ethyl esters) to dietary therapy in patients admitted for coronary artery bypass grafting demonstrated a lower incidence of vein graft occlusion in the treatment group. After 1 year of therapy, the vein graft occlusion rate per distal anastomoses was 27% in the group receiving Lovaza (omega-3-acid ethyl esters) compared to 33% in the control group (odds ratio [OR], 0.77; 95% CI, 0.60 to 0.99; p = 0.034) (*Eritsland et al 1996*).
- An RCT comparing Lovaza (omega-3-acid ethyl esters) to placebo in patients who were scheduled for elective coronary angioplasty demonstrated no difference in the rate of restenosis. This event occurred in 40.6% of the treated stenoses in the Lovaza (omega-3-acid ethyl esters) group and in 35.4% of the treated stenoses in the placebo group (OR, 1.25; 95% CI, 0.87 to 1.80; p = 0.21) (*Johansen et al 1999*).
- An RCT comparing Lovaza (omega-3-acid ethyl esters) to placebo in patients with an acute MI demonstrated no difference in the rate of cardiovascular events and revascularizations. Of the patients receiving Lovaza (omega-3-acid ethyl esters), 28% experienced at least 1 cardiac event compared to 24% of patients in the placebo group (p = 0.74).

There was no significant difference between the groups concerning the number, type, or severity of cardiac events (*Nilsen et al 2001*).

- An RCT comparing Lovaza (omega-3-acid ethyl esters) to placebo in patients with confirmed symptomatic paroxysmal atrial fibrillation (AF) that required cardioversion, who had at least 2 episodes of AF in the 6 months before randomization, or both, demonstrated no significant difference in the rate of recurrence of symptomatic AF. At 12 months, 56 of 297 participants (18.9%) in the placebo group and 69 of 289 participants (24%) in the omega-3 PUFA group had a recurrent symptomatic AF (HR, 1.28; 95% CI, 0.90 to 1.83; p = 0.17) (*Macchia et al 2013*).
- A Cochrane systematic review of 86 RCTs examined the effects of fish- and plant-based omega-3 FA on CVD. Increased intake of EPA or DHA had little or no effect on all-cause mortality, cardiovascular mortality, cardiovascular events, stroke, or arrhythmia; however, increased intake may provide a slight benefit for CHD mortality and CHD events. Evidence included in this review was primarily from supplement trials (*Abdelhamid et al 2020*). Another meta-analysis of omega-3 FA found no evidence of reduction in CHD events or major vascular events in patients at risk for cardiovascular events (*Aung et al 2018*).
- More recent meta-analyses, which include the REDUCE-IT trial, have found benefits from both TG lowering and omega-3 supplementation with CVD. In an analysis of 3 TG-reducing therapies, lowering of TG levels was associated with a reduction in major vascular events (RR, 0.84; 95% CI, 0.75 to 0.94 per 1 mmol/L [0.92 per 40 mg/dL] reduction in TG) (*Marston et al 2019*). An evaluation of the impact of omega-3 supplements on the risk of CVD pooled data from 13 trials found that supplementation was associated with a modest, but significant, reduction in both CVD death (RR, 0.93; 95% CI, 0.88 to 0.99) and total CVD events (RR, 0.97; 95% CI, 0.94 to 0.99) (*Hu et al 2019*).

CLINICAL GUIDELINES

- The 2018 ACC/AHA management of blood cholesterol guidelines emphasize adherence to lifestyle and statin therapy before considering the addition of an LDL-lowering nonstatin drug. Omega-3 FA and fibrates are recommended in patients with TGs ≥ 500 mg/dL (*Grundy et al 2019*).
- Other guidelines (NLA and the AACE/ACE) suggest a potential role for other lipid-lowering therapies when treating hypertriglyceridemia including fibric acid derivatives, niacin, and omega-3 FA (*Jacobson et al 2015, Handelsman et al 2020*).
- The 2019 AHA omega-3 FA for hypertriglyceridemia guideline estimated that doses of omega-3 FA of 4 g/day are associated with TG lowering of ≥ 30% in those with very high TG (> 500 mg/dL) and between 20% to 30% in patients with TG levels between 200 to 499 mg/dL (*Skulas-Ray et al 2019*). Based on the available data, all prescription omega-3 FA are comparably effective, but direct comparisons are lacking.
- The NLA released a position statement on the use of Vascepa (icosapent ethyl) in high- and very high-risk patients based on new data from the REDUCE-IT trial (*Orringer et al 2019*). For patients ≥ 45 years of age with clinical ASCVD, or ≥ 50 years of age with type 2 diabetes and at least 1 additional risk factor, Vascepa (icosapent ethyl) is recommended for additional ASCVD reduction if the patient is already on a maximally tolerated statin, with or without ezetimibe, and has TG levels between 135 to 499 mg/dL.
- Several guidelines (AACE/ACE, ADA, and AHA) recommend the addition of Vascepa (icosapent ethyl) in patients with type 2 diabetes and either CAD or ASCVD risk factors who have elevated TG levels (> 135 mg/dL per AHA guideline and 135 to 499 mg/dL per AACE/ACE and ADA guidelines), despite use of maximally tolerated statins (*ADA 2021, Arnold et al 2020, Garber et al 2020)*.
- The 2021 ACC expert consensus decision pathway on the management of ASCVD risk reduction in patients with hypertriglyceridemia stratifies patients into 5 management groups and provides algorithmic guidance based on triglyceride levels including optimizing diet and lifestyle interventions, statin therapy, glycemic control, and optional interventions to consider with persistent hypertriglyceridemia (*Virani et al 2021*).
  - In adults with clinical ASCVD and adults aged ≥ 40 years with DM and no ASCVD, LDL-C management should be addressed with maximally tolerated statins, with or without ezetimibe, to achieve goals. Vascepa (icosapent ethyl) can be considered in cases of persistent fasting hypertriglyceridemia (TG 150 to 499 mg/dL) through shared decision making and patient preference.
  - Adults aged ≥ 20 years with no ASCVD or DM with TG ≥ 150 mg/dL to 499 mg/dL should be screened for secondary causes of elevated TG levels and optimized on diet and lifestyle. ASCVD risk should be calculated and addressed with statin therapy through shared decision making.

- Adults aged ≥ 20 years with TG ≥ 500 mg/dL should be screened for secondary causes of high levels of TG, optimized on diet and lifestyle changes, and evaluated for the risk of ASCVD. Fibrates or prescription omega-3 fatty acids should be considered. For those with ASCVD risk, statin therapy should be considered.
- In patients 40 to 75 years without ASCVD or DM with mild to moderate hypertriglyceridemia, there are no data to support omega-3 FA dietary supplements for ASCVD risk reduction or to lower triglycerides, although dietary intake of foods rich in omega-3 fatty acids is encouraged.

SAFETY SUMMARY

- Omega-3 FA have precautions for use in patients with hepatic impairment and fish allergy; these agents may also prolong bleeding time. Lovaza (omega-3 acid ethyl esters) may be associated with increases in LDL-C. Additionally, Vascepa and Lovaza have a warning of atrial fibrillation or flutter.
- The most common adverse reactions associated with Lovaza (incidence > 3% and greater than placebo) were eructation, dyspepsia, and taste perversion.
- The most common adverse reactions associated with Vascepa in a cardiovascular outcomes trial (incidence ≥ 3% and ≥ 1% more frequent than placebo) were musculoskeletal pain, peripheral edema, constipation, gout, and atrial fibrillation.

DOSING AND ADMINISTRATION

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

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Lovaza (omega-3-acid ethyl esters)	Soft gelatin capsule	Oral	Once daily or in 2 divided doses	
Vascepa (icosapent ethyl)	Soft gelatin capsule	Oral	Twice daily	Should be administered with food

See the current prescribing information for full details.

CONCLUSION

- Prescription omega-3 FA are approved by the FDA for the treatment of severe hypertriglyceridemia. There are approved generic formulations of Lovaza (omega-3-acid ethyl esters) and Vascepa (icosapent ethyl).
- In patients with an elevated TG level (≥ 500 mg/dL), a fibric acid derivative or niacin should be initiated before LDL-C lowering therapy to prevent pancreatitis. Omega-3 FA represent an alternative to fibric acid derivatives and niacin for the treatment of hypertriglyceridemia. Select clinical trials suggest that relatively high doses of omega-3-FA, in the form of fish, fish oils or high-linolenic acid oils, will reduce the risk for major coronary events in persons with established CHD; however, the overall body of literature offers conflicting evidence that fish oil supplements are beneficial for preventing CVD or improving outcomes.
- The REDUCE-IT trial offered evidence that the addition of Vascepa (icosapent ethyl) 2 g twice daily to statin therapy in patients at high risk for ischemic events with high TG levels can help reduce cardiovascular outcomes (*Bhatt et al 2019*). Based on these data, the AACE/ACE, ADA, AHA, and NLA have published recommendations for the use of icosapent ethyl in high- and very-high ASCVD risk patients who meet similar criteria to the REDUCE-IT trial population (*ADA 2021, Arnold et al 2020, Garber et al 2020, Orringer et al 2019, Virani et al 2021*). Additionally, the AHA considers icosapent ethyl as first-line treatment for patients with CAD and type 2 diabetes with TG levels > 135 mg/dL, despite maximally tolerated statin doses (*Arnold et al 2020*). Recently, the STRENGTH trial demonstrated that the addition of high dose Epanova (omega-3 CA), compared with corn oil, did not result in a significant difference of a composite outcome of major adverse cardiovascular events, in statin-treated patients at high cardiovascular risk (*Nicholls et al 2020*).

- Clinical trials have demonstrated that prescription omega-3 acid ethyl esters can effectively lower TGs, as well as positively affect other lipid/lipoprotein parameters when used as monotherapy or in combination with fenofibrate or statins.
- It is estimated that doses of omega-3 FA of 4 g/day are associated with TG lowering of ≥ 30% in those with very high TG (> 500 mg/dL) and between 20% to 30% in patients with TG levels between 200 to 499 mg/dL (*Skulas-Ray et al 2019*).
- In select placebo-controlled trials, Lovaza (omega-3-acid ethyl esters) was associated with an increase in LDL-C levels from baseline compared to placebo.
- In placebo-controlled trials, Vascepa (icosapent ethyl) was not associated with an increase in LDL-C levels from baseline compared to placebo.
- Select cardiovascular outcomes studies have suggested a decrease in cardiovascular outcomes with Lovaza (omega-3 acid ethyl esters) and Vascepa (icosapent ethyl); however, certain trials have demonstrated no benefit compared to a control group.
- The 2018 ACC/AHA guidelines emphasize adherence to lifestyle and statin therapy before considering the addition of an LDL-C lowering nonstatin drug. Omega-3 FA are a reasonable addition for patients with persistently elevated severe hypertriglyceridemia, along with implementing a very low-fat diet (*Grundy et al 2019*).
- The 2021 ACC expert consensus decision pathway on the management of ASCVD risk reduction in patients with hypertriglyceridemia indicates that Vascepa (icosapent ethyl) can be considered in some instances of persistent fasting hypertriglyceridemia through shared decision making and patient preference. In patients 40 to 75 years without ASCVD or DM with mild to moderate hypertriglyceridemia, there is no data to support supplementation with Vascepa (icosapent ethyl); dietary intake of foods rich in omega-3 fatty acids is encouraged in these patients.

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Publication Date: January 3, 2022

Therapeutic Class Overview
Anticonvulsants

INTRODUCTION

- Epilepsy is a disease of the brain defined by any of the following (*Fisher et al 2014*):
  - At least 2 unprovoked (or reflex) seizures occurring > 24 hours apart;
  - 1 unprovoked (or reflex) seizure and a probability of further seizures similar to the general recurrence risk (at least 60%) after 2 unprovoked seizures, occurring over the next 10 years;
  - Diagnosis of an epilepsy syndrome.
- Types of seizures include generalized seizures (previously called primary generalized), focal seizures (previously called partial), and seizures of unknown onset (*Fisher et al 2017A, Fisher et al 2017B, Nguyen et al 2020*). Seizure classifications from the International League against Epilepsy (ILAE) were updated in 2017.
  - Generalized seizures affect both sides of the brain and are classified by the type of symptoms:
    - Motor seizures: can be further classified by the type of motor symptoms
      - Tonic-clonic (previously called grand mal): begin with stiffening of the limbs, followed by jerking of the limbs and face
      - Myoclonic: characterized by rapid, brief contractions of body muscles, usually on both sides of the body at the same time
      - Atonic: characterized by abrupt loss of muscle tone; they are also called drop attacks or akinetic seizures and can result in injury due to falls
    - Nonmotor (absence) seizures (previously called petit mal): typical symptoms include brief lapses of awareness, sometimes with staring, that begin and end abruptly; they are more common in children than adults and may be accompanied by brief myoclonic jerking of the eyelids or facial muscles, a loss of muscle tone, or automatisms.
  - Focal seizures are located in just 1 area of the brain and are classified by the level of awareness and type of symptoms on onset of the seizure:
    - Focal aware (previously called simple) vs focal impaired awareness (previously called complex): retained awareness relates to ability for patient to remain aware of self and environment during a seizure
    - Motor onset vs nonmotor onset: grouped by earliest most prominent sign, either motor (eg, atonic, clonic, or tonic movements) or nonmotor (eg, autonomic or sensory symptoms)
    - Focal to bilateral tonic-clonic (previously called secondarily generalized seizures): describes pattern of a seizure that propagates to involve both sides of the brain
  - Seizures of unknown onset are classified by the type of symptoms, but onset is unable to be classified
  - Any seizure type can lead to status epilepticus, which is characterized by prolonged, uninterrupted seizure activity.
- There is variation between the ILAE classifications and many of the Food and Drug Administration (FDA)-approved indications for antiepileptic drugs (AEDs) (*Nguyen et al 2020*). For example, a “focal aware” seizure corresponds to the prior term “simple partial seizure,” a “focal impaired awareness” seizure corresponds to the prior term “complex partial seizure,” “generalized” seizure corresponds to the prior term “primary generalized,” “generalized tonic-clonic” seizure corresponds to the prior term “grand mal,” and “absence” seizure corresponds to the prior term “petit mal.”
- A number of epilepsy syndromes have also been described; these are defined by groups of features that tend to occur together such as having a similar seizure type, age of onset, part of the brain involved, and electroencephalogram (EEG) pattern (*Epilepsy Foundation 2013*). An example is a childhood epilepsy syndrome called Lennox-Gastaut syndrome (LGS), which is characterized by several seizure types including tonic (stiffening) and atonic (drop) seizures. In LGS, there is a classic EEG pattern seen and intellectual development is usually impaired (*Epilepsy Foundation 2020*).
- Epilepsy management is focused on the goals of 1) controlling seizures, 2) avoiding treatment-related adverse effects (AEs), and 3) maintaining or restoring quality of life. Management options vary based on the seizure type. It is usually appropriate to refer patients to a neurologist to establish the epilepsy diagnosis and formulate the management strategy (*Schachter 2021*).
  - A correct diagnosis is essential to proper treatment selection. For example, absence seizures are commonly confused with complex partial seizures. However, drugs that reduce absence seizures are generally ineffective for complex

partial seizures, and the most effective drugs for complex partial seizures may be ineffective against or even increase the frequency of absence seizures.

