OPTUMRx®

Silver State Scripts Board Meeting

MARCH 24, 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: February 11, 2022

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 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-Mar-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: 962 136 816#

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 December 9, 2021.
b. Status Update by DHCFP.

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

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

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

b. **For Possible Action:** Discussion and possible adoption of Neurological Agents - Antiparkinsonian Agents - Non-ergot Dopamine Agonists.

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

c. **For Possible Action:** Discussion and possible adoption of Psychotropic Agents - ADHD Agents.

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

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

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

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

6. Established Drug Classes

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

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

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

8. 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_NzIxYWI0YjgtZWZkMS00NjRkLThiN2YtNjM5MWQzODNhMmMw%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

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
June 23, 2022	1:00 PM	Hampton Inn Tropicana, Las Vegas	None

Web References

Preferred Drug List:

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

Medicaid Services Manual (MSM) Chapter 1200:

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

Silver State Scripts Board Bylaws:

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

The Division of Health Care Financing and Policy Public Notices:

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

Definition of "Therapeutic Alternative"

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

Standard Preferred Drug List Exception Criteria

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

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

OPTUMRx®

Current Preferred Drug List

Preferred Products	PA Criteria	Non-Preferred Products
Analgesics		
Analgesic/Miscellaneous		
Neuropathic Pain/Fibromyalgia Agents		
DULOXETINE GABAPENTIN LYRICA® SAVELLA® *¥ (Fibromyalgia only)	* PA required *¥No PA required for drugs in this class if ICD-10 - M79.1; M60.0-M60.9, M61.1.*	CYMBALTA® GRALISE® LIDOCAINE PATCH * LIDODERM® * LYRICA® CR HORIZANT® QUTENZA® *
Tramadol and Related Drugs		
TRAMADOL TRAMADOL/APAP		CONZIPR® NUCYNTA® RYZOLT® RYBIX® ODT TRAMADOL ER ULTRACET® ULTRAM® ULTRAM® ER
Opiate Agonists		
MORPHINE SULFATE SA TABS (ALL GENERIC EXTENDED RELEASE) QL FENTANYL PATCH QL BUTRANS® NUCYNTA® ER	PA required for Fentanyl Patch General PA Form: 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
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) - Oral		
CELECOXIB CAP DICLOFENAC POTASSIUM		CAMBIA® POWDER

Preferred Products	PA Criteria	Non-Preferred Products
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	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
Antivirals		
Alpha Interferons		
PEGASYS® PEGASYS® CONVENIENT PACK		

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

	Preferred Products	PA Criteria	Non-Preferred Products
	CLARITHROMYCIN TABS/SUSP ERYTHROMYCIN BASE ERYTHROMYCIN ESTOLATE ERYTHROMYCIN ETHYLSUCCINATE ERYTHROMYCIN STEARATE		DIFICID® ZITHROMAX® ZMAX®
Quinolones			
Quinolones - 2nd Generation			
	CIPROFLOXACIN TABS CIPRO® SUSP	PA Required	FLOXIN® OFLOXACIN
Quinolones - 3rd Generation			
	LEVOFLOXACIN MOXIFLOXACIN	PA Required	AVELOX® LEVAQUIN®
Autonomic Agents			
Sympathomimetics			
Self-Injectable Epinephrine			
	EPINEPHRINE AUTO INJ EPINEPHRINE®	* PA required	ADRENACLICK® QL AUVI-Q® * SYMJEPI®
Biologic Response Modifiers			
Immunomodulators			
Targeted Immunomodulators			
	ACTEMRA® AVSOLA® CIMZIA® COSENTYX® ENBREL® HUMIRA® INFLECTRA® KEVZARA® KINERET® OLUMIANT® ORENCIA® OTEZLA® RENFLEXIS® SILIQ® SIMPONI® STELARA® TALTZ® XELJANZ®	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
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® EPROSARTAN HYZAAR® IRBESARTAN MICARDIS® TELMISARTAN TEVETEN®
Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors)		
BENAZEPRIL BENAZEPRIL HCTZ CAPTOPRIL CAPTOPRIL HCTZ ENALAPRIL	£ PREFERRED FOR AGES 10 AND UNDER ǂ NONPREFERRED FOR OVER 10 YEARS OLD	ACCURETIC® EPANED® ǂ FOSINOPRIL MAVIK® MOEXIPRIL

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

Preferred Products	PA Criteria	Non-Preferred Products
ORENITRAM® REVATIO ® TADALAFIL		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 LOVASTATIN PRAVASTATIN ROSUVASTATIN SIMVASTATIN		ALTOPREV® AMLODIPINE/ATORVASTATIN CADUET® CRESTOR® QL EZALLOR® FLUVASTATIN FLUVASTATIN XL LESCOL® LESCOL XL® LIPITOR® LIPTRUZET® LIVALO® MEVACOR® PRAVACHOL® SIMCOR® VYTORIN® ZOCOR® ZYPITAMAG®