- When possible, monotherapy with a single AED is the preferred treatment approach. Use of monotherapy increases the probability of treatment adherence, provides a wider therapeutic index, and is associated with fewer idiosyncratic reactions, teratogenic effects, and potential drug interactions. However, data are conflicting on the benefits of mono- vs polytherapy. When combination therapy is needed, it is recommended to select products with different mechanisms of action and AE profiles. There is little comparative clinical data to support the use of specific combinations (*Schachter 2021*).
- Several broad classes of AEDs are available, including barbiturates, benzodiazepines, hydantoins, and miscellaneous agents (see Table 1).
- Several newer products with different mechanisms of action have been approved in the past several years for use in childhood epilepsy syndromes such as LGS and Dravet syndrome. These include cannabidiol (Epidiolex), stiripentol (Diacomit), and fenfluramine (Fintepla).
- Everolimus tablets for oral suspension (Afinitor Disperz) received an expanded indication in April 2018 for use in partial-onset seizures associated with tuberous sclerosis complex (TSC). This product is a kinase inhibitor that also has several oncology indications.
- Intranasal formulations of benzodiazepines have also been recently approved for the acute treatment of seizures, including midazolam nasal spray (Nayzilam) and diazepam nasal spray (Valtoco).
- Several of the AEDs are used for additional indications beyond the management of epilepsy, including (but not limited to) bipolar disorder, migraine prophylaxis, and several types of neuropathic pain. These additional indications are listed in Table 2; however, this review primarily focuses on the use of AEDs for the management of epilepsy. Additionally, brands and formulations that are FDA-approved and marketed only for non-epilepsy indications are not included within this review; these include gabapentin tablets (Gralise), gabapentin enacarbil extended-release tablets (Horizant), pregabalin extended-release tablets (Lyrica CR), and everolimus oral tablets (Afinitor, Zortress).
- Medispan class: Antianxiety agents, benzodiazepines; Anticonvulsants, AMPA glutamate receptor antagonists; Anticonvulsants, anticonvulsants – misc; Anticonvulsants, carbamates; Anticonvulsants, GABA modulators; Anticonvulsants, hydantoins; Anticonvulsants, succinimides; Anticonvulsants, valproic acid; Hypnotics/Sedatives/Sleep Disorder Agents, barbiturate hypnotics

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Barbiturates	
Pentobarbital (Nembutal)	✔
Phenobarbital* (Luminal†, Solfoton†)	✔
Primidone (Mysoline)	✔
Benzodiazepines	
Clobazam (Onfi; Sympazan)	✔ §§
Clonazepam (Klonopin§)	✔
Clorazepate (Tranxene T-Tab§)	✔
Diazepam (Diastat, Diastat AcuDial, Diazepam Intensol, Valium§, Valtoco)	✔ ‖
Midazolam (Nayzilam, Seizalam)	-
Hydantoins	
Fosphenytoin (Cerebyx, Sesquient‡)	✔ ‖
Phenytoin (Dilantin§, Phenytek**)	✔ ‖
Miscellaneous	
Brivaracetam (Briviact)	-
Cannabidiol (Epidiolex)	-
Carbamazepine (Carbatrol, Epitol**, Equetro, Tegretol§, Tegretol-XR)	✔
Cenobamate (Xcopri)	-
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	✔
Eslicarbazepine (Aptiom)	-¶
Ethosuximide (Zarontin)	✔

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

* Not FDA approved
† Brand product not currently marketed; generic is available
§ Brand marketing status may vary by strength and/or formulation
‡ Sesquient was approved by the FDA in November 2020; anticipated availability is unknown. The Sesquient formulation allows for storage at room temperature, unlike other fosphenytoin products.
‖ Generic availability may vary by strength, brand and/or formulation
¶ Generic eslicarbazepine FDA-approved in June 2021; anticipated availability is unknown
** Branded generic
†† Branded generic; not currently marketed
§§Generic available for Onfi tablets and oral suspension; only brand name (Sympazan) oral soluble film is available

(*Clinical Pharmacology 2022, Drugs@FDA 2022, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2022*)

INDICATIONS

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

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

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

Indications	Brivaracetam	Cannabidiol	Carbamazepine	Cenobamate	Clobazam	Clonazepam	Clorazepate	Diazepam	Divalproex Sodium	Eslicarbazepine	Ethosuximide	Everolimus	Felbamate	Fenfluramine	Fosphenytoin	Gabapentin	Lacosamide	Lamotrigine	Levetiracetam
Relief of skeletal muscle spasm, spasticity, athetosis, and stiff-man syndrome								A											
Seizures associated with tuberous sclerosis complex (TSC)		✔ *										A*							
TSC for the treatment of subependymal giant cell astrocytoma (SEGA)												✓*							

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

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

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

Indications	Midazolam	Methsuximide	Oxcarbazepine	Pentobarbital	Perampanel	Phenobarbital†	Phenytoin	Pregabalin	Primidone	Rufinamide	Stiripentol	Tiagabine	Topiramate	Valproic acid	Vigabatrin	Zonisamide
Migraine prophylaxis													✔ *	✔ *		
Postherpetic neuralgia								✔								
Sedative for anxiety, tension, and apprehension																
Neuropathic pain associated with diabetic peripheral neuropathy								✔								
Neuropathic pain associated with spinal cord injury								✔								
Fibromyalgia								✔								
Short-term treatment of insomnia¥				✔												

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

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

- Brivaracetam:
  - Treatment of partial-onset seizures in patients ≥ 1 month of age
- Cannabidiol:
  - Treatment of seizures associated with LGS, Dravet syndrome, or TSC in patients ≥ 1 year of age
- Carbamazepine:
  - Partial seizures with complex symptomatology (psychomotor, temporal lobe); patients with these seizures appear to show greater improvement than those with other types; generalized tonic-clonic seizures (grand mal); mixed seizure patterns which include the above, or other partial or generalized seizures
  - Absence seizures (petit mal) do not appear to be controlled; carbamazepine has been associated with increased frequency of generalized convulsions in these patients
  - Treatment of pain associated with true trigeminal neuralgia; beneficial results also reported in glossopharyngeal neuralgia
  - Bipolar indication is for an extended-release capsule formulation (Equetro) only: treatment of patients with acute manic or mixed episodes associated with bipolar I disorder
- Cenobamate:
  - Treatment of partial-onset seizures in adult patients
- Clobazam:
  - Seizures associated with LGS in patients ≥ 2 years of age
- Clonazepam:
  - In patients with absence seizures who have failed to respond to succinimides, clonazepam may be useful
- Diazepam:
  - Oral diazepam (tablets, solution, concentrate) may be used adjunctively in convulsive disorders; it has not proved useful as sole therapy.
  - Injectable diazepam is a useful adjunct in status epilepticus and severe recurrent convulsive seizures

- Diazepam nasal spray and rectal gel are indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (ie, seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 6 years of age (nasal spray) or ≥ 2 years of age (rectal gel)

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

- Levetiracetam:
  - Tablets, oral solution, injection, and tablets for oral suspension:
    - Treatment of partial-onset seizures in patients ≥ 1 month of age (tablets, oral solution, and injection [Keppra]); treatment for partial-onset seizures in patients ≥ 4 years of age and weighing > 20 kg (tablets for oral suspension [Spritam])
    - Adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents ≥ 12 years of age with JME
    - Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and children ≥ 6 years of age with idiopathic generalized epilepsy
  - The extended-release tablets are only indicated for treatment of partial-onset seizures in patients ≥ 12 years of age
- Methsuximide:
  - Control of absence (petit mal) seizures that are refractory to other drugs
- Midazolam:
  - Nasal spray: Acute treatment of intermittent, stereotypic episodes of frequent seizure activity (ie, seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 12 years of age
  - IM injection: Treatment of status epilepticus in adults
- Oxcarbazepine immediate-release formulations:
  - Monotherapy in the treatment of partial seizures in adults and children 4 to 16 years of age
  - Adjunctive therapy in the treatment of partial seizures in adults and children 2 to 16 years of age
- Oxcarbazepine extended-release tablets:
  - Treatment of partial-onset seizures in adults and children ≥ 6 years of age
- Pentobarbital:
  - In anesthetic doses in the emergency control of certain acute convulsive episodes, eg, those associated with status epilepticus, cholera, eclampsia, meningitis, tetanus, and toxic reactions to strychnine or local anesthetics
- Perampanel:
  - Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy ≥ 4 years of age
  - Adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in patients with epilepsy ≥ 12 years of age
- Phenobarbital (not FDA-approved):
  - Phenobarbital tablets are indicated for use as an anticonvulsant; the elixir is indicated for the treatment of generalized and partial seizures; the injection is indicated as an anticonvulsant for the treatment of generalized tonic-clonic and cortical focal seizures, in the emergency control of certain acute convulsive episodes, and in pediatric patients as an anticonvulsant
- Phenytoin oral formulations:
  - Treatment of tonic-clonic (grand mal) and complex partial (psychomotor, temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery (the oral suspension does not have the neurosurgery indication)
- Phenytoin injection:
  - Treatment of generalized tonic-clonic status epilepticus and prevention and treatment of seizures occurring during neurosurgery
  - Can be substituted as short-term use for oral phenytoin when oral phenytoin administration is not possible
- Pregabalin:
  - Adjunctive therapy for treatment of partial-onset seizures in patients ≥ 1 month of age
- Primidone:
  - Control of grand mal, psychomotor, and focal epileptic seizures; may control grand mal seizures refractory to other anticonvulsant therapy
- Rufinamide:
  - Adjunctive treatment of seizures associated with LGS in adults and pediatric patients ≥ 1 year of age
- Stiripentol:
  - Treatment of seizures associated with Dravet syndrome in patients ≥ 2 years of age taking clobazam; no clinical data to support its use as monotherapy

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

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

CLINICAL EFFICACY SUMMARY

- Overall, the anticonvulsants have demonstrated efficacy for their FDA-approved uses. Clinical trial data demonstrating efficacy of the anticonvulsants for the treatment of epilepsy is described in the prescribing information for the individual products, particularly for anticonvulsants more recently approved by the FDA. However, the prescribing information for some older, conventional products (eg, benzodiazepines, carbamazepine, ethosuximide, methsuximide, phenytoin, and primidone) and non-FDA approved products (eg, phenobarbital) do not contain efficacy data in their prescribing information.
- When possible, monotherapy with a single AED is the preferred treatment approach. This increases the probability of treatment adherence, provides a wider therapeutic index, and is associated with fewer idiosyncratic reactions, teratogenic effects, and potential drug interactions. However, data are conflicting on the benefits of mono- vs polytherapy (*Schachter 2021*). Most patients with epilepsy are treated with anticonvulsant monotherapy (*Nevitt et al 2017*).
- No single AED is clearly the most effective. Comparative efficacy data for the management of epilepsy are limited, and trials have generally not shown significant differences among drugs in terms of efficacy. However, the quality of the data is limited and generally derived from short-term trials (*Karceski 2021*).
- An evidence review summarized AED efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes (*Glauser et al 2013*). This publication provides conclusions based on a review of 64 randomized trials and 11 meta-analyses. Conclusions include the following:
  - As initial monotherapy for adults with newly diagnosed or untreated partial-onset seizures:
    - Carbamazepine, levetiracetam, phenytoin, and zonisamide are established as efficacious/effective.
    - Valproate is probably efficacious/effective.
    - Gabapentin, lamotrigine, oxcarbazepine, phenobarbital, topiramate, and vigabatrin are possibly efficacious/effective.
    - Clonazepam and primidone are potentially efficacious/effective.
  - As initial monotherapy for children with newly diagnosed or untreated partial-onset seizures:
    - Oxcarbazepine is established as efficacious/effective.

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

- Data for individuals with generalized seizures are still limited and additional randomized trials are needed.

- The relative efficacy among valproate, lamotrigine, phenytoin, carbamazepine, ethosuximide, topiramate, levetiracetam, and phenobarbital as monotherapy for generalized (n = 7 studies) or absence seizures (n = 3 studies) was evaluated in a systematic review and network meta-analysis (*Campos et al 2018*). The outcomes analyzed were seizure freedom and withdrawal due to inefficacy. Compared to valproate, phenytoin had a lower odds of seizure freedom (odds ratio, 0.50; 95% credible Interval [CrI] 0.27 to 0.87) in patients with generalized tonic-clonic seizures. Lamotrigine had the highest probability of seizure freedom and valproate had the highest probability of withdrawal due to inefficacy in these patients. For absence seizures, ethosuximide and valproate were found to have a higher probability of seizure freedom compared to lamotrigine.
- A meta-analysis estimated the comparative efficacy of achieving seizure freedom with 22 antiepileptic drugs and placebo in children and adolescents (*Rosati et al 2018*). For the treatment of newly diagnosed focal epilepsy (n = 4 studies), point estimates suggested superiority of carbamazepine and lamotrigine; however, this was not statistically significant. For refractory focal epilepsy (n = 9 studies), levetiracetam and perampanel were more effective than placebo in mixed comparisons. Ethosuximide and valproic acid were more effective than lamotrigine for absence seizures. The authors concluded that better designed comparative studies with appropriate length of follow-up, well-defined outcomes, and reliable inclusion criteria are needed to validate these results.
- A meta-analysis compared monotherapy with carbamazepine or phenytoin in children and adults with focal onset seizures (simple or complex focal and secondarily generalized), or generalized onset tonic-clonic seizures (with or without other generalized seizure types). Results demonstrated that the time to treatment failure (primary outcome) did not significantly differ between treatment groups. The time to first seizure after randomization and 6-month and 12-month remission were also similar between groups (*Nevitt et al 2019).*
- As many as 20% to 40% of patients with epilepsy can be considered refractory to drug treatment, referred to as drug-resistant epilepsy. Treatment of drug-resistant epilepsy may include additional anticonvulsant drug trials, epilepsy surgery, vagus nerve stimulation, responsive cortical stimulation, deep brain stimulation, cannabinoids, and dietary changes (the ketogenic diet) (*Sirven 2021*).
  - Combination AED regimens are an option for the treatment of drug-resistant epilepsy. However, robust clinical evidence of suitable combinations of AEDs has been difficult to generate due to the large number of possible combinations of drugs and doses. Examples of combinations for which there is some evidence of efficacy include valproate plus lamotrigine for partial-onset and generalized seizures, valproate plus ethosuximide for absence seizures, and lamotrigine plus topiramate for various seizure types; however, even this evidence is fairly limited. In general, when considering combination therapy, it is recommended to combine medications with different mechanisms of action, and to be mindful of the overall drug load to minimize AEs. Two-drug therapy should be attempted before considering addition of a third drug, and higher numbers of drugs should be avoided as they are associated with a very low likelihood of additional seizure reduction (*Kwan et al 2011*).
  - A meta-analysis examined the efficacy of newer AEDs (eslicarbazepine, brivaracetam, perampanel, and lacosamide) vs levetiracetam as adjunctive therapy for uncontrolled partial-onset seizures. Most patients in this meta-analysis were on at least 2 other AEDs at the time of treatment. In this analysis, eslicarbazepine, lacosamide, and brivaracetam were non-inferior to levetiracetam in terms of efficacy, but all newer AEDs except brivaracetam had worse tolerability profiles than levetiracetam at high doses (*Zhu et al 2017*).
  - A network meta-analysis examined the efficacy of AEDs (including brivaracetam, eslicarbazepine acetate, gabapentin, lacosamide, levetiracetam, lamotrigine, oxcarbazepine, pregabalin, perampanel, rufinamide, tiagabine, topiramate, vigabatrin, and zonisamide) for adjunctive use in patients with refractory partial-onset seizures while using monotherapy (*Zhao et al 2017*). The efficacy outcomes studied were 50% responder rate and state of seizure freedom. The authors concluded that topiramate, levetiracetam, pregabalin, and oxcarbazepine were preferable for their relatively high efficacy and low risk of AEs. Rufinamide was the least preferable medication due to its low efficacy and high risk of AEs.
  - A systematic review and network meta-analysis evaluated the efficacy and safety of 6 AEDs in LGS (*Zhang et al 2022*). A total of 8 RCTs were included in the analysis, which evaluated the use of lamotrigine, rufinamide, cannabidiol, topiramate, clobazam, and felbamate.
    - Based on the proportion of patients achieving at least a 50% reduction in drop seizures (reported for 5 AEDs in 7 RCTs), all active AEDs were considered superior to placebo therapy. Based on the surface under the cumulative ranking curve (SUCRA), rufinamide, cannabidiol, and topiramate were ranked highest, followed by clobazam and lamotrigine; however, there were no significant differences among these AEDs.

- For the proportion of patients achieving a 75% reduction in drop seizures (reported for 4 AEDs in 5 RCTs), clobazam was ranked highest, followed by cannabidiol therapy; both were demonstrated to be superior to placebo. For topiramate and rufinamide, no significant differences were found vs placebo.
- When evaluating safety, lamotrigine, cannabidiol, and felbamate ranked highest (worst) for serious AEs; however, cannabidiol was the only AED with a significantly higher incidence of serious AEs vs placebo. No substantial difference was observed between the active AEDs.

- A network meta-analysis was conducted to evaluate the efficacy of 17 newer AEDs for treatment of refractory partial-onset epilepsy with or without secondary generalization (*Hu et al 2018*). The primary outcome was seizure freedom, which was defined as a 100% seizure reduction in the maintenance or double-blind treatment period of the trial. Safety was assessed by the withdrawal rate due to treatment-emergent AEs. Based on results of 54 studies that evaluated the efficacy outcome, the most effective agents included tiagabine, brivaracetam, and valproic acid, and the least effective agents included rufinamide, lamotrigine, and zonisamide. Products with favorable safety included levetiracetam, brivaracetam, and perampanel, while those with the least favorable safety included retigabine (not available in the United States), oxcarbazepine, and rufinamide. The authors stated that agents with the best outcomes in terms of efficacy and safety included levetiracetam, vigabatrin, valproic acid, and brivaracetam.

Recently approved agents

- Cannabidiol (Epidiolex) was approved in June 2018 for use in pediatric patients 2 years of age and older with LGS or Dravet syndrome (*FDA news release 2018*). It is the first FDA-approved drug for treatment of patients with Dravet syndrome and is the first approved drug that contains a purified substance, cannabidiol, derived from marijuana. Its approval for these 2 indications was based on 3 placebo-controlled trials in patients refractory to other treatments. Cannabidiol, along with use of other agents demonstrated a significant reduction in seizure frequency compared to placebo (*Thiele et al 2018*; *Devinsky et al 2018; Devinsky et al 2017*). A combined analysis of these trials and an additional randomized dose-ranging trial found that cannabidiol was effective in the overall population as well as in patients using it in conjunction with clobazam (*Gunning et al 2021*). In July 2020, cannabidiol was FDA-approved for a third indication, treatment of seizures associated with TSC, and the age range for all 3 indications was aligned to include pediatric patients 1 year of age and older (*FDA news release 2020)*. In a placebo-controlled trial of 224 patients with TSC and seizures inadequately controlled with ≥ 1 concomitant AED, cannabidiol resulted in a significant reduction in seizure frequency compared to placebo (*Thiele at al 2021*). To date, no comparative trials vs other AEDs have been published.
- Everolimus tablets for oral suspension (Afinitor Disperz) received an expanded indication for adjunctive use in TSC-associated partial-onset seizures in April 2018. Results of a randomized, double-blind, placebo-controlled study of 366 patients with inadequately controlled seizures on 2 or more AEDs demonstrated a significant reduction in seizure frequency compared to placebo (*French et al 2016*).
- In August 2018, the FDA approved a second drug, stiripentol (Diacomit), for use in the treatment of seizures associated with Dravet syndrome. Two multicenter placebo-controlled studies evaluated the addition of stiripentol to clobazam and valproate therapy in patients 3 years to less than 18 years of age with Dravet syndrome. Responder rates (seizure frequency reduced by 50%) with respect to generalized tonic-clonic seizures were significantly lower with stiripentol compared to placebo (*Chiron et al 2000, Diacomit prescribing information 2020).*
- In May 2019, a nasal spray formulation of midazolam (Nayzilam) was approved for the acute treatment of cluster seizures in adults and adolescents. In one randomized controlled trial in patients with seizure clusters while receiving a stable AED regimen, the proportion of patients who experienced treatment success (seizure termination within 10 minutes and no recurrence for the next 6 hours) was significantly higher with midazolam nasal spray compared to placebo (53.7% vs 34.4%, p = 0.0109) with similar tolerability (*Detyniecki et al 2019*).
- Cenobamate was approved in late 2019 and its efficacy has yet to be compared to other AEDs. The approval of this agent was based on 2 multicenter, randomized, double-blind, placebo-controlled studies that enrolled 655 adults with partial-onset seizures with or without generalization who were not adequately controlled with 1 to 3 other AEDs (*Chung et al 2020, Krauss et al 2020*). The results of these trials demonstrated that cenobamate significantly reduced the frequency of seizures occurring in a 28-day period. In the first trial, the median percent change in seizure frequency from baseline was -55.6% with cenobamate and -21.5% with placebo. In the second trial, the median percent change ranged from -36.3% to -55.3% with cenobamate and was -24.3% with placebo.
- In June 2020, the FDA approved a third drug, fenfluramine (Fintepla), for use in the treatment of seizures associated with Dravet syndrome. Two randomized, double-blind, placebo-controlled studies evaluated fenfluramine in patients 2 to

18 years of age with Dravet syndrome who were inadequately controlled with 1 to 4 other AEDs (*Lagae et al 2020, Nabbout et al 2019*). In both trials, fenfluramine significantly reduced the frequency of convulsive seizures occurring in a 28-day period as compared to placebo. In the first trial, in patients not receiving stiripentol, fenfluramine at a dose of 0.7 mg/kg/day demonstrated a 62.3% greater reduction in mean monthly convulsive seizure frequency (MCSF) over 14 weeks compared with placebo. In the second trial, in patients who were receiving a stiripentol-inclusive AED regimen, fenfluramine at a dose of 0.4 mg/kg/day showed a 54% greater reduction in MCSF over 15 weeks compared with placebo.

Status epilepticus

- A 2019 randomized controlled trial of children and adults with benzodiazepine-refractory convulsive status epilepticus compared the efficacy of intravenous (IV) levetiracetam (n = 145 patients), fosphenytoin (n = 118), or valproate (n = 121) in this setting. Results demonstrated that each agent led to seizure cessation and improved alertness by 1 hour in approximately 50% of patients, with no significant differences between groups (*Kapur et al 2019*).
- A meta-analysis of 9 randomized controlled trials evaluated the efficacy and safety of levetiracetam vs phenytoin as second-line treatment for benzodiazepine-resistant status epilepticus in children and adults. The efficacy outcomes included seizure cessation and seizure recurrence within 24 hours. The authors did not find a significant difference in efficacy between levetiracetam and phenytoin in the overall population or in the subgroup analysis of pediatric patients. AEs were similar across both groups except for a higher incidence of cardiac instability, reported mainly as hypotension, in the phenytoin group (*DeMott et al 2020).*

CLINICAL GUIDELINES

- **Efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy**. American Academy of Neurology and American Epilepsy Society (*French et al 2004A, Kanner et al, 2018A*).
  - A 2018 update to the 2004 guideline focuses on treatment of new-onset epilepsy with second and third generation AEDs. The 2004 publication summarizes the efficacy, tolerability, and safety of gabapentin, lamotrigine, topiramate, tiagabine, oxcarbazepine, levetiracetam, and zonisamide for the treatment of children and adults with newly diagnosed partial and generalized epilepsies.
  - The recommendations from the 2004 guideline include the following:
    - Patients with newly diagnosed epilepsy who require treatment can be initially treated with standard AEDs such as carbamazepine, phenytoin, valproic acid, or phenobarbital, or on the newer AEDs lamotrigine, gabapentin, oxcarbazepine, or topiramate. Choice will depend on individual patient characteristics.
    - Lamotrigine can be included in the options for children with newly diagnosed absence seizures.
  - The 2018 recommendations include the following:
    - As monotherapy in adult patients with new-onset focal epilepsy or unclassified generalized tonic-clonic seizures:
      - Lamotrigine use should be considered to decrease seizure frequency.
      - Lamotrigine use should be considered and gabapentin use may be considered to decrease seizure frequency in patients aged ≥ 60 years.
      - Levetiracetam and zonisamide use may be considered to decrease seizure frequency.
      - Vigabatrin appears to be less efficacious than carbamazepine immediate-release and may not be offered; furthermore, the toxicity profile precludes vigabatrin use as first-line therapy.
      - Pregabalin 150 mg per day is possibly less efficacious than lamotrigine 100 mg per day.
      - There is insufficient evidence to consider use of gabapentin, oxcarbazepine, or topiramate over carbamazepine.
      - There is insufficient evidence to consider use of topiramate instead of phenytoin in urgent treatment of new-onset or recurrent focal epilepsy, unclassified generalized tonic-clonic seizures, or generalized epilepsy presenting with generalized tonic-clonic seizures.
      - Data are lacking to support or refute use of third-generation AEDs (eslicarbazepine, ezogabine [no longer marketed], lacosamide, perampanel, pregabalin, and rufinamide), clobazam, felbamate, or vigabatrin for new-onset epilepsy.
      - Data are lacking to support or refute use of newer AEDs in treating unclassified generalized tonic-clonic seizures.
    - Ethosuximide or valproic acid should be considered before lamotrigine to decrease seizure frequency in children with absence epilepsy. An exception would be if there are compelling AE-related concerns with use of ethosuximide or valproic acid.

- The guideline does not address newly approved agents including cannabidiol, everolimus, stiripentol, cenobamate, or fenfluramine.

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

- **Evidence-based guideline: management of an unprovoked first seizure in adults.** Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society (*Krumholz et al 2015*; reaffirmed in 2018 and 2021).
  - This practice guideline makes recommendations based on a consideration of the evidence for prognosis and treatment of adults with an unprovoked first seizure.
  - Recommendations include the following:

        - Adults presenting with an unprovoked first seizure should be informed that the chance for a recurrent seizure is greatest within the first 2 years after a first seizure (21% to 45%).
        - Clinicians should also advise such patients that clinical factors associated with an increased risk of seizure recurrence include a prior brain insult such as a stroke or trauma, an EEG with epileptiform abnormalities, a significant brain-imaging abnormality, or a nocturnal seizure.
        - Clinicians should advise patients that, although immediate AED therapy, as compared with delay of treatment pending a second seizure, is likely to reduce the risk of a seizure recurrence in the 2 years subsequent to a first seizure, it may not improve quality of life.
        - Clinicians should advise patients that over the longer term (> 3 years), immediate AED treatment is unlikely to improve the prognosis for sustained seizure remission.
        - Patients should be advised that their risk for AED AEs ranges from 7% to 31% and that these AEs are predominantly mild and reversible.
    - Immediate AED therapy after an unprovoked first seizure is likely to reduce seizure recurrence risk. A reduction in risk may be important, particularly for adults, for whom seizure recurrences may cause serious psychological and social consequences such as loss of driving privileges and limitations on employment. However, immediate AED treatment is not well accepted and is debated. Decisions should be based on weighing the risk of recurrence against the AEs of AED therapy, and should take patient preferences into account.
    - It is accepted that when a patient has a second or additional seizures, an AED should be initiated because the risk of subsequent seizures is very high.

- **Evidence-based guideline: treatment of convulsive status epilepticus in children and adults.** Guideline Committee of the American Epilepsy Society (*Glauser et al 2016*).
    - This publication provides conclusions and a treatment algorithm based on a structured literature review of randomized trials of anticonvulsant treatments for seizures lasting longer than 5 minutes. A total of 38 trials were included.
    - For treatment in the adult population, conclusions included the following:
        - IM midazolam, IV lorazepam, IV diazepam (with or without phenytoin), and IV phenobarbital are established as efficacious at stopping seizures lasting at least 5 minutes.
        - IV lorazepam is more effective than IV phenytoin in stopping seizures lasting at least 10 minutes.
        - There is no difference in efficacy between IV lorazepam followed by IV phenytoin, IV diazepam plus phenytoin followed by IV lorazepam, and IV phenobarbital followed by IV phenytoin.
        - IV valproic acid has similar efficacy to IV phenytoin or continuous IV diazepam as second therapy after failure of a benzodiazepine.
        - Insufficient data exist in adults about the efficacy of levetiracetam as either initial or second therapy.
        - In adults with status epilepticus without established IV access, IM midazolam is established as more effective compared with IV lorazepam.
        - No significant difference in effectiveness has been demonstrated between lorazepam and diazepam in adults with status epilepticus.
    - For treatment in the pediatric population, conclusions included the following:
        - IV lorazepam and IV diazepam are established as efficacious at stopping seizures lasting at least 5 minutes.
        - Rectal diazepam, IM midazolam, intranasal midazolam, and buccal midazolam are probably effective at stopping seizures lasting at least 5 minutes.
        - Insufficient data exist in children about the efficacy of intranasal lorazepam, sublingual lorazepam, rectal lorazepam, valproic acid, levetiracetam, phenobarbital, and phenytoin as initial therapy.
        - IV valproic acid has similar efficacy but better tolerability than IV phenobarbital as second therapy after failure of a benzodiazepine.
        - Insufficient data exist in children regarding the efficacy of phenytoin or levetiracetam as second therapy after failure of a benzodiazepine.
        - In children with status epilepticus, no significant difference in effectiveness has been established between IV lorazepam and IV diazepam.
        - In children with status epilepticus, non-IV midazolam (IM/intranasal/buccal) is probably more effective than diazepam (IV/rectal).
    - Conclusions included the following (age not specified):

    - Insufficient data exist about the comparative efficacy of phenytoin and fosphenytoin. Fosphenytoin is better tolerated compared with phenytoin. When both are available, fosphenytoin is preferred based on tolerability, but phenytoin is an acceptable alternative.
  - The overall treatment algorithm directs that:
    - A benzodiazepine (IM midazolam, IV lorazepam, or IV diazepam) is recommended as the initial therapy of choice in the first phase of treatment (5 to 20 minutes after the beginning of the seizure). Although IV phenobarbital is established as efficacious and well tolerated as initial therapy, its slower rate of administration positions it as an alternative initial therapy. For prehospital settings or where first-line benzodiazepine options are not available, rectal diazepam, intranasal midazolam, and buccal midazolam are reasonable initial therapy alternatives.
    - In the second phase of treatment (from 20 to 40 minutes after the beginning of the seizure), reasonable options include fosphenytoin, valproic acid, and levetiracetam. There is no clear evidence that any of these options is better than the others. Because of AEs, IV phenobarbital is a reasonable second-therapy alternative if none of the 3 recommended therapies are available.
    - There is no clear evidence to guide therapy in the third phase of therapy (≥ 40 minutes after the beginning of the seizure).

- **Evidence-based guideline update: medical treatment of infantile spasms.** Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (*Go et al 2012*; reaffirmed in 2018 and 2021)
  - This publication provides updated recommendations for the treatment of infantile spasms. The literature review included an evaluation of 26 published articles on this topic.
  - Recommendations include the following:
    - Evidence is insufficient to recommend the use of prednisolone, dexamethasone, and methylprednisolone as being as effective as adrenocorticotropic hormone (ACTH) for short-term treatment of infantile spasms.
    - Low-dose ACTH should be considered as an alternative to high-dose ACTH for treatment of infantile spasms.
    - ACTH or vigabatrin may be offered for short-term treatment of infantile spasms; evidence suggests that ACTH may be offered over vigabatrin.
    - Evidence is insufficient to recommend other therapies (valproic acid, vitamin B6, nitrazepam [not available in the United States], levetiracetam, zonisamide, topiramate, the ketogenic diet, or novel/combination therapies) for treatment of infantile spasms.
    - Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to vigabatrin in infants with cryptogenic infantile spasms, to possibly improve developmental outcome.
    - A shorter lag time to treatment of infantile spasms with either hormonal therapy or vigabatrin may be considered to improve long-term cognitive outcomes.
  - There is a lack of sufficient randomized trials to provide definitive answers to key questions related to treatment of infantile spasms.

- **Practice parameter: treatment of the child with a first unprovoked seizure.** Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (*Hirtz et al 2003*; reaffirmed in 2018 and 2021)
  - This parameter reviews published literature relevant to the decision to begin treatment after a child or adolescent experiences a first unprovoked seizure and presents evidence-based practice recommendations. Treatment during the neonatal period is not addressed.
  - Recommendations include the following:
    - Treatment with AEDs is not indicated for the prevention of the development of epilepsy.
    - Treatment with AEDs may be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the risks of pharmacologic and psychosocial AEs.
  - The majority of children who experience a first unprovoked seizure will have few or no recurrences. Treatment with AEDs after a first seizure as opposed to after a second seizure has not been shown to improve prognosis for long-term seizure remission.
  - Treatment has been shown in several studies combining both children and adults to reduce the risk of seizure recurrence; however, there is a relative paucity of data from studies involving only children after a first seizure.

- **Summary of recommendations for the management of infantile seizures**. Task force report for the ILAE Commission of Pediatrics (*Wilmshurst et al 2015*).
  - This publication recommends an approach to the standard and optimal management of infants with seizures. When possible, recommendations are evidence-based; however, when no evidence was available, recommendations are based on expert opinion and standard practice.
  - Recommendations/findings include the following:
    - There is no indication for initiation of chronic AEDs for simple febrile seizures. However, in the acute treatment of febrile seizures, it is important to treat seizures lasting 10 minutes or longer.
    - In an otherwise healthy infant, a policy of "wait and see" is reasonable after the first afebrile seizure. However, this is a rare event and close monitoring is essential.
    - Treatment options with established or probable efficacy include the following:
      - Focal seizures: levetiracetam
      - Epileptic spasms: High-dose or low-dose ACTH
      - Dravet syndrome: stiripentol
    - Treatment options with possible efficacy include the following:
      - Generalized seizures: levetiracetam, valproate, lamotrigine, topiramate, clobazam
      - Epileptic spasms: prednisone, vigabatrin
      - Benign infantile convulsions: carbamazepine, phenobarbital, valproate
      - Dravet syndrome: topiramate, zonisamide, valproate
      - Benign myoclonic epilepsy of infancy: valproate, topiramate, lamotrigine, clonazepam
      - Provoked or situational seizures: carbamazepine
    - There is no clear evidence supporting an optimal duration of treatment; this is dependent on seizure type.

- **Guidelines on neonatal seizures**. World Health Organization (WHO) (*WHO 2011*).
  - This document was prepared based on a systematic review of the literature and involved cooperation between the WHO, the ILAE, and the International Bureau of Epilepsy (IBE).
  - Recommendations include the following:
    - Phenobarbital should be used as the first-line agent for treatment of neonatal seizures and should be made readily available in all settings.
    - In neonates who continue to have seizures despite administering the maximum tolerated dose of phenobarbital, either a benzodiazepine, phenytoin, or lidocaine may be used as the second-line agent for control of seizures (use of phenytoin or lidocaine requires cardiac monitoring).
    - In neonates with a normal neurological examination and/or normal EEG, stopping AEDs may be considered if the neonate has been seizure-free for > 72 hours; the drug(s) should be reinstituted if seizures recur.
    - In neonates in whom seizure control is achieved with a single AED, the drug can be discontinued abruptly without tapering the dose. In neonates requiring > 1 AED for seizure control, the drugs may be stopped one at a time, with phenobarbital being the last drug to be withdrawn.

- **Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes.** Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society (*Harden et al 2009A*; reaffirmed in 2013; update in progress)
  - This publication summarizes evidence for selected issues regarding the clinical management of women with epilepsy (WWE) who are pregnant or planning to be pregnant.
  - Recommendations include the following:
    - If possible, avoidance of the use of valproate as part of polytherapy during the first trimester of pregnancy should be considered to decrease the risk of major congenital malformations (MCMs).
    - If possible, avoidance of the use of valproate monotherapy during the first trimester of pregnancy may be considered to decrease the risk of MCMs.
    - To reduce the risk of MCMs, the use of valproate during the first trimester of pregnancy should be avoided, if possible, compared to the use of carbamazepine.
    - To reduce the risk of MCMs, avoidance of the use of polytherapy with valproate during the first trimester of pregnancy, if possible, should be considered, compared to polytherapy without valproate.

        - To reduce the risk of MCMs, avoidance of the use of valproate during the first trimester of pregnancy, if possible, may be considered, compared to the use of phenytoin or lamotrigine.
        - To reduce the risk of MCMs, avoidance of the use of AED polytherapy during the first trimester of pregnancy, if possible, compared to monotherapy should be considered.
        - Limiting the dosage of valproate or lamotrigine during the first trimester, if possible, should be considered to lessen the risk of MCMs.
        - Avoidance of the use of valproate, if possible, should be considered to reduce the risk of neural tube defects and facial clefts, and may be considered to reduce the risk of hypospadias.
        - Avoidance of phenytoin, carbamazepine, and phenobarbital, if possible, may be considered to reduce the risk of specific MCMs: cleft palate for phenytoin use, posterior cleft palate for carbamazepine use, and cardiac malformations for phenobarbital use.
        - Carbamazepine exposure probably does not produce cognitive impairment in offspring of WWE.
        - Avoiding valproate in WWE during pregnancy, if possible, should be considered to reduce the risk of poor cognitive outcomes.
        - Avoiding phenytoin and phenobarbital in WWE during pregnancy, if possible, may be considered to reduce the risk of poor cognitive outcomes.
        - Monotherapy should be considered in place of polytherapy, if possible, for WWE who take AEDs during pregnancy to reduce the risk of poor cognitive outcomes.
        - For WWE who are pregnant, avoidance of valproate, if possible, should be considered compared to carbamazepine to reduce the risk of poor cognitive outcomes.
        - For WWE who are pregnant, avoidance of valproate, if possible, may be considered compared to phenytoin to reduce the risk of poor cognitive outcomes.
    - Valproate has the most data showing an association with risk from in utero exposure. If a change from valproate to another AED is planned, it is prudent to make this change well before pregnancy.
    - Although many of the recommendations in this parameter suggest minimizing AED exposure during pregnancy, for most WWE, discontinuing AEDs is not a reasonable or safe option. Discontinuing AEDs may expose the mother and fetus to physical injury from accidents due to seizure activity.