Preferred Products	PA Criteria	Non-Preferred Products
Niacin Agents		
NIASPAN® (Brand only) NIACIN ER (ALL GENERICS)		NIACOR®
Omega-3 Fatty Acids		
OMEGA-3-ACID VASCEPA®		LOVAZA®
PCSK9 Inhibitors		
PRALUENT® REPATHA®		
Dermatological Agents		
Antipsoriatic Agents		
DOVONEX® CREAM SORILUX® (FOAM) TACLONEX® SUSP VECTICAL® (OINT)		CALCITENE® CALCIPOTRIENE CALCIPOTRIENE OINT/BETAMETHAZONE DUOBRII® LOTION ENSTILAR ® (AER) TACLONEX OINT
Topical Analgesics		
CAPSAICIN FLECTOR® LIDOCAINE LIDOCAINE HC LIDOCAINE VISCOUS LIDOCAINE/PRILOCAINE LIDODERM® QL PENNSAID® VOLTAREN® GEL		DICLOFENAC (gel/sol) EMLA® 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

Preferred Products	PA Criteria	Non-Preferred Products
		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
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®		AURYXIA ® FOSRENOL® LANTHANUM CARBONATE

Preferred Products	PA Criteria	Non-Preferred Products
RENAGEL® RENVELA®		PHOSLO® SEVELAMER CARBONATE SEVELAMER HCL VELPHORO®
Gastrointestinal Agents		
Antiemetics		
Pregnancy-induced Nausea and Vomiting Treatment		
BONJESTA® OTC Doxylamine 25mg/Pyridoxine 10mg		DICLEGIS® DOXYLAMINE-PYRIDOXINE TAB 10-10
Serotonin-receptor antagonists/Combo		
GRANISETRON QL ONDANSETRON QL	PA required for all medication in this class	AKYNZEO® ANZEMET® QL SANCUSO® ZOFRAN® QL ZUPLENZ® QL BARHEMSYS®
Antiulcer Agents		
H2 blockers		
FAMOTIDINE RANITIDINE RANITIDINE SYRUP*	*PA not required for < 12 years	
Proton Pump Inhibitors (PPIs)		
DEXILANT® NEXIUM® POWDER FOR SUSP* OMEPRAZOLE PANTOPRAZOLE	PA required if exceeding 1 per day *for children ≤ 12 yrs.	ACIPHEX® ESOMEPRAZOLE LANSOPRAZOLE NEXIUM® CAPSULES PREVACID® PRILOSEC® PRILOSEC® OTC TABS PROTONIX® RABEPRAZOLE SODIUM
Functional Gastrointestinal Disorder Drugs		
AMITIZA® LINZESS®	 PA required	LUBIPROSTONE MOTEGRITY® MOVANTIK® RELISTOR® SYMPROIC® TRULANCE® ZELNORM®
Gastrointestinal Anti-inflammatory Agents		
APRISO® ASACOL®SUPP		BALSALAZIDE® ASACOL HD®

	Preferred Products	PA Criteria	Non-Preferred Products
	CANASA® COLAZAL® DELZICOL® PENTASA® SULFASALAZINE DR SULFASALAZINE IR		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® VIOKACE®
Genitourinary Agents			
Benign Prostatic Hyperplasia (BPH) Agents			
5-Alpha Reductase Inhibitors			
	DUTASTERIDE FINASTERIDE		AVODART® DUTASTERIDE/TAMSULOSIN JALYN® PROSCAR®
Alpha-Blockers			
	ALFUZOSIN DOXAZOSIN TAMSULOSIN TERAZOSIN		CARDURA® FLOMAX® MINIPRESS® PRAZOSIN RAPAFLO® SILODOSIN UROXATRAL®
Bladder Antispasmodics			
	BETHANECHOL OXYBUTYNIN TABS/SYRUP/ER SOLIFENACIN TOVIAZ®		DARIFENACIN DETROL® DETROL LA® DITROPAN XL® ENABLEX® FLAVOXATE GELNIQUE® MYRBETRIQ® OXYTROL® SANCTURA® TOLTERODINE TROSPIUM VESICARE® VESICARE® LS