- **Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding.** Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society (*Harden et al 2009B*; reaffirmed in 2013; update in progress)
    - This publication summarizes evidence for selected issues regarding the clinical management of WWE who are pregnant or planning to be pregnant.
    - Recommendations include the following:
        - The fact that phenobarbital, primidone, phenytoin, carbamazepine, levetiracetam, valproate, gabapentin, lamotrigine, oxcarbazepine, and topiramate cross the placenta may be factored into the clinical decision regarding the necessity of AED treatment for a woman with epilepsy.
        - Monitoring of lamotrigine, carbamazepine, and phenytoin levels during pregnancy should be considered.
        - Monitoring of levetiracetam and oxcarbazepine (as monohydroxy derivative) levels during pregnancy may be considered.
        - There is insufficient evidence to support or refute a change in phenobarbital, valproate, primidone, or ethosuximide levels related to pregnancy, but this lack of evidence should not discourage monitoring levels of these AEDs during pregnancy.
        - Valproate, phenobarbital, phenytoin, and carbamazepine may not transfer into breast milk to as great an extent as primidone, levetiracetam, gabapentin, lamotrigine, and topiramate.
    - Although many of the AEDs were shown to cross the placenta or enter breast milk, studies were limited in duration and did not systematically evaluate neonatal symptoms.

- **Practice advisory update summary: Antiseizure medication withdrawal in seizure-free patients.** Report of the American Academy of Neurology Guideline Subcommittee (*Gloss et at 2021,* an update to the 1996 practice parameter)
    - This publication addresses the available evidence on the risk of seizure development in adult and pediatric patients who have been seizure-free and may be considering discontinuing AED treatment. Clinicians should provide

counseling noting that recurrent seizures increase the risk of status epilepticus or death, although existing data do not suggest an increased risk of status epileptus or death after AED withdrawal. Clinicians must explore contributors to patients' quality of life as part of shared decision-making. Additional recommendations include:

- In adult patients:
  - In adults who are seizure-free for at least 2 years, there should be a discussion between the clinician and the patient or caregiver about the risks and benefits of AED withdrawal, noting that there is possibly higher seizure recurrence in patients after AED withdrawal, and if seizures recur, there is a small chance they will no longer respond to medications.
  - It is unknown if EEG or imaging studies inform the decision to withdraw AEDs.
  - The risk of seizure recurrence in patients who have had epilepsy surgery is uncertain.
- In pediatric patients:
  - In children who are seizure-free for 18 to 24 months who do not have an electroclinical syndrome suggesting otherwise, a discussion of the risks and benefits of discontinuing AEDs should take place. This discussion should include acknowledgement that if seizures recur after discontinuing AEDs, there is a small chance they will no longer respond to treatment.
  - Clinicians should discuss with children and their families that AED discontinuation can be considered since discontinuation does not clearly increase the risk of seizure.
  - In children seizure-free for 18 to 24 months in whom AED withdrawal is being considered, an EEG should be ordered. If no epileptiform activity is shown, AED discontinuation can be offered, and tapering should occur no faster than 25% every 10 to 14 days.
  - Clinicians must consider the history of the patient's electroclinical syndrome when counseling about discontinuation of AEDs.

- Guidelines also support the use of AEDs for several common non-epilepsy indications:
  - The American Academy of Neurology and American Headache Society state that AEDs with established efficacy for migraine prevention include valproate, divalproex sodium, and topiramate; carbamazepine is noted to be possibly effective (*Silberstein et al 2012;* reaffirmed in 2015; update in progress). An American Academy of Neurology guideline for pediatric migraine prevention noted that children and adolescents with migraine receiving topiramate are probably more likely than those receiving placebo to have a reduction in migraine or headache day frequency, whereas there was insufficient evidence to support the efficacy of extended-release divalproex sodium for reducing frequency (*Oskoui et al 2019*).
  - The American Academy of Neurology, American Association of Neuromuscular and Electrodiagnostic Medicine, and American Academy of Physical Medicine and Rehabilitation state that, for relief of painful diabetic neuropathy, pregabalin is established as effective, and gabapentin and valproate are probably effective (*Bril et al 2011*; update in progress).
  - The American Diabetes Association (ADA) recommends pregabalin, gabapentin, and duloxetine as initial pharmacologic treatments for neuropathic pain in diabetes (*ADA 2022*). Carbamazepine may be effective and considered for the treatment of painful diabetic peripheral neuropathy.
  - A retired guideline from The American Academy of Neurology states that gabapentin and pregabalin are of benefit in reducing pain from postherpetic neuralgia (*Dubinsky et al 2004; retired February 27, 2018*).
  - American Psychiatric Association guidelines describe the key role of AEDs in the management of bipolar disorder, including the following (*Hirschfeld et al 2002*):
    - First-line pharmacological treatment for more severe manic or mixed episodes is either lithium plus an antipsychotic or valproate plus an antipsychotic; for less ill patients, monotherapy with lithium, valproate, or an antipsychotic may be sufficient. For mixed episodes, valproate may be preferred over lithium. Carbamazepine and oxcarbazepine are alternatives.
    - First-line pharmacological treatment for bipolar depression is either lithium or lamotrigine. When an acute depressive episode of bipolar disorder does not respond to first-line medication treatment, the next steps include adding lamotrigine, bupropion, or paroxetine.
    - The initial treatment for patients who experience rapid cycling should include lithium or valproate; an alternative is lamotrigine.
    - The medications with the best empirical evidence to support their use in maintenance treatment include lithium and valproate; possible alternatives include lamotrigine, carbamazepine, or oxcarbazepine.

- Note: This guideline was published in 2002 and cannot be assumed to be current; however, AEDs continue to be recommended for both acute (mania or hypomania) and maintenance phases of bipolar disorder *(Post 2022, Stovall 2020)*.

SAFETY SUMMARY

- Tolerability and safety are as important as efficacy in determining the overall effectiveness of epilepsy treatment (*Schachter 2021*).
- Common AEs among AEDs include the following (*Fintepla prescribing information 2020, Schachter 2021*):
  - Systemic AEs:
    - nausea, vomiting, constipation, diarrhea, anorexia
    - rash
    - hyponatremia (carbamazepine, eslicarbazepine, oxcarbazepine)
    - weight gain (pregabalin, perampanel, valproate), weight loss (felbamate, topiramate, stiripentol, fenfluramine)
  - Neurologic AEs:
    - headache
    - somnolence, sedation, drowsiness, lethargy, fatigue
    - dizziness, vertigo
    - tremor, anxiety, nervousness, insomnia
    - aggression, irritability, hyperactivity
    - depression, mood alteration
    - confusion
    - ataxia
    - blurred or double vision
- Examples of rare but serious AEs include the following (*Schachter 2021, individual package inserts*):
  - suicidal ideation and behavior (AEDs as a class, except everolimus)
  - neutropenia, leukopenia, pancytopenia, agranulocytosis, thrombocytopenia, and/or aplastic anemia (brivaracetam, carbamazepine, divaloprex, ethosuximide, felbamate, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, primidone, stiripentol, valproate, vigabatrin, zonisamide)
  - anaphylaxis or angioedema (brivaracetam, fosphenytoin, gabapentin, levetiracetam, phenytoin, pregabalin)
  - severe skin rashes, Stevens-Johnson syndrome (SJS), and/or toxic epidermal necrolysis (TEN) (carbamazepine, cenobamate, clobazam, divaloprex, eslicarbazepine, ethosuximide, fosphenytoin, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, primidone, rufinamide, tiagabine, topiramate, valproate, zonisamide)
  - hepatic failure (carbamazepine, divaloprex, ethosuximide, felbamate, phenytoin, phenobarbital, primidone, valproate)
  - hepatocellular injury (cannabidiol)
  - prolonged PR interval, atrioventricular block, changes in QT interval, and/or cardiac rhythm or conduction abnormalities (cenobamate, eslicarbazepine, lacosamide, lamotrigine, rufinamide)
  - serum sickness (carbamazepine, ethosuximide, phenytoin, phenobarbital, primidone, valproate)
  - multiorgan hypersensitivity (carbamazepine, cenobamate, ethosuximide, gabapentin, lacosamide, lamotrigine, oxcarbazepine, perampanel, phenytoin, rufinamide, valproate, zonisamide)
  - severe neuropsychiatric effects/hostility/aggression (brivaracetam, clonazepam, levetiracetam, perampanel)
  - hemophagocytic lymphohistiocytosis (HLH) (lamotrigine)
  - cardiac AEs, including bradycardia and cardiac arrest (phenytoin)
  - abnormal magnetic resonance imaging signals in infants (vigabatrin)
  - intramyelinic edema (vigabatrin)
  - serotonin syndrome (fenfluramine)
  - significant elevation in blood pressure including hypertensive crisis (fenfluramine)
  - respiratory depression, especially in the setting of underlying respiratory impairment or concurrent use of opioids (gabapentin, pregabalin)
  - Hyperammonemia and hyperammonemic encephalopathy (divaloprex)
  - Hypothermia (divaloprex)
  - Increased rates of pneumonia (when cannabidiol is given concomitantly with clobazam)
- A number of AEDs carry boxed warnings related to potentially serious AEs; these include the following:

- Carbamazepine:
  - Serious and sometimes fatal dermatologic reactions, including TEN and SJS, have been reported. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. Patients with ancestry in genetically at-risk populations (across broad areas of Asia) should be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine.
  - Aplastic anemia and agranulocytosis have been reported. If a patient exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely, and discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.
- Clobazam, clonazepam, clorazepate, diazepam, and midazolam:
  - Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Concomitant prescribing should be reserved for use in patients for whom alternative treatment options are inadequate, and patients should be followed for signs and symptoms of respiratory depression and sedation.
- Clobazam, diazepam and midazolam:
  - Use of benzodiazepines may expose users to risks of abuse, misuse, and addiction, which may result in overdose or death; continued use of benzodiazepines may lead to physical dependence, especially with high doses and longer treatment duration. Abrupt discontinuation may result in acute, potentially life-threatening, withdrawal reactions. In some cases, protracted withdrawal symptoms can occur, which can last weeks to more than 12 months. Before prescribing and throughout treatment, each patient should be assessed for abuse, misuse, and addiction. For patients using benzodiazepines more frequently than recommended, the agents should be gradually tapered when discontinuing to minimize withdrawal reactions.
- Felbamate
  - Use is associated with a marked increase in the incidence of aplastic anemia. Felbamate should only be used in patients whose epilepsy is so severe that the risk of aplastic anemia is deemed acceptable. Routine blood testing cannot be reliably used to reduce the incidence of aplastic anemia, but it will in some cases allow detection of hematologic changes before the syndrome declares itself clinically. Felbamate should be discontinued if any evidence of bone marrow depression occurs.
  - Cases of acute liver failure have been reported. Felbamate should not be prescribed for anyone with a history of hepatic dysfunction. Treatment should be initiated only in individuals without active liver disease and with normal baseline serum transaminases. It has not been proven that periodic serum transaminase testing will prevent serious injury, but it is generally believed that early detection of drug-induced hepatic injury along with immediate withdrawal of the suspect drug enhances the likelihood for recovery. Serum transaminases should be monitored at baseline and periodically thereafter. Felbamate should be discontinued if either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) become increased to ≥ 2 times the upper limit of normal, or if clinical signs and symptoms suggest liver failure, and should not be considered for retreatment.
- Fenfluramine:
  - Use of serotonergic drugs with 5-HT2B receptor agonist activity (eg, fenfluramine) is associated with valvular heart disease and pulmonary arterial hypertension. Echocardiogram assessments are required before, during, and after treatment with fenfluramine, and the benefits vs risks of initiating or continuing treatment with this product must be considered based on echocardiogram findings.
  - Due to the risks of valvular heart disease and pulmonary arterial hypertension, fenfluramine is available only through a risk evaluation and mitigation strategy (REMS) program (*FDA REMS 2021*). Healthcare providers who prescribe fenfluramine and pharmacies that dispense the product must be certified. Each patient must be enrolled in the REMS program. Prescribers must ensure that periodic cardiovascular monitoring is performed and report any AE suggestive of valvular heart disease and/or pulmonary hypertension to the fenfluramine REMS program.
- Fosphenytoin and phenytoin:
  - There is a cardiovascular risk associated with rapid IV infusion rates. The rate of administration should not exceed recommendations, and careful cardiac monitoring is required.
- Lamotrigine:
  - Cases of life-threatening serious skin rashes, including SJS and TEN, and/or rash-related death have been caused by lamotrigine. Benign rashes are also caused by lamotrigine; however, it is not possible to predict which rashes will prove to be serious. Lamotrigine should be discontinued at the first sign of a rash, unless the rash is clearly not drug related.
- Perampanel:

        - Serious or life-threatening psychiatric and behavioral AEs including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported. Patients should be monitored for these reactions and for changes in mood, behavior, or personality. The dose should be reduced if these symptoms occur, and it should be discontinued if symptoms are severe or worsening.
    - Valproic acid and divalproex sodium:
        - Hepatotoxicity, including fatalities, have been reported, usually during the first 6 months of treatment. Serum liver tests are required and patients should be monitored closely. There is an increased risk of valproate-induced acute liver failure and resultant deaths in patients with mitochondrial disease. Valproic acid and divalproex sodium are contraindicated in patients known to have mitochondrial disorders caused by polymerase gamma (POLG) gene mutations, and in children < 2 years of age who are suspected of having a mitochondrial disorder.
        - There is a risk to fetuses exposed in utero, particularly neural tube defects, other major malformations, and decreased intelligence quotient (IQ). Valproate should not be given to a woman of childbearing potential unless the drug is essential to the management of her medical condition, and women should use effective contraception while using valproate.
        - Pancreatitis, including fatal hemorrhagic cases, has occurred. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation.
    - Vigabatrin:
        - Vigabatrin can cause permanent bilateral concentric visual field constriction, including tunnel vision that can result in disability. In some cases, vigabatrin may also damage the central retina and may decrease visual acuity. Baseline and periodic vision assessment are recommended. However, this assessment cannot always prevent vision damage, and once detected, vision loss due to vigabatrin is not reversible. Vigabatrin should be withdrawn from patients who fail to show substantial clinical benefit.
        - Due to the risks of vision loss, vigabatrin is available only through a REMS program (*FDA REMS 2021*). Healthcare providers who prescribe vigabatrin and pharmacies that dispense the product must be specially certified. Each patient must be enrolled in the REMS program. Prescribers must ensure that periodic visual monitoring is performed and report any AE suggestive of vision loss to the vigabatrin REMS program.
- Everolimus is an antineoplastic, immunosuppressant agent associated with several AEs.
    - The most common AE that occurred in trials for TSC-associated partial-onset seizures was stomatitis.
    - More serious AEs include:
        - non-infectious pneumonitis
        - infections
        - hypersensitivity reactions
        - angioedema (when taken with an angiotensin-converting enzyme inhibitor)
        - renal failure
        - impaired wound healing
        - myelosuppression
        - reduced immune response with vaccination
        - hyperglycemia
        - hyperlipidemia
        - embryo-fetal toxicity
- Topiramate:
    - Topiramate can decrease lumbar bone mineral density, which has been correlated with decreased serum bicarbonate in some patients, reflective of metabolic acidosis. Topiramate monotherapy has demonstrated negative effects on patient growth (both height and weight gain) when used over long periods. Increases in urinary calcium and decreases in urinary citrate have also been observed, increasing the risk of kidney stones and/or nephrocalcinosis.
        - Although decreases in bone mineral density have been observed in pediatric patients of all ages, patients 6 to 9 years of age are most commonly affected.

DOSING AND ADMINISTRATION

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

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Barbiturates				
Pentobarbital (Nembutal)	injection	IV, IM	Single dose	Acute use only. If needed, additional small increments may be given after the initial dose.
Phenobarbital* (Luminal†, Solfoton†)	tablets, elixir, injection	oral, IV, IM	2 to 3 times per day	IV/IM single dose may also be used for acute convulsions. May be repeated in 6 hours.
Primidone (Mysoline)	tablets	oral	3 to 4 times per day	
Benzodiazepines				
Clobazam (Onfi, packaazan)	tablets, oral suspension, oral film	oral	1 or 2 times per day	Daily doses > 5 mg should be given in divided doses 2 times per day. Sympazan should be applied on top of the tongue where it adheres and dissolves.
Clonazepam (Klonopin)	tablets, orally disintegrating tablets (wafers)	oral	3 times per day	
Clorazepate (Tranxene T-Tab)	tablets	oral	2 to 3 times per day	
Diazepam (Diastat, Valium, Valtoco)	tablets, oral solution, oral concentrate, rectal gel, injection, nasal spray	oral, rectal, IV, IM, intranasal	2 to 4 times per day (oral tablets, solution, concentrate) Acute treatment: single dose followed by a second dose 4 to 12 hours after the first dose (rectal gel) or 4 hours after the first dose (nasal spray) as needed Acute treatment (IV/IM): single dose; may be repeated every 10 to 15 minutes up to maximum dose of 30 mg	The nasal spray and rectal gel should be used to treat no more than 1 episode every 5 days and no more than 5 episodes per month.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Midazolam (Nayzilam, Seizalam)	nasal spray	Intranasal, IM	Intranasal: Single dose followed by a second dose given at least 10 minutes after the first dose if needed IM: Single dose	Intranasal: Should be used to treat no more than 1 episode every 3 days and no more than 5 episodes per month. IM: Should be administered by a healthcare professional. After administration, monitoring of respiratory and cardiac function is recommended until the patient is stabilized.
Hydantoins				
Fosphenytoin (Cerebyx, Sesquient)	injection	IV, IM	2 times per day or other divided doses based on drug levels	Generally used in acute situations as a loading dose; may be given in divided doses when substituted for oral phenytoin.
Phenytoin (Dilantin, Phenytek)	extended-release capsules, chewable tablets, oral suspension, injection	oral, IV, IM	2 to 4 times per day	Capsules are extended-release and may be suitable for once-daily dosing in some adults.
Miscellaneous				
Brivaracetam (Briviact)	tablets, oral solution, injection	oral, IV	2 times per day	The injection may be used when oral administration is temporarily not feasible.
Cannabidiol (Epidiolex)	oral solution	oral	2 times per day	The provided oral syringe should be used to measure an accurate dose.
Carbamazepine (Carbatrol, Epitol, Equetro, Tegretol, Tegretol-XR)	tablets, chewable tablets, oral suspension, extended-release tablets, extended-release capsules	oral	2 to 4 times per day	Immediate-release tablets are given 2 to 3 times per day and the suspension is given 4 times per day. Carbatrol and Equetro are twice-daily extended-release capsule formulations; these capsules may be opened and sprinkled on soft food. Tegretol-XR is a twice-daily extended-release tablet formulation; these tablets must be swallowed whole.
Cenobamate (Xcopri)	Tablets	oral	once daily	The recommended titration schedule should not be exceeded.
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	delayed-release tablets, delayed-release sprinkle capsules, extended-release tablets	oral	2 to 3 times per day (once daily for extended-release tablets)	Delayed-release tablets and extended-release tablets should be swallowed whole. Sprinkle capsules may be opened and sprinkled on soft food. Delayed-release tablet

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				and capsule doses > 250 mg per day should be given in divided doses.
Eslicarbazepine (Aptiom)	tablets	oral	once daily	Tablets may be crushed.
Ethosuximide (Zarontin)	capsules, oral solution/syrup	oral	once daily or in divided doses	
Everolimus (Afinitor Disperz)	tablets for oral suspension	oral	once daily	Should be taken at the same time each day with or without food. Suspension should be prepared using water only and administered immediately after preparation. The suspension should be discarded if not taken within 60 minutes of preparation. Dose adjustments are made based on trough drug concentration.
Felbamate (Felbatol)	tablets, oral suspension	oral	3 or 4 times per day	
Fenfluramine (Fintepla)	oral solution	oral	2 times per day	The provided oral syringe should be used to measure an accurate dose.
Gabapentin (Neurontin)	tablets, capsules, oral solution	oral	3 times per day	Capsules should be swallowed whole.
Lacosamide (Vimpat)	tablets, oral solution, injection	oral, IV	2 times per day (oral route) 2 or 3 times per day IV	
Lamotrigine (Lamictal, Lamictal ODT, Lamictal XR, Subvenite)	tablets, chewable dispersible tablets, orally disintegrating tablets, extended-release tablets	oral	2 times per day (once daily for extended-release tablets)	Only whole tablets should be administered. Extended-release tablets must not be chewed or crushed.
Levetiracetam (Keppra, Keppra XR, Roweepra, Roweepra XR, Spritam, Elepsia XR)	tablets, tablets for oral suspension, oral solution, extended-release tablets, injection	oral, IV	2 times per day (once daily for extended-release tablets)	Tablets and extended-release tablets should not be chewed or crushed. Tablets for oral suspension (Spritam) can be dissolved in liquid and swallowed or allowed to disintegrate in the mouth.
Methsuximide (Celontin)	capsules	oral	2 to 4 times per day (*Lexicomp 2021*)	
Oxcarbazepine (Oxtellar XR, Trileptal)	tablets, oral suspension, extended-release tablets	oral	2 times per day (once daily for extended-release tablets)	In conversion of oxcarbazepine immediate-release to Oxtellar XR, higher doses of Oxtellar XR may be necessary. Extended-release

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				tablets must not be chewed or crushed.
Perampanel (Fycompa)	tablets, oral suspension	oral	once daily at bedtime	The provided oral syringe should be used to measure an accurate dose.
Pregabalin (Lyrica)	capsules, oral solution	oral	2 to 3 times per day	
Rufinamide (Banzel)	tablets, oral suspension	oral	2 times per day	Tablets can be administered whole, as half tablets, or crushed.
Stiripentol (Diacomit)	capsules, powder for oral suspension	oral	2 to 3 times per day	Capsules must be swallowed whole with a glass of water during a meal. Powder should be mixed with water and taken immediately after mixing during a meal.
Tiagabine (Gabitril)	tablets	oral	2 to 4 times per day	
Topiramate (Topamax, Topamax Sprinkle, Topiragen, Trokendi XR, Qudexy XR, Eprontia)	tablets, sprinkle capsules, extended-release capsules, extended-release sprinkle capsules, oral solution	oral	2 times per day (once daily for extended-release capsule formulations)	Sprinkle capsules may be opened and sprinkled on soft food. Extended-release capsules (Trokendi XR) must not be chewed or crushed, but extended-release sprinkle capsules (Qudexy XR) may be sprinkled on soft food.
Valproic acid/ valproate sodium (Depakene†, Depacon†)	capsules, oral solution/ syrup, injection	oral, IV	1 to 4 times per day (*Lexicomp 2021*)	Capsules should be swallowed whole without chewing to avoid local irritation of the mouth and throat. If the total dose exceeds 250 mg, it should be given in divided doses.
Vigabatrin (Sabril, Vigadrone)	tablets, powder for oral solution	oral	2 times per day	Powder for oral solution is supplied in individual dose packets to be mixed with water before administration.
Zonisamide (Zonegran)	capsules	oral	1 or 2 times per day	Capsules must be swallowed whole.

* Not FDA approved
† Brand product not currently marketed; generic is available

CONCLUSION

- Several classes of AEDs are available, including barbiturates, benzodiazepines, hydantoins, and miscellaneous agents. These products vary in terms of their indications for specific seizure types and indications other than epilepsy.
- Overall, the anticonvulsants have demonstrated efficacy for their FDA-approved uses. When possible, monotherapy with a single AED is the preferred treatment approach; however, data are conflicting on the benefits of mono- vs polytherapy.
- Patients who are refractory to monotherapy may be treated with combination therapy. When considering combination therapy, it is recommended to combine medications with different mechanisms of action and AE profiles.

- Comparative efficacy data for the management of epilepsy are limited.
- Tolerability and safety are as important as efficacy in determining the overall effectiveness of epilepsy treatment. Both systemic AEs and neurologic AEs commonly occur. Some AEDs are associated with rare but serious AEs, and careful patient selection and monitoring are required.
- Epilepsy management can be complex and is often performed by neurologists. Availability of a variety of AEDs supports the ability of clinicians to select the most clinically appropriate agent for individual patients.
- Anticonvulsants are also established as effective for several non-epilepsy indications, including (but not limited to) bipolar disorder, migraine prophylaxis, and neuropathic pain.

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Publication Date: March 6, 2022

Therapeutic Class Overview
Ophthalmic Agents, Intraocular Pressure (IOP)-Modifying

INTRODUCTION

- Glaucoma is an optic neuropathy that causes gradual degeneration of the cells making up the optic nerve. Glaucoma is among the leading causes of blindness worldwide, with an estimated 6.9 million people with severe visual impairment or blindness due to glaucoma (*WHO 2019*). Open-angle glaucoma is the most common form in those of European or African descent; other forms include angle-closure, developmental, and secondary glaucoma (*Jacobs 2020a*). Patients with open-angle glaucoma do not typically have symptoms, and it is usually detected with a comprehensive eye exam. If left untreated, progression to visual field loss and blindness can occur. The exact etiology of open-angle glaucoma is unknown. Major risk factors for developing open-angle glaucoma include advanced age, African or Hispanic/Latino descent, elevated intraocular pressure (IOP), family history of glaucoma, low ocular perfusion pressure, type 2 diabetes mellitus, and myopia (*Ellis et al 2000, Gedde et al 2021, Girkin et al 2004, Lesk et al 2007*).
- Elevated IOP is the only major risk factor for glaucoma that is directly treatable. Available evidence suggests that lowering IOP inhibits or reduces the progression of optic nerve damage (*Jacobs 2020b*). Treatment may be initiated in patients with an elevated IOP despite having no visual field loss or optic nerve damage. An IOP > 22 to 25 mmHg is generally considered to be elevated and would be treated by most clinicians; however, this number varies according to screening methods, risk factors, and disease progression (*Jacobs 2020a*). In general, a target IOP that is 25 to 30% lower than baseline is reasonable (*Jacobs 2020b*). The target IOP should be individualized based on response to therapy and disease progression in order to maintain IOP within a range that is unlikely to adversely affect patients' health-related quality of life.
- The American Academy of Ophthalmology (AAO) recommends an initial target IOP reduction of 20 to 30% from pretreated baseline IOP. However, depending on the severity of disease, this target may vary since there is no consensus target IOP below which further vis0ual loss and optic nerve damage will be prevented (*Gedde et al 2021*).
- The current treatment of glaucoma focuses on decreasing IOP by 1 of 3 methods: laser therapy, surgery, or medical intervention (*Gedde et al 2021*). Medical intervention or laser therapy is generally used as initial therapy prior to surgical treatment (*Jacobs 2020b*). Medical intervention includes 6 classes of ophthalmic drugs used for the long-term management of glaucoma: alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, miotics or parasympathomimetics, prostaglandin analogues, and rho kinase (ROCK) inhibitors (*Gedde et al 2021, Jacobs 2020b*). These treatments reduce IOP by either decreasing the amount of aqueous humor produced by the ciliary body or by increasing uveoscleral outflow. Miotics, prostaglandin analogues, and ROCK inhibitors increase aqueous outflow, while beta-blockers and carbonic anhydrase inhibitors decrease aqueous humor production. Alpha-agonists decrease the amount of aqueous humor formed and increase its outflow.
- The current guidelines by the AAO generally recommend ophthalmic prostaglandin analogues as first-line pharmacologic therapy in patients with elevated IOP (*Gedde et al 2021*). Combination or monotherapy with agents from an alternative pharmacologic class is recommended for patients who experience intolerable adverse events or who do not achieve the optimal IOP reduction with first-line agents (*Jacobs 2020b*).
- Presbyopia ("aging sight") is a common, non-refractive and irreversible error of the eye that affects visual acuity, occurring normally due to aging, and usually begins at ≥ 40 years of age. The average age of those first reporting symptoms is between 42 to 44 years of age. Presbyopia has most commonly been treated with use of lenses, including convex lenses ("reading glasses") or in combination with lens with correction for distance viewing (eg, bifocals, trifocals, etc.). In the United States (U.S.), presbyopia is the most common cause of visual impairment, with 76 million Americans born between 1946 and 1964 (*AAO 2021, Katz et al 2021, Mian 2021*).
- Medispan Classes: Beta-Blockers – Ophthalmic; Miotics – Cholinesterase Inhibitors; Miotics – Direct Acting; Ophthalmic Carbonic Anhydrase Inhibitors; Ophthalmic Rho Kinase Inhibitors; Ophthalmic Selective Alpha-Adrenergic Agonists; Prostaglandins – Ophthalmic; Alpha Adrenergic Agonist and Carbonic Anhydrase Inhibitor Combination; Beta-blockers – Ophthalmic Combinations
  - Note that bimatoprost is also available as Latisse (bimatoprost ophthalmic solution) 0.03%, which is indicated to treat hypotrichosis of the eyelashes by increasing their growth including length, thickness, and darkness. Latisse is applied nightly directly to the skin of the upper eyelid margin at the base of the eyelashes using an applicator.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Alpha-Agonists	
Alphagan P (brimonidine tartrate ophthalmic solution) 0.1%*	-
Alphagan P (brimonidine tartrate ophthalmic solution) 0.15%*	✔
brimonidine tartrate ophthalmic solution 0.2% ‡	✔
Iopidine (apraclonidine ophthalmic solution) 0.5% and 1% §	✔
Beta-Blockers	
betaxolol hydrochloride ophthalmic solution 0.5% ‖	✔
Betimol (timolol ophthalmic solution) 0.25% and 0.5% ¶	-
Betoptic S (betaxolol hydrochloride ophthalmic suspension) 0.25%	-
carteolol hydrochloride ophthalmic solution 1% #	✔
Istalol (timolol maleate ophthalmic solution) 0.5%	✔
levobunolol hydrochloride ophthalmic solution 0.5% ††	✔
Timoptic (timolol maleate ophthalmic solution) 0.25% and 0.5%	✔
Timoptic in Ocudose (timolol maleate ophthalmic solution) 0.25% and 0.5%	-
Timoptic-XE (timolol maleate ophthalmic gel forming solution [GFS]) 0.25% and 0.5%	✔
Carbonic Anhydrase Inhibitors	
Azopt (brinzolamide ophthalmic suspension) 1%	✔
Trusopt (dorzolamide hydrochloride ophthalmic solution) 2%	✔
Miotics	
Isopto Carpine (pilocarpine ophthalmic solution) 1%, 2%, and 4%§§	✔
Vuity (pilocarpine ophthalmic solution) 1.25%	-
Prostaglandin Analogues¥	
bimatoprost ophthalmic solution 0.03% **	✔
Lumigan (bimatoprost ophthalmic solution) 0.01% **	-
Travatan Z (travoprost ophthalmic solution) 0.004%	✔
Vyzulta (latanoprostene bunod ophthalmic solution) 0.024%	-
Xalatan (latanoprost ophthalmic solution) 0.005%	✔
Xelpros (latanoprost ophthalmic emulsion) 0.005%	-
Zioptan (tafluprost ophthalmic solution) 0.0015%	- ‡‡
ROCK Inhibitor	
Rhopressa (netarsudil ophthalmic solution) 0.02%	-
Combinations	
Combigan (brimonidine tartrate/timolol maleate ophthalmic solution) 0.2%/0.5%	✔
Cosopt (dorzolamide hydrochloride/timolol maleate ophthalmic solution) 2%/0.5%	✔
Cosopt PF (dorzolamide hydrochloride/timolol maleate ophthalmic solution) 2%/0.5%	✔
Rocklatan (latanoprost/netarsudil ophthalmic solution) 0.005%/0.02%	-
Simbrinza (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%	-

* Does not contain benzalkonium chloride; contains Purite 0.005% as a preservative.
‡ Branded Alphagan 0.2% is no longer marketed.
§ Apraclonidine 0.5% is available generically. Iopidine 1% strength is available as a branded product only.
‖ Brand Betoptic is no longer available.
¶ Formulated as timolol hemihydrate.
# Brand Ocupress is no longer available.
¥ A bimatoprost 10 mcg ocular implant for intracameral administration (Durysta) was approved in March 2020 for reduction of IOP in patients with open-angle glaucoma or ocular hypertension. Due to its method of administration, this product is outside the scope of this review and will not be discussed further.

** Allergan discontinued brand Lumigan (bimatoprost) 0.03% in 2012; the discontinuation was not due to safety concerns. Generic bimatoprost 0.03% is available, but generic 0.01% is not.
†† Brand Betagan is no longer available.
‡‡ A generic is approved by the Food and Drug Administration (FDA) but is not currently marketed.
§§ Brand Isopto Carpine 4% is no longer available.

(*Drugs@FDA 2022, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2022*)

INDICATIONS

Table 2A. Food and Drug Administration Approved Indications (Part 1 of 2)

Drug	Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension	Short-term adjunctive therapy in patients on maximally tolerated medical therapy who require additional IOP reduction	Control or prevent postsurgical elevations in IOP that occur in patients after argon laser trabeculoplasty, argon laser iridotomy, or Nd:YAG posterior capsulotomy	Reduction of elevated IOP in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP
Alpha-Agonists				
Alphagan P (brimonidine tartrate)*	✔			
Iopidine (apraclonidine)		✔ (0.5% only)	✔ (1% only)	
Beta-Blockers				
Betimol (timolol)	✔			
Betoptic S (betaxolol) †	✔ ‡			
carteolol hydrochloride	✔ ‡			
Istalol (timolol maleate)	✔			
levobunolol hydrochloride	✔ ‡			
Timoptic / Timoptic in Ocudose (timolol maleate)	✔			
Timoptic-XE (timolol maleate GFS)	✔			
Carbonic Anhydrase Inhibitors				
Azopt (brinzolamide)	✔			
Trusopt (dorzolamide)	✔			
Prostaglandin Analogues				
Lumigan (bimatoprost) §	✔			
Travatan Z (travoprost)	✔			
Xalatan (latanoprost)	✔			
Vyzulta (latanoprostene bunod)	✔			
Xelpros (latanoprost)	✔			
Zioptan (tafluprost)	✔			
ROCK Inhibitor				

Drug	Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension	Short-term adjunctive therapy in patients on maximally tolerated medical therapy who require additional IOP reduction	Control or prevent postsurgical elevations in IOP that occur in patients after argon laser trabeculoplasty, argon laser iridotomy, or Nd:YAG posterior capsulotomy	Reduction of elevated IOP in patients with glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequately controlled IOP
Rhopressa (netarsudil)	✔			
Combinations				
Combigan (brimonidine/timolol) ‖				✔
Rocklatan (latanoprost/netarsudil)	✔			
Cosopt / Cosopt PF (dorzolamide/timolol) ¶	✔			
Simbrinza (brinzolamide/brimonidine)	✔			

* Generic brimonidine 0.2% shares the same indication as brand Alphagan P.
† Generic betaxolol ophthalmic solution shares the same indication as brand Betoptic S ophthalmic suspension.
‡ Products are indicated for reduction of elevated IOP in patients with chronic open-angle glaucoma or ocular hypertension.
§ Generic bimatoprost 0.03% shares the same indication as brand Lumigan.
‖ The IOP-lowering of Combigan dosed twice a day was slightly less than that seen with the concomitant administration of timolol maleate ophthalmic solution, 0.5% dosed twice a day, and brimonidine tartrate ophthalmic solution, 0.2% dosed 3 times per day.
¶ Cosopt / Cosopt PF are indicated for the reduction of IOP in patients with open-angle glaucoma or ocular hypertension who are insufficiently responsive to beta-blockers (failed to achieve target IOP after multiple measurements over time). The IOP-lowering of Cosopt twice daily was slightly less than that seen with the concomitant administration of timolol 0.5% twice daily and dorzolamide 2% 3 times daily.