Preferred Products	PA Criteria	Non-Preferred Products
Hematological Agents		
Anticoagulants		
Oral		
COUMADIN® ELIQUIS® * JANTOVEN® PRADAXA® * QL WARFARIN XARELTO ® *	* No PA required if approved diagnosis code transmitted on claim	SAVAYSA®*
Injectable		
FONDAPARINUX ENOXAPARIN FRAGMIN®		ARIXTRA® INNOHEP® LOVENOX®
Erythropoiesis-Stimulating Agents		
ARANESP® QL RETACRIT®	PA required Quantity Limit	EPOGEN® QL MIRCERA® QL PROCRIT® QL
Platelet Inhibitors		
AGGRENOX® 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®		GLUCOPHAGE®

	Preferred Products	PA Criteria	Non-Preferred Products
	METFORMIN EXT-REL (Glucophage XR®) METFORMIN EXT-REL (Glucophage XR®) METFORMIN (Glucophage®) METFORMIN ER (GEN GLUMETZA) RIOMET®		GLUCOPHAGE XR® GLUMETZA® METFORMIN (GEN FORTAMET)
Dipeptidyl Peptidase-4 Inhibitors			
	JANUMET® JANUMET XR® JANUVIA® JENTADUETO® KOMBIGLYZE XR® ONGLYZA® TRADJENTA®		ALOGLIPTIN ALOGLIPTIN-METFORMIN ALOGLIPTIN-PIOGLITAZONE KAZANO® NESINA® OSENI®
Incretin Mimetics			
	BYDUREON® BYDUREON® PEN BYETTA® 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®

Preferred Products	PA Criteria	Non-Preferred Products
Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors		
FARXIGA® GLYXAMBI® INVOKANA® INVOKAMET® JARDIANCE® SYNJARDY® SYNJARDY® XR XIGDUO XR®		INVOKAMET® XR QTERN® SEGLUROMET® STEGLATRO® STEGLUJAN™ TRIJARDY® XR
Sulfonylureas		
DIABETA® GLIMEPIRIDE (Amaryl®) GLIPIZIDE (Glucotrol®) GLIPIZIDE EXT-REL (Glucotrol XL®) GLYBURIDE MICRONIZED (Glynase®) GLYBURIDE (Diabeta®) METAGLIP®		AMARYL® CHLORPROPAMIDE GLYNASE® GLUCOTROL® GLUCOTROL XL® GLYBURIDE/METFORMIN (Glucovance®) GLUCOVANCE® GLIPIZIDE/METFORMIN (Metaglip®) TOLAZAMIDE TOLBUTAMIDE
Thiazolidinediones		
PIOGLITAZONE		ACTOPLUS MET XR® ACTOPLUS MET® ACTOS® AVANDAMET® AVANDARYL® AVANDIA® DUETACT® PIOGLITAZONE/METFORMIN PIOGLITAZONE/GLIMEPR
Anti-Hypoglycemic Agents		
GLUCAGON EMERGENCY KIT		BAQSIMI® GVOKE®
Pituitary Hormones		
Growth hormone modifiers		
GENOTROPIN® NORDITROPIN®	PA required for entire class Form FA-67	HUMATROPE® NUTROPIN AQ® OMNITROPE® NUTROPIN® SAIZEN® SEROSTIM®

	Preferred Products	PA Criteria	Non-Preferred Products
			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 CHLORZOXAZONE CYCLOBENZAPRINE DANTROLENE METHOCARBAMOL		

Preferred Products	PA Criteria	Non-Preferred Products
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 GABITRIL® LAMACTAL ODT® LAMACTAL XR® LAMICTAL® LAMOTRIGINE LEVETIRACETAM LYRICA®	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
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
Hydantoins		
CEREBYX® DILANTIN® ETHOTOIN FOSPHENYTOIN PEGANONE® PHENYTEK® PHENYTOIN PRODUCTS		
Anti-Migraine Agents		
Calcitonin Gene-Related Peptide (CGRP) Receptor Antagonists		
AIMOVIG®	PA required for all products	UBRELVY®

Preferred Products	PA Criteria	Non-Preferred Products
AJOVY® EMGALITY® NURTEC® ODT		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
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®

Preferred Products	PA Criteria	Non-Preferred Products
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®
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®

Preferred Products	PA Criteria	Non-Preferred Products
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®
Ophthalmic Nonsteroidal Anti-inflammatory Drugs (NSAIDs)		
DICLOFENAC FLURBIPROFEN ILEVRO® KETOROLAC NEVANAC®		ACULAR® ACULAR LS® ACUVAIL® BROMDAY® BROMFENAC® PROLENSA®
Ophthalmics for Dry Eye Disease		
ARTIFICIAL TEARS RESTASIS®		CEQUA® RESTASIS® MULTIDOSE XIIDRA®
Otic Agents		
Otic Anti-infectives		
Otic Quinolones		
CIPRODEX® CIPRO HC® OTIC SUSP OFLOXACIN		CIPROFLOXACIN SOL 0.2% CETRAXAL® OTIPRIO® OTOVEL® SOLN
Psychotropic Agents		
ADHD Agents		
ADDERALL XR® AMPHETAMINE SALT COMBO IR ATOMOXETINE CONCERTA® DAYTRANA®	PA required for entire class	ADDERALL® ADHANSIA® XR ADZENYS® AMPHETAMINE ER SUSP