(*Prescribing information: Alphagan P 2013, apraclonidine 2022, Azopt 2021, betaxolol hydrochloride ophthalmic solution 2022, Betimol 2018, Betoptic S 2021, bimatoprost ophthalmic solution 0.03% 2020, brimonidine tartrate ophthalmic solution 2018, carteolol hydrochloride ophthalmic solution 2012, Combigan 2015, Cosopt 2020, Cosopt PF 2017, levobunolol ophthalmic solution 2016, Iopidine 2021, Istalol 2019, Lumigan 2020, Rocklatan 2020, Rhopressa 2019, Simbrinza 2021, Timoptic 2020, Timoptic in Ocudose 2020, Timoptic-XE 2021, Travatan Z 2020, Trusopt 2020, Vyzulta 2019, Xalatan 2020, Xelpros 2021, Zioptan 2021*)

Table 2B. Food and Drug Administration Approved Indications (Part 2 of 2)

Drug	Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension	Induction of miosis	Management of acute angle-closure glaucoma	Prevention of postoperative elevated IOP associated with laser surgery	Presbyopia
Miotics					
Isopto Carpine (pilocarpine)	✔	✔	✔	✔	
Vuity (pilocarpine)					✔

(*Prescribing information: Isopto Carpine 2020, Vuity 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

Drug Class Comparisons

- In a large systematic review of medical therapy compared to various surgical treatments, evidence was insufficient to show that medical, laser, or surgical treatments of open-angle glaucoma prevented progressive visual field loss, optic nerve damage, any kind of patient-reported outcomes, or visual impairment. Very little direct comparative evidence is available (*Boland et al 2012, Boland et al 2013*).
- A network meta-analysis included 114 randomized controlled trials (N = 20,725) evaluating single active ophthalmic agents for the treatment of primary open-angle glaucoma (*Li et al 2016*). All trials compared active first-line drugs to no treatment or placebo or another single topical agent for glaucoma. The mean reductions in IOP at 3 months (reported as mmHg) were as follows: bimatoprost 5.61 (95% confidence interval [CI], 4.94 to 6.29), latanoprost 4.85 (95% CI, 4.24 to 5.46), travoprost 4.83 (95% CI, 4.12 to 5.54), levobunolol 4.51 (95% CI, 3.85 to 5.24), tafluprost 4.37 (95% CI, 2.94 to 5.83), timolol 3.70 (95% CI, 3.16 to 4.24), brimonidine 3.59 (95% CI, 2.89 to 4.29), carteolol 3.44 (95 % CI, 2.42 to 4.46), levobetaxolol 2.56 (95% CI, 1.52 to 3.62), apraclonidine 2.52 (95% CI, 0.94 to 4.11), dorzolamide 2.49 (95% CI, 1.85 to 3.13), brinzolamide 2.42 (95% CI, 1.62 to 3.23), betaxolol 2.24 (95% CI, 1.59 to 2.88), and unoprostone 1.91 (95% CI, 1.15 to 2.67). The authors concluded that the ophthalmic prostaglandin analogues have the greatest effect on IOP.
- Another network meta-analysis of 106 trials (N = 18,523) that compared single agents to each other or placebo and reported 3-month IOP outcomes did not find significant differences between latanoprostene bunod and latanoprost, tafluprost, or bimatoprost (both 0.01% and 0.03%). Bimatoprost 0.03% was ranked highest for likelihood of being the most effective, followed by latanoprostene bunod and then bimatoprost 0.01% (*Harasymowycz et al 2021*).
- A network meta-analysis evaluated 72 randomized controlled trials (N = 19,916) that reported efficacy and safety of medications for the treatment of primary open-angle glaucoma or ocular hypertension over at least 3 months (*Li et al 2018*). A total of 15 treatments were directly compared for change in IOP. Compared to prostaglandin analogues, beta-blockers showed relatively weaker ability to lower IOP, followed by alpha-agonists and carbonic anhydrase inhibitors. The most powerful combinations for dual therapy included prostaglandin analogues with another agent for lowering IOP; combinations with 2 non-prostaglandin analogues had lower efficacy in controlling IOP than monotherapy with a prostaglandin analogue. More severe hyperemia was associated with prostaglandin analogues compared to any other monotherapy, with beta-blockers having the lowest effect on the incidence of hyperemia. Most 2-drug combinations with prostaglandin analogues also led to serious hyperemia except the combination of prostaglandin analogues and alpha-agonists.
- A network meta-analysis evaluated data from 28 randomized controlled trials in patients with primary open-angle glaucoma or ocular hypertension for peak (N = 6841) and trough (N = 6953) effect of 8 drugs (*van der Valk et al 2009*). The studies assessed bimatoprost, travoprost, latanoprost, brimonidine, timolol, dorzolamide, betaxolol, and brinzolamide. All drugs differed from placebo in reducing IOP. At the peak, the largest reduction in mean IOP was observed with the prostaglandin analogues – bimatoprost, travoprost, and latanoprost. At the trough, the largest reduction in mean IOP was also with the prostaglandin analogues with bimatoprost followed by latanoprost and travoprost.
- The ophthalmic prostaglandin analogues have consistently demonstrated comparable or greater efficacy when compared to dorzolamide/timolol (*Coleman et al 2003, Fechtner et al 2004, Konstas et al 2008, Lesk et al 2008, Ozturk et al 2007, Sharpe et al 2008*). Bimatoprost 0.03% significantly reduced the mean IOP compared to dorzolamide/timolol in a 6-week crossover trial (p = 0.03) (*Sharpe et al 2008*). In patients uncontrolled on beta-blocker monotherapy, bimatoprost also significantly reduced the mean IOP at 8 AM compared to dorzolamide/timolol in a 3-month study (*Coleman et al 2003*). However, in a small study of 65 patients with primary open-angle glaucoma or ocular hypertension, the efficacy of lowering IOP was similar between bimatoprost and dorzolamide/timolol over a 6 month study period (p = 0.48) (*Ozturk et al 2007*). A meta-analysis of 14 randomized controlled trials found that latanoprost was associated with greater efficacy in lowering the diurnal mean IOP compared to the combination of dorzolamide/timolol in patients who were inadequately controlled with timolol monotherapy. Latanoprost was as effective as dorzolamide/timolol in patients without prior timolol treatment (*Cheng et al 2009*).
- A meta-analysis of 11 randomized controlled trials with 1256 patients with open-angle glaucoma or ocular hypertension showed significant reductions in IOP with latanoprost compared to timolol. Latanoprost resulted in an average 1.6 mmHg further lowering in IOP compared to timolol (p < 0.001) (*Zhang et al 2001*).

Alpha-Agonists

- The comparative clinical trial data regarding the safety and efficacy of the ophthalmic alpha-agonists are limited. When the ophthalmic alpha-agonists are used for the management of postoperative elevations in IOP, both ophthalmic brimonidine and apraclonidine are effective treatment options with similar efficacy (*Barnes et al 1999, Chen et al 2001, Chen 2005, Sterk et al 1998*).
- In a meta-analysis of 2 double-blind, multicenter, parallel group, randomized controlled trials, brimonidine purite 0.1%, brimonidine purite 0.15%, and brimonidine 0.2% were compared for safety and tolerability over 12 months. In 1 study, brimonidine purite 0.15% had lower ocular treatment-related adverse events including allergic conjunctivitis, conjunctival hyperemia, and eye discharge compared to brimonidine 0.2% ($p \leq 0.025$). The second study found a statistically significantly lower overall incidence of treatment-related adverse events with brimonidine purite 0.1% compared to brimonidine 0.2% ($p = 0.014$). The pooled data demonstrated a reduced overall incidence of treatment-related adverse events proportional to the reductions in the concentration of the active ingredient ($p < 0.001$) (*Cantor et al 2009*).
- A Cochrane review of 22 randomized controlled trials (N = 2112) assessed the effectiveness of medications administered perioperatively to prevent temporarily increased IOP after laser trabeculoplasty in patients with open-angle glaucoma (*Zhang et al 2017*). Compared to placebo, fewer patients who received any IOP-lowering medication (apraclonidine, acetazolamide, brimonidine, pilocarpine) experienced IOP increase ≥ 10 mmHg within 2 hours (risk ratio, 0.05; 95% CI, 0.01 to 0.20; moderate-certainty evidence). This effect was maintained up to 24 hours after the operation. In 3 studies, perioperative brimonidine was associated with higher rates of conjunctival blanching compared to placebo. In a comparison of perioperative brimonidine vs apraclonidine (3 randomized controlled trials), the review was unable to determine whether brimonidine or apraclonidine was better in preventing IOP increases within 2 hours after surgery due to inconsistency, imprecision of the estimated effect, and study bias (risk ratio, 2.28; 95% CI, 0.32 to 16.03; very low-certainty evidence). The authors concluded that it is unclear whether 1 medication in the alpha-agonist class is better than another. There was no notable difference between apraclonidine and pilocarpine in the mean change in IOP measurement from pre-procedure to 2 hours after surgery.

Beta-Blockers

- Timolol has been a frequent comparator in numerous clinical trials with agents for the treatment of glaucoma and ocular hypertension. Head-to-head studies in the ophthalmic beta-blocker class involving patients with open-angle glaucoma or ocular hypertension have shown that all treatments are efficacious in decreasing IOP from baseline; however, conflicting results were seen when groups were compared to each other. Studies that reported adverse events categorized all events as mild to moderate; the most frequent adverse events reported included burning or stinging upon instillation and tearing (*Berry et al 1984, Berson et al 1985, Evans et al 1999, Geyer et al 1998, Halper et al 2002, Krieglstein et al 1987, Miki et al 2004, Mundorf et al 2004, Schenker et al 2000, Shedden et al 2001, Sonty et al 2009, Stewart et al 1986, Stewart et al 2002, Vogel et al 1989, Walters et al 1998, Watson et al 2001*).
- Studies involving patients with open-angle glaucoma or ocular hypertension comparing betaxolol 0.5% to timolol maleate 0.5% have found conflicting results with regard to decrease in IOP from baseline (*Berry et al 1984, Evans et al 1999, Miki et al 2004, Stewart et al 1986, Vogel et al 1989*).
  - Specifically, 1 study found that betaxolol 0.5% maintained the decrease in IOP that occurred from earlier treatment with timolol maleate 0.5% (*Miki et al 2004*).
  - In another study, betaxolol 0.5% was not found to significantly lower IOP after a washout period following treatment with timolol maleate 0.5% ($p = 0.09$) (*Evans et al 1999*).
  - In a separate study, betaxolol 0.5% was shown to produce a significant decrease in IOP from baseline at weeks 1 through 12 when both the mean IOP value averaged for both eyes and the worse eye were analyzed ($p \leq 0.001$). In this same study, timolol maleate 0.5% was not found to produce a significant decrease in IOP during weeks 1 through 8 when the mean IOP was averaged for both eyes ($p \leq 0.05$), as well as at week 12 when the worse eye was analyzed (p values not reported) (*Vogel et al 1989*).
  - Additional studies have found that the difference from baseline in IOP was significant for both betaxolol and timolol groups, and there was no difference between groups in the reduction of IOP (*Berry et al 1984, Stewart et al 1986*).
  - All studies reported mild adverse events including burning or stinging upon instillation and tearing. Although several studies have reported that betaxolol 0.5% was associated with more burning and/or stinging upon instillation than timolol 0.5%, only 1 study found this difference to be statistically significant (*Berry et al 1984, Vogel et al 1989*).
- One study compared ophthalmic formulations of betaxolol 0.5% to carteolol hydrochloride 1% and timolol 0.25% and found that all 3 treatments significantly decreased IOP from baseline. However, carteolol 1% and timolol 0.25% achieved greater reductions in IOP than betaxolol 0.5% initially and maintained this difference through the follow up period (p

values not reported). Eventually, betaxolol 0.5% achieved the same level of IOP after 12 months. In this study, the lowest number of adverse events was reported in the carteolol 1% group, followed by timolol 0.25%, and betaxolol 0.5% groups (p values not reported) (*Watson et al 2001*).

- Studies involving levobunolol 0.25%, 0.5%, and 1% found this agent to significantly decrease IOP from baseline; however, significant treatment differences in IOP reduction were not found when compared to ophthalmic formulations of metipranolol 0.6%, timolol maleate 0.25%, or timolol GFS 0.5% (*Berson et al 1985, Geyer et al 1998, Halper et al 2002, Krieglstein et al 1987, Walters et al 1998*).
  - Specifically, when levobunolol 0.5% was compared to metipranolol 0.6%, both groups saw significant differences from baseline IOP after 12 weeks of treatment with decreases of -7.2 mmHg in the levobunolol 0.5% group and -7.4 mmHg in the metipranolol 0.6% group (p value not reported) (*Krieglstein et al 1987*).
  - The majority of studies did not report significant differences in adverse events between treatment groups. However, in a study between levobunolol 0.5% and timolol GFS 0.5%, significantly more patients in the levobunolol 0.5% group experienced at least 1 adverse event ($p = 0.024$). Additionally, the incidence of burning and/or stinging was found to be significantly higher in the levobunolol 0.5% group ($p < 0.001$) (*Halper et al 2002*).
- Studies comparing different formulations of ophthalmic timolol consisted of timolol-LA (Istalol), timolol maleate 0.5%, timolol in sorbate 0.5%, and timolol maleate GFS 0.5% (Timoptic-XE) (*Mundorf et al 2004, Schenker et al 2000, Shedden et al 2001, Sonty et al 2009, Stewart et al 2002*). The studies showed that all forms of ophthalmic timolol significantly decreased IOP from baseline, and no significant differences were found with regard to reductions in IOP between formulations.
  - One study found that timolol-LA (Istalol) significantly decreased heart rate when compared to timolol maleate 0.5% ($p < 0.05$) and also caused more stinging and burning ($p = 0.001$) (*Mundorf et al 2004*).
  - A separate study that compared timolol maleate GFS 0.5% to timolol 0.5% found that the patients in the GFS group had significantly more blurred vision as well as tearing ($p = 0.04$ for both). However, the same study also found that timolol 0.5% caused significantly more burning and stinging when compared to the GFS ($p = 0.04$). It was also found that timolol maleate GFS 0.5% caused less decline in heart rate after 12 weeks of treatment ($p = 0.024$); however, this was not found to be significant at 24 weeks of treatment (*Shedden et al 2001*).

Beta-Blockers compared to other drug classes

- When beta-blockers were compared to single entity formulations of carbonic anhydrase inhibitors and prostaglandin analogues, conflicting results were found with regard to the difference in IOP-lowering effect (*Cantor et al 2001, Haneda et al 2006, Ikeda et al 2008, March et al 2000, Rusk et al 1998, Silver 1998, Strahlman et al 1995, Varma et al 2009, Walters et al 2004*).
  - In studies between betaxolol 0.25% and brimonidine 0.2% as well as dorzolamide 2%, no significant differences were seen between groups (*Cantor et al 2001, Rusk et al 1998, Strahlman et al 1995*).
  - Similar results were found in studies comparing timolol 0.5% to brinzolamide 1% and latanoprost 0.005% as well as in a study comparing carteolol 1% and latanoprost 0.005% (*Haneda et al 2006, March et al 2000, Varma et al 2009*).
  - In a separate study comparing timolol GFS 0.5% to bimatoprost 0.03% and latanoprost 0.005%, it was found that bimatoprost 0.03% significantly reduced IOP from baseline when compared to timolol GFS 0.5% ($p < 0.001$). This same study also showed that latanoprost 0.005% provided significantly more IOP reduction from baseline when compared to timolol GFS 0.5% ($p < 0.002$) (*Walters et al 2004*).
  - In an additional study, latanoprost 0.005% was found to provide significantly more IOP reduction from baseline when compared to betaxolol 0.25%, carteolol 1%, and nipradilol 0.25% ($p < 0.05$) (*Ikeda et al 2008*).

Carbonic Anhydrase Inhibitors

- Trials that support the FDA-approved indications for ophthalmic formulations of brinzolamide and dorzolamide evaluated the effectiveness of these agents over 1 week to 18 months and demonstrated that carbonic anhydrase inhibitors are a viable treatment option for the management of elevated IOP (*Azopt prescribing information 2021, Trusopt prescribing information 2014*). However, the efficacy of ophthalmic carbonic anhydrase inhibitors appears to be inferior to other newer pharmacologic options for treating open-angle glaucoma (*Jacobs 2020b*).
- Single agent ophthalmic carbonic anhydrase inhibitors, brinzolamide and dorzolamide, were evaluated in a multicenter, parallel-group study. Reduction in IOP from baseline was statistically significant in each group ($p < 0.001$); however, the changes in IOP from baseline were comparable between the treatment groups (p value not reported) (*Silver 1998*). In a safety trial, significantly fewer patients reported ocular discomfort, specifically burning and stinging, with brinzolamide

compared to dorzolamide ($p < 0.001$). Taste disturbance was reported in up to 12% of patients in the brinzolamide group, while only 8.5% of patients in the dorzolamide group experienced this adverse event (*Silver 2000*).
- Similar reductions in IOP were also observed when the agents were used in combination with timolol (*Michaud et al 2001*).

Carbonic Anhydrase Inhibitors compared to other classes
- The single agent carbonic anhydrase inhibitors were compared to beta-blockers (*March et al 2000, Rusk et al 1998, Strahlman et al 1995*). Brinzolamide was compared to timolol, while dorzolamide was compared to timolol and betaxolol. In these trials, timolol demonstrated a greater reduction in IOP than both brinzolamide and dorzolamide.
  - In a double-blind, multicenter, parallel-group, randomized controlled trial, timolol 0.5% was associated with a statistically significant reduction in IOP compared to brinzolamide, administered either twice or 3 times daily ($p = 0.0002$) (*March et al 2000*).
  - When dorzolamide 2% was compared to betaxolol 0.5% or timolol 0.5% in a 1 year, double-blind, parallel-group, randomized controlled trial, all 3 treatment groups exhibited comparable IOP lowering from baseline (23, 21, and 25%, respectively; p value not reported) (*Strahlman et al 1995*).
  - Another multicenter randomized controlled trial found dorzolamide and betaxolol to be comparable in terms of IOP reduction from baseline (p value not reported) (*Rusk et al 1998*).
  - The safety and efficacy of brinzolamide and dorzolamide were compared to brimonidine. All 3 groups in this study received the study treatment as add-on therapy to a prostaglandin analogue of the clinicians' choice. Brimonidine was associated with a significantly greater reduction in IOP than either brinzolamide or dorzolamide after 1 and 4 months of therapy ($p < 0.001$ for both groups) (*Bournias et al 2009*).

Miotics
- The clinical trial data regarding the safety and efficacy of the ophthalmic miotics (eg, pilocarpine products) are very limited. These agents have been available for many years and are recognized as an established treatment option (*Jacobs 2021b*).
- The safety and efficacy of Vuity (pilocarpine) were evaluated in 2 multicenter, parallel-group, randomized controlled trials (GEMINI 1 and GEMINI 2), which included a total of 750 adults (n = 375 administered Vuity) aged 40 to 55 years diagnosed with presbyopia. The proportion of patients gaining ≥ 3 lines in high contrast, binocular distance corrected near visual acuity (DCNVA), without losing ≥ 1 line (5 letters) of corrected distance visual acuity (CDVA) with the same refractive correction was significantly greater with pilocarpine vs vehicle (31% vs 8% in GEMINI 1; 26% vs 11% in GEMINI 2; $p < 0.01$ in each trial) at Day 30 (hour 3). A total of 6 (1.6%) patients and 4 (1.1%) patients treated with Vuity or vehicle, respectively, discontinued due to treatment-emergent adverse events (*Vuity prescribing information 2021, Waring et al 2021*).

Miotics compared to other drug classes
- For the treatment of glaucoma, ophthalmic pilocarpine has demonstrated comparable efficacy to reduce IOP to ophthalmic carbonic anhydrase inhibitors, beta-blockers, and prostaglandin analogues (*Bayer et al 2004, Diestelhorst et al 2000, Hartenbaum et al 1999*). A trial evaluated pilocarpine plus a beta-blocker and found that pilocarpine was an effective agent at reducing IOP with comparable efficacy to prostaglandin analogues (*Diestelhorst et al 2000*).
- In a head-to-head trial comparing apraclonidine to pilocarpine administered 15 minutes before ophthalmic surgery, no significant differences were observed between the agents in their ability to reduce IOP after surgery (*Ren et al 1999*).

Prostaglandin Analogues
- Several meta-analyses with the prostaglandin analogues have been published. Ophthalmic bimatoprost appears to have the greatest efficacy in reducing IOP; however, trials have not consistently demonstrated a difference in IOP reduction between travoprost and latanoprost (*Aptel et al 2008, Cheng et al 2008, Honrubia et al 2009, Li et al 2006, Lin et al 2014, Sawada et al 2012, Tang et al 2019*).
  - A systematic review of 32 randomized controlled trials compared prostaglandin analogues for primary open-angle glaucoma, using timolol as a reference comparator. The analysis found that bimatoprost was most likely to achieve treatment success, defined as a 30% reduction in IOP (relative risk, 1.59; 95% CI, 1.28 to 1.98). The relative risk for treatment success with latanoprost was 1.32 (95% CI, 1.00 to 1.74), for travoprost was 1.33 (95% CI, 1.03 to 1.72),

and for tafluprost was 1.1 (95% CI, 0.85 to 1.42). In terms of tolerability, bimatoprost was associated with the highest risk of developing hyperemia, while latanoprost had the lowest risk (*Lin et al 2014*).
  - The results of a meta-analysis with 8 trials (N = 1610) demonstrated that reductions in IOP were significantly greater with bimatoprost 0.03% compared to travoprost at 8 AM (p = 0.004) and 12 PM (p = 0.02), but not at 4 PM (p = 0.19) or 9 PM (p = 0.07). Bimatoprost 0.03% also demonstrated greater reductions in IOP compared to latanoprost at all time points. There were no statistically significant differences between latanoprost and travoprost at any time point (*Aptel et al 2008*).
  - Results from a meta-analysis by Li et al did not demonstrate a significant difference in IOP reductions between bimatoprost 0.03% and travoprost (p = 0.8) or latanoprost and travoprost (p = 0.07) in 12 studies with 3048 patients with open-angle glaucoma or ocular hypertension (*Li et al 2006*).
  - A meta-analysis of 13 trials evaluating adverse events associated with the ophthalmic prostaglandin analogues showed that latanoprost had a lower incidence of conjunctival hyperemia compared to both bimatoprost 0.03% and travoprost (p < 0.0001 for both) (*Honrubia et al 2009*).
  - A meta-analysis (17 trials, N = 2433) comparing latanoprost 0.005%, travoprost 0.004%, and bimatoprost 0.03% found that bimatoprost 0.03% was associated with greater IOP reduction after 3 and 6 months of therapy compared to latanoprost 0.005% and after 3 months of therapy compared to travoprost 0.004%. Latanoprost 0.005% had the lowest rates of conjunctival hyperemia (*Tang et al 2019*).
- Tafluprost was FDA approved in 2012, several years after other prostaglandin analogues; therefore, tafluprost data have not been included in many meta-analyses. Available trials and meta-analyses suggest that tafluprost may have a similar IOP-lowering effect as latanoprost, but less than that of travoprost (*Konstas et al 2013, Schnober et al 2010, Traverso et al 2010, Uusitalo et al 2010b, Yang et al 2020*).
  - One trial found no significant difference in IOP reduction from baseline between tafluprost and travoprost following 6 weeks of treatment (difference, 0.17 mmHg; 95% CI, -1.268 to 1.608; p = 0.811) (*Traverso et al 2010*).
  - In a 6-week crossover trial, travoprost significantly reduced IOP from baseline compared to tafluprost (7.2 vs 6.6 mmHg; p = 0.01). Adverse events were similar between the treatment groups (*Schnober et al 2010*).
  - In a randomized, double-blind trial (n = 533), tafluprost demonstrated non-inferiority to latanoprost after 24 months (p < 0.05). No difference in the incidence of adverse events was reported between treatments (*Uusitalo et al 2010b*).
  - A randomized trial compared IOP fluctuations among patients with newly diagnosed open-angle glaucoma who received latanoprost 0.005%, travoprost 0.004%, and tafluprost 0.0015%. Patients underwent IOP measurement at 8 AM, 2 PM, and 8 PM at baseline and weeks 2 and 6. At all time points, IOP reductions and fluctuations were similar between treatment groups. Tolerability was also similar between groups (*Faseeh et al 2021*).
  - Results from a similar trial demonstrated a significantly lower incidence of ocular irritation/burning, tearing, itching, dry eye sensation, and conjunctival hyperemia when switched from latanoprost to tafluprost due to ocular intolerance (p < 0.001 for all). Tafluprost also significantly reduced IOP compared to baseline treatment with latanoprost (16.4 vs 16.8 mmHg; p = 0.049) (*Uusitalo et al 2010a*).
  - Tafluprost 0.0015% (preservative-free) once daily was compared to timolol 0.5% (preservative-free) twice daily for monotherapy treatment of 643 patients with glaucoma or ocular hypertension in a double-blind, active control, randomized controlled trial. Tafluprost was non-inferior to timolol in IOP reduction at all visits and time points based upon a prespecified non-inferiority margin of 1.5 mmHg. Conjunctival hyperemia was more frequently reported with tafluprost (4.4%) than timolol (1.2%; p = 0.016) (*Chabi et al 2012*).
- A pooled analysis of 2 similarly designed, Phase 3, double-masked, active control, multicenter, non-inferiority trials (APOLLO and LUNAR; n = 840 total) found that latanoprostene bunod 0.024% administered once daily led to greater reductions in mean IOP when compared to timolol maleate 0.5% administered twice daily at all evaluation time points (IOP was measured at 8 AM, 12 PM, and 4 PM at week 2, week 6, and months 3, 6, 9, and 12) (p < 0.001 for all) (*Medeiros et al 2016, Weinreb et al 2016, Weinreb et al 2018*). A greater proportion of patients treated with latanoprostene bunod vs timolol attained a mean IOP ≤ 18 mmHg and an IOP reduction ≥ 25% from baseline (p < 0.001). Patients who switched over from timolol to latanoprostene bunod also experienced additional IOP lowering (p ≤ 0.009). Efficacy was maintained through 12 months of therapy.
- Latanoprostene bunod was also evaluated in a 28-day, Phase 2, randomized, investigator-masked, active control, multicenter, dose-ranging study (n = 413). The objective of the study was to assess the efficacy and safety of latanoprostene bunod vs latanoprost 0.005%, and to determine the optimum drug concentrations of latanoprostene bunod in reducing IOP. Patients were randomized into 1 of 5 treatment groups, including 4 different concentrations of latanoprostene bunod (0.006%, 0.012%, 0.024%, and 0.040%) and latanoprost 0.005% (*Weinreb et al 2015*).

- Efficacy for latanoprostene bunod was dose-dependent and reached a plateau at 0.024% to 0.040%. Latanoprostene bunod 0.024% led to significantly greater reductions in mean diurnal IOP compared with latanoprost 0.005% at day 28 (-9 mmHg vs -7.77 mmHg, respectively; p = 0.005).
- A significantly greater proportion of patients had mean diurnal IOP ≤ 18 mmHg in the latanoprostene bunod 0.024% group at all measurement time points (p ≤ 0.046) compared to the latanoprost group.

ROCK Inhibitor

- The safety and efficacy of netarsudil were evaluated in three Phase 3, randomized, double-masked, active control, parallel-group, multicenter trials. Patients were randomized to ophthalmic netarsudil or timolol maleate 0.5%. In these trials, the primary efficacy endpoint was the mean IOP, measured at multiple time points (8 AM, 12 PM, and 4 PM at week 2, week 6, and 3 months). Netarsudil was considered to be non-inferior to timolol if the upper limit of the 2-sided 95% CIs around the difference (netarsudil – timolol) was within 1.5 mmHg at all time points and was within 1.0 mmHg at a majority of the time points (*Rhopressa Prescribing Information 2019, Serle et al 2018*).
  - Overall, netarsudil 0.02% dosed once a day demonstrated statistically significant reductions of up to 5 mmHg in IOP from baseline in the clinical trials.
  - In ROCKET-1, netarsudil failed in its primary endpoint; netarsudil was not non-inferior to timolol in patients with baseline IOP < 27 mmHg. However, netarsudil was non-inferior to timolol in patients with a baseline IOP < 25 mmHg in a post-hoc analysis. Netarsudil did have an IOP-lowering effect at baseline IOPs ≥ 25 mmHg, but was not statistically non-inferior to timolol when including these patients (*Serle et al 2018*).
  - In ROCKET-2, netarsudil achieved success in its primary endpoint, demonstrating non-inferiority to timolol in patients with a baseline IOP < 25 mmHg (*Serle et al 2018*).
  - In ROCKET-4, netarsudil achieved success in its primary endpoint, demonstrating non-inferiority to timolol in patients with a baseline IOP < 25 mmHg in the per-protocol population. In a secondary endpoint analysis, non-inferiority of netarsudil to timolol was demonstrated in patients with baseline IOP < 27 mmHg and < 30 mmHg in the per-protocol population (*Khouri et al 2019*).
  - Safety analyses have demonstrated that the drug is well-tolerated, with conjunctival hyperemia as the most frequent adverse event, and maintains consistently lowered IOP through 12 months of therapy (*Kahook et al 2019*).
- In a pooled analysis of data from the ROCKET-1 to 4 studies, efficacy of netarsudil 0.02% (n = 494) demonstrated non-inferiority to timolol 0.5% (n = 510) in patients with open-angle glaucoma or ocular hypertension with an IOP < 25 mmHg. The mean IOP through 3 months of treatment was 16.4 to 18.1 mmHg with netarsudil compared to 16.8 to 17.6 mmHg with timolol. Conjunctival hyperemia occurred more often with netarsudil (54.4%) compared to timolol (10.4%) (*Singh et al 2020*).
- Netarsudil was also evaluated in a 28-day, Phase 2, dose-response, double-masked, active control, parallel-group, multicenter trial evaluating netarsudil compared with latanoprost solution, in patients with open-angle glaucoma or ocular hypertension. The study found that netarsudil 0.02% was less effective than latanoprost by approximately 1 mmHg in patients with unmedicated IOPs of 22 to 35 mmHg (differences from latanoprost in the change from baseline mean diurnal IOP for netarsudil 0.02% were 0.9 mmHg at day 14 and 1.2 mmHg at day 28) (*Bacharach et al 2015*).

Fixed Dose Combinations

- Combigan (brimonidine/timolol)
  - The combination of brimonidine/timolol has been shown to be safe and effective in reducing mean IOP from baseline (*Craven et al 2005, Goñi et al 2005, Sherwood et al 2006*). In clinical trials comparing the fixed combination to the individual components, the reduction of IOP with brimonidine/timolol dosed twice a day was slightly less than that seen with the concomitant administration of timolol maleate ophthalmic solution 0.5% dosed twice a day and brimonidine tartrate ophthalmic solution 0.2% dosed 3 times per day.
  - The combination of brimonidine/timolol was compared to latanoprost 0.005% in 148 patients with glaucoma or ocular hypertension in a randomized, investigator-masked study (*Katz et al 2012*). The primary outcome, mean diurnal IOP at 12 weeks, did not demonstrate a significant difference between treatment groups at any time point or mean change from baseline at any time point at week 12. The reported mean diurnal IOP at week 12 was 17.8 mmHg for brimonidine/timolol and 17.9 mmHg for latanoprost (p = 0.794). The between-group mean difference in diurnal IOP at week 12 was -0.14 mmHg (95% CI, -1.27 to 0.98), demonstrating non-inferiority of fixed brimonidine/timolol to latanoprost based on predefined criteria. Nine patients in the combination group discontinued the study compared to

2 patients treated with latanoprost, mostly due to adverse effects. Treatment-related adverse events were reported in 16.4% of patients treated with brimonidine/timolol compared to 10.7% treated with latanoprost.

- Simbrinza (brinzolamide/brimonidine)
  - The efficacy and safety of the combination of brinzolamide/brimonidine were established in 2 double-blind, multicenter, randomized controlled trials. The brinzolamide/brimonidine 1%/0.2% combination was shown to significantly lower the mean IOP compared to either monotherapy (eg, brinzolamide and brimonidine) at all time points of the day in 2 identical, 3-month studies. Adverse events were mostly ocular in nature, and the combination group had a higher percentage of patients reporting adverse events compared to each monotherapy group (*Katz et al 2013, Nguyen et al 2013, Realini et al 2013*).
    - An additional trial comparing the combination to each monotherapy evaluated secondary efficacy endpoints and safety over 6 months. The combination of brinzolamide/brimonidine had higher rates of adverse events and discontinuation rates. The mean IOP reductions after 6 months were similar to those observed after 3 months (*Whitson et al 2013*). Another trial evaluating twice daily dosing was conducted after the U.S. approval of the thrice daily dosing. Results were similar to those previously observed (*Aung et al 2014*).
    - In another trial, compared with dorzolamide/timolol, brinzolamide/brimonidine provided significantly greater morning IOP reductions at 12 weeks (*Kozobolis et al 2017*).
- Cosopt / Cosopt PF (dorzolamide/timolol)
  - In a study comparing dorzolamide/timolol to the individual components, the combination product was more effective at reducing IOP from baseline at all time periods over 3 months of treatment (*Clineschmidt et al 1998*).
  - One open-label study evaluated the safety and efficacy of dorzolamide/timolol preservative-free formulation (*Renieri et al 2010*). Patients receiving the preservative-free product experienced a statistically significant reduction in IOP from baseline (p value not reported). Local tolerability improved in 79.3% of patients who switched to this formulation from other anti-glaucoma therapies. Of note, 84% of patients switching from Cosopt experienced an improvement in tolerability with the preservative-free dorzolamide/timolol formulation.
- Rocklatan (netarsudil/latanoprost)
  - The efficacy and safety of the combination of netarsudil/latanoprost were established in 2 double-masked, multicenter, randomized controlled trials. In both, the fixed-dose combination was compared to its individual components, and patients were followed for 12 months and 3 months, respectively. Both trials found that netarsudil/latanoprost significantly lowered the mean IOP compared to either monotherapy (eg, netarsudil and latanoprost) at all time points through month 3. The IOP reductions were maintained for 12 months in the longer duration trial. Adverse events were mostly ocular in nature, and the combination group experienced higher rates of conjunctival hyperemia, eye pruritis, and cornea verticillata compared to each monotherapy group (*Asrani et al 2019, Asrani et al 2020, Rocklatan Prescribing Information 2020*).
- Cosopt (dorzolamide/timolol) vs Combigan (brimonidine/timolol)
  - Combined dorzolamide/timolol was compared to brimonidine/timolol, and both demonstrated significant reductions in IOP from baseline. The differences between groups were not found to be significant in any of the 3 studies (p value not reported) (*Gulkilik et al 2011, Martinez et al 2010, Siesky et al 2012*). However, 2 other studies had conflicting findings. In a crossover study of 20 patients, brimonidine/timolol had significantly lower mean diurnal IOP than dorzolamide/timolol after 6 weeks (16.28 vs 17.23 mmHg, respectively; $p = 0.03$) (*Garcia-Feijoo et al 2010*). In a crossover study of 77 patients, dorzolamide/timolol was associated with a greater reduction in the mean 24-hour IOP level from baseline, compared to brimonidine/timolol (mean difference, 0.7 mmHg; $p < 0.001$). Likewise, the peak and minimum 24-hour IOP levels were significantly lower with dorzolamide/timolol compared to brimonidine/timolol ($p = 0.03$ and $p = 0.012$, respectively) (*Konstas et al 2012*). It is not clear how population size and duration of the crossover studies affected these results.