Preferred Products	PA Criteria	Non-Preferred Products
DESOXYN® DEXMETHYLPHENIDATE DEXTROAMPHETAMINE SA TAB DEXTROAMPHETAMINE TAB FOCALIN XR® GUANFACINE ER JORNAY PM® METADATE CD® METHYLIN® METHYLPHENIDATE METHYLPHENIDATE ER (All forms generic extended release) METHYLPHENIDATE SOL QELBREE® RITALIN LA® STRATTERA® VYVANSE®	Children's Form: Form FA-69 Adult Form: Form FA-68	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 MYDAYIS® PROCENTRA® QUILLICHEW® QUILLIVANT® XR SUSP RELEXXII® RITALIN® ZENZEDI®
Antidepressants		
Other		
BUPROPION BUPROPION SR BUPROPION XL DULOXETINE MIRTAZAPINE MIRTAZAPINE RAPID TABS PRISTIQ® TRAZODONE VENLAFAXINE (ALL FORMS)	PA required for members under 18 years old *No PA required if ICD-10 - M79.1; M60.0-M60.9, M61.1.*	APLENZIN® BRINTELLIX® (Discontinued) CYMBALTA® DESVENLAFAXINE FUMARATE EFFEXOR® (ALL FORMS) FETZIMA® FORFIVO XL® KHEDEZLA® TRINTELLIX® VIIBRYD® WELLBUTRIN®
Selective Serotonin Reuptake Inhibitors (SSRIs)		
CITALOPRAM ESCITALOPRAM FLUOXETINE	PA required for members under 18 years old	CELEXA® FLUVOXAMINE QL LEXAPRO®

Preferred Products	PA Criteria	Non-Preferred Products
PAROXETINE PEXEVA® SERTRALINE		LUVOX® PAROXETINE ER PAXIL® PROZAC® SARAFEM® ZOLOFT®
Antipsychotics		
Atypical Antipsychotics – Oral/Topical		
ARIPIPRAZOLE CLOZAPINE FANAPT® INVEGA® LATUDA® NUPLAZID®* OLANZAPINE QUETIAPINE QUETIAPINE XR REXULTI® RISPERIDONE SAPHRIS® VRAYLAR® ZIPRASIDONE	 PA required for Ages under 18 years old PA Forms: Form FA-70A (ages 0-5) Form FA-70B (ages 6-18) *(No PA required Parkinson's related psychosis ICD code on claim)	ABILIFY® ABILIFY MYCITE ® ASENAPINE CAPLYTA® CLOZARIL® FAZACLO® GEODON® PALIPERIDONE RISPERDAL® SECUADO® SEROQUEL® SEROQUEL XR® ZYPREXA®
Atypical Antipsychotics – Long Acting Injectable		
ABILIFY® MAINTENA ARISTADA® ARISTADA® INITIO 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®

Preferred Products	PA Criteria	Non-Preferred Products
		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® OLOPATADINE		ASTEPRO® PATANASE®
Respiratory Anti-inflammatory Agents		
Leukotriene Receptor Antagonists		
MONTELUKAST ZAFIRLUKAST ZYFLO® ZYFLO CR®		ACCOLATE® SINGULAIR® ZILEUTON ER
Nasal Corticosteroids		
FLUTICASONE TRIAMCINOLONE ACETONIDE		BECONASE AQ® FLONASE® FLUNISOLIDE NASACORT AQ® NASONEX® OMNARIS® QNASL® RHINOCORT AQUA® VERAMYST® XHANCE™ ZETONNA®
Phosphodiesterase Type 4 Inhibitors		
DALIRESP® QL	PA required	
Long-acting/Maintenance Therapy		
ADVAIR® DISKUS ADVAIR HFA® ANORO ELLIPTA® BREO ELLIPTA® BUDESONIDE NEBS*		AEROSPAN HFA® AIRDUO® ALVESCO® ARCAPTA NEOHALER® ARMONAIR®

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

Meeting Minutes

Silver State Scripts Board

Meeting Minutes

Date of Meeting: Thursday, December 9, 2021, at 1:00 PM

Name of Organization: The State of Nevada, Department of Health and Human Services, Division of Health Care Financing and Policy (DHCFP), Silver State Scripts Board.

Agenda Item	Record	Notes
Closed Executive Session		
Financial Review of Drug Classes with Proposed Changes	Chairman Decerbo called the meeting