CLINICAL GUIDELINES

American Academy of Ophthalmology (AAO) – Primary Open-Angle Glaucoma *(Gedde et al 2021)*

- Medical therapy is presently the most common initial intervention to lower IOP. There are many drugs available for initial therapy, and medication choice may be influenced by potential cost, side effects, dosing schedules, and the degree of IOP lowering needed.
- Prostaglandin analogues are the most frequently used initial eye drops for lowering IOP. They are the most efficacious drugs for lowering IOP, are relatively safe, and are used once daily. They are often considered as initial medical therapy

unless other considerations such as contraindications, cost, side effects, intolerance, or patient refusal preclude their use.
  - Other agents include beta-blockers, alpha-agonists, ROCK inhibitors, topical and oral carbonic anhydrase inhibitors, and parasympathomimetics.
  - The AAO guidelines do not recommend 1 ophthalmic prostaglandin analogue over another.
- If a single medication is effective in lowering IOP but the target IOP is not reached, combination therapy or switching to an alternative therapy may be appropriate. Similarly, if a drug fails to reduce IOP sufficiently despite good adherence to therapy, it can be replaced with an alternative agent until effective medical treatment, whether alone or in combination, is established.

American Optometric Association (AOA) – Care of the Patient with Open Angle Glaucoma (*AOA 2010*)
- The 2010 AOA guideline (currently under review) provides a summary of the efficacy and adverse effects for the various classes of pharmacologic therapy for open-angle glaucoma, but does not specifically recommend 1 class over another. Combination therapy can be considered in patients who have not achieved optimal IOP reduction with a prostaglandin analogue.

American Optometric Association (AOA) – Care of the Patient with Visual Impairment (*AOA 2007*)

The 2007 AOA guideline defines presbyopia as a reduction in accommodative ability that occurs normally with age and necessitates a plus lens addition for satisfactory seeing at near states. The AOA recommend that all visually impaired patients should undergo refraction to ensure optimal correction for best visual acuity and to determine the amount of magnification needed for certain tasks.

SAFETY SUMMARY

- Contraindications
  - Alpha-agonists are contraindicated in patients who have hypersensitivity to the ingredients or clonidine (apraclonidine).
    - Products containing apraclonidine are contraindicated in patients receiving monoamine oxidase inhibitors.
    - Products containing brimonidine are contraindicated in neonates and infants < 2 years of age.
  - Ophthalmic beta-blockers (as single entity agents or in combinations) are contraindicated in patients with a history of bronchial asthma or severe chronic obstructive pulmonary disease, cardiogenic shock, second or third degree atrio-ventricular block, sinus bradycardia, overt cardiac failure, and known hypersensitivity to any component of the product.
- Warnings
  - Alpha-agonists may potentiate syndromes associated with vascular insufficiency and should be used with caution in patients with severe cardiovascular disease, depression, cerebral or coronary insufficiency, Raynaud's phenomenon, orthostatic hypotension, or thromboangiitis obliterans.
  - Beta-Blockers
    - Ophthalmic beta-blockers, as single entities or in combinations, may mask signs and symptoms of hypoglycemia; use with caution in patients with diabetes mellitus.
    - Ophthalmic beta-blockers may cause systemic adverse events including cardiovascular and respiratory adverse events. Beta-blockers may mask symptoms of hyperthyroidism such as tachycardia, and thyroid storm can occur with abrupt beta-blocker discontinuation.
    - Due to the potential for systemic effects with ophthalmic timolol use, exercise caution in patients with cardiac disease, diabetes, and anaphylactic reactions, as beta-blockers may alter response.
  - Warnings for the carbonic anhydrase inhibitors include the risk of corneal edema, bacterial keratitis, ocular adverse effects, and sulfonamide hypersensitivity.
    - Oral and ophthalmic carbonic anhydrase inhibitors should not be used concurrently due to the possibility of additive systemic effects.
    - Due to the brinzolamide component, Simbrinza labeling contains warnings for sulfonamide hypersensitivity reactions, and corneal edema in patients with low endothelial cell counts.
  - Miotics
    - The miosis caused by the ophthalmic miotics usually causes difficulty in dark adaptation; therefore, patients should be advised to exercise caution in night driving and other hazardous occupations in poor illumination.

        - Rare cases of retinal detachment have been reported when used in certain susceptible patients and those with pre-existing retinal disease; therefore, a thorough examination of the retina, including fundoscopy, is advised in all patients prior to the initiation of ophthalmic miotics.
        - Caution is advised when administering ophthalmic pilocarpine solution (Isopto Carpine) for control of IOP in pediatric patients with primary congenital glaucoma.
        - Ophthalmic pilocarpine solution (Vuity) is not recommended when iritis is present because adhesions (synechiae) may form between the iris and lens. Contact lenses should be removed prior to drug instillation, and 10 minutes should be allowed to pass prior to reinserting contact lenses.
    - Prostaglandin analogue class warnings include the risk of hyperpigmentation of ocular tissues and eyelash changes with darkening and thickening of eyelashes. Drugs in this class should be used with caution in patients with intraocular inflammation or macular edema.
    - ROCK inhibitor
        - Bacterial keratitis: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface.
- Adverse reactions
    - Alpha-Agonists
        - The most common adverse events (5 to 20% of patients) with brimonidine included allergic conjunctivitis, burning sensation, conjunctival folliculosis, conjunctival hyperemia, eye pruritus, hypertension, ocular allergic reaction, oral dryness, and visual disturbance.
        - Common adverse events (5 to 15% of patients) with apraclonidine included ocular discomfort, ocular hyperemia, ocular pruritus, and dry mouth.
        - The alpha-agonists can potentially cause systemic adverse effects including somnolence and dizziness.
    - Beta-blockers
        - Local ocular adverse events reported with ophthalmic beta-blockers include blurred vision and instillation reactions (itching, burning, tearing).
    - Carbonic Anhydrase Inhibitors
        - Adverse events are primarily limited to local ocular effects including blurred vision, conjunctival hyperemia, foreign body sensation, ocular burning/stinging, ocular discharge, ocular pruritus, and pain.
        - Ophthalmic carbonic anhydrase inhibitors also are associated with alterations of taste that have been reported in up to 30% of patients.
    - Miotics
        - Most adverse events reported with the miotics are associated with the eye. The most common adverse events reported with ophthalmic pilocarpine solutions were blurred vision, eye irritation, eye pain, accommodative change, and/or visual impairment with Isopto Carpine and headache and conjunctival hyperemia with Vuity.
    - Prostaglandin Analogues
        - The most frequently reported adverse events associated with these agents are ocular in nature and include burning/stinging, hyperemia, pruritus, iris pigmentation changes, and growth and darkening of eyelashes.
    - ROCK inhibitor
        - The most common adverse event with Rhopressa was conjunctival hyperemia (53%). Other common (approximately 20%) ocular adverse reactions reported were corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5 to 10% of patients.
            - Corneal verticillata occurred in approximately 20% of the patients in controlled clinical studies. The corneal verticillata seen in Rhopressa-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes in patients. Most corneal verticillata resolved upon discontinuation of treatment.

- Drug interactions
    - Alpha-agonists may reduce pulse and blood pressure when administered with antihypertensives. When used with central nervous system depressants, alpha-agonists may have an additive or potentiating effect. Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine; it is not known whether the concurrent use of these agents with ophthalmic alpha-agonists can interfere with their IOP-lowering effect. Concomitant therapy of brimonidine and monoamine oxidase inhibitors may result in hypotension.

- Drug interactions with ophthalmic beta-blockers include the potentiation of the effects of calcium channel blockers, beta-blockers, clonidine, and quinidine on the cardiovascular system.

DOSING AND ADMINISTRATION

- See the current prescribing information for full details.
- In general, patients should remove their contact lenses prior to the instillation of ophthalmic products.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Alpha-Agonists				
Alphagan P (brimonidine); brimonidine 0.2%	Ophthalmic solution Alphagan P does not contain benzalkonium chloride; instead, Purite 0.005% (0.05 mg/mL) is used for the preservative.	Ophthalmic	Three times daily	Safety and effectiveness have not been studied in pediatric patients < 2 years of age; contraindicated in pediatric patients < 2 years. Pregnancy Category B*
Iopidine (apraclonidine)	Ophthalmic solution	Ophthalmic	1% solution: once before and once after procedure 0.5% solution: Three times daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Beta-Blockers				
betaxolol hydrochloride	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C‡
Betimol (timolol)	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C‡
Betoptic S (betaxolol hydrochloride)	Ophthalmic suspension	Ophthalmic	Twice daily	Safety and efficacy in lowering IOP have been demonstrated in pediatric patients in a 3 month, multicenter, double-masked, active control trial. Pregnancy: Unclassified†
carteolol hydrochloride	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy Category C‡

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Istalol (timolol maleate)	Ophthalmic solution	Ophthalmic	Once daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
levobunolol hydrochloride	Ophthalmic solution	Ophthalmic	Once or twice daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Timoptic, Timoptic in Ocudose (timolol maleate)	Ophthalmic solution Benzalkonium chloride 0.01% is added as a preservative in Timoptic; the Ocudose solution is preservative-free.	Ophthalmic	Twice daily	Timoptic in Ocudose units should be discarded after a single administration to 1 or both eyes. Safety and effectiveness of timolol have been established when administered in pediatric patients aged 2 years and older. Pregnancy: Unclassified†
Timoptic-XE (timolol maleate GFS)	Ophthalmic gel forming solution	Ophthalmic	Once daily	Safety and effectiveness of timolol have been established when administered in pediatric patients aged 2 years and older. Pregnancy: Unclassified†
Carbonic Anhydrase Inhibitors				
Azopt (brinzolamide)	Ophthalmic suspension	Ophthalmic	Three times daily	A 3-month clinical trial with brinzolamide 1% dosed twice daily in pediatric patients 4 weeks to 5 years did not demonstrate a reduction in IOP from baseline. Pregnancy: Unclassified†
Trusopt (dorzolamide)	Ophthalmic solution	Ophthalmic	Three times daily	Dorzolamide and its metabolite are excreted predominantly by the kidney; therefore, dorzolamide is not recommended in patients with severe renal impairment. Safety and IOP-lowering effectiveness of dorzolamide have been demonstrated in pediatric patients in a 3 month, multicenter, double-masked, active-control trial.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Pregnancy: Unclassified†
Miotics				
Isopto Carpine (pilocarpine)	Ophthalmic solution	Ophthalmic	Up to 4 times daily (varies by indication) Induction of miosis prior to procedure and prevention of postoperative elevated IOP: 15 to 60 minutes prior to surgery Management of acute angle-closure glaucoma: Initial: 1 drop up to 3 times over a 30-minute period; Maintenance: 4 times daily Reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension: 4 times daily Dosing in children < 2 years of age: 3 times daily; children ≥ 2 years of age should follow adult dosing	Safety and effectiveness in pediatric patients have been established. Pregnancy Category C‡
Vuity (pilocarpine)	Ophthalmic solution	Ophthalmic	Once daily	Studies did not include patients aged ≥ 65 years; it is unknown if they respond differently from younger patients. Presbyopia does not occur in children. There are no adequate studies of Vuity in pregnant women. If > 1 topical ophthalmic products are being used, products should be administered ≥ 5 minutes apart.
Prostaglandin Analogues				
Lumigan (bimatoprost) 0.01%; generic bimatoprost 0.03%	Ophthalmic solution	Ophthalmic	Once daily	Use in pediatric patients < 16 years of age is not recommended due to potential

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				safety concerns related to increased pigmentation following long-term chronic use. Pregnancy: Unclassified†
Travatan Z (travoprost)	Ophthalmic solution	Ophthalmic	Once daily	Use in pediatric patients < 16 years of age is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy: Unclassified†
Xalatan (latanoprost)	Ophthalmic solution Latanoprost 0.005% solution contains benzalkonium chloride 0.02%	Ophthalmic	Once daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Vyzulta (latanoprostene bunod)	Ophthalmic solution	Ophthalmic	Once daily	Use in pediatric patients < 16 years of age is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy: Unclassified†
Xelpros (latanoprost)	Ophthalmic emulsion	Ophthalmic	Once daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Zioptan (tafluprost)	Ophthalmic solution	Ophthalmic	Once daily	Use in pediatric patients is not recommended due to potential safety concerns related to increased pigmentation following long-term chronic use. Pregnancy Category C‡
ROCK Inhibitor				
Rhopressa (netarsudil)	Ophthalmic solution	Ophthalmic	Once daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Combinations				
Combigan (brimonidine/timolol)	Ophthalmic solution	Ophthalmic	Twice daily	Safety and effectiveness of Combigan have been established in children ages 2 to

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				16 years of age; contraindicated in pediatric patients < 2 years. Pregnancy: Unclassified†
Cosopt/Cosopt PF (dorzolamide /timolol)	Ophthalmic solution Benzalkonium chloride 0.0075% is added as a preservative in Cosopt; Cosopt PF is preservative-free.	Ophthalmic	Twice daily	Safety and effectiveness of dorzolamide and timolol have been established when administered separately in children aged 2 years and older. Use of these drug products in children is supported by evidence from adequate and well-controlled studies in children and adults. Cosopt PF units should be discarded after a single administration to 1 or both eyes. Pregnancy: Unclassified†
Rocklatan (latanoprost/netarsudil)	Ophthalmic solution Contains benzalkonium chloride 0.02% as a preservative	Ophthalmic	Once daily	Safety and effectiveness in pediatric patients have not been established. Pregnancy: Unclassified†
Simbrinza (brinzolamide/ brimonidine)	Ophthalmic suspension	Ophthalmic	Three times daily	Brinzolamide has been studied in pediatric glaucoma patients 4 weeks to 5 years of age; brimonidine has been studied in pediatric patients 2 to 7 years of age. Simbrinza is contraindicated in neonates and infants < 2 years of age. Not studied in patients with severe renal impairment (creatinine clearance < 30 mL/min); since brinzolamide and its metabolite are excreted predominantly by the kidney, Simbrinza is not recommended in such patients. Pregnancy Category C‡

*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.
‡Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- Treatment of glaucoma currently focuses on decreasing IOP by 1 of 3 methods: laser therapy, surgery, or medical intervention (*Gedde et al 2021*). A target IOP between 25 and 30% lower than baseline is reasonable (*Gedde et al 2021, Jacobs 2020b*). Medical intervention includes 6 classes of ophthalmic agents used for the long-term management of glaucoma: alpha-agonists, beta-blockers, carbonic anhydrase inhibitors, miotics, prostaglandin analogues, and ROCK inhibitors. The current guidelines by the AAO generally recommend ophthalmic prostaglandin analogues as first-line pharmacologic therapy in patients with elevated IOP (*Gedde et al 2021*).
  - Combination therapy with agents from other therapeutic classes should be used if the reduction in IOP on monotherapy is unsatisfactory (*Gedde et al 2021*). Combination therapy can be given as separate drops or in fixed-dose combinations, which include brimonidine/timolol, brimonidine/brinzolamide, dorzolamide/timolol, and latanoprost/netarsudil.
  - Adherence is often poor with glaucoma treatment as the disease is asymptomatic for many years, and eye drops may be difficult to use or cause adverse effects (*Gedde et al 2021, Jacobs 2020b*).
- Among the ophthalmic prostaglandin analogues, studies have demonstrated statistically significant differences in IOP-lowering ability among agents in the class. However, the differences are generally small, and the clinical significance of these differences has not been established. Bimatoprost is generally considered to have the greatest IOP-reducing effect among the ophthalmic prostaglandin analogues (*Aptel et al 2008, Cheng et al 2008, Kammer et al 2010, Li et al 2016, Lin et al 2014, Weinreb et al 2018, Tang et al 2019*).
  - In addition to conjunctival hyperemia, ocular adverse events with the prostaglandin analogues include eye irritation, increase in the number and length of eyelashes, and changes in iris and lash pigmentation; the latter 2 are most notable if only 1 eye is treated. The ophthalmic prostaglandin analogues are considered to be better tolerated compared to other classes of medications used for the management of glaucoma (*Jacobs 2020b*).
- Several ophthalmic agents in these drug classes are used for other indications. Ophthalmic apraclonidine 1% is FDA-approved to control or prevent postsurgical elevations in IOP, while ophthalmic apraclonidine 0.5% is indicated as short-term adjunctive therapy in patients on maximally tolerated medical therapy that require additional IOP reduction. Ophthalmic pilocarpine, more specifically Isopto Carpine, is indicated for the control of IOP, management of acute angle-closure glaucoma, prevention of postoperative elevated IOP associated with laser surgery, and reduction of elevated IOP in patients with open-angle glaucoma or ocular hypertension; Vuity is indicated for presbyopia, which is an additional treatment option to reading glasses.

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Publication Date: February 3, 2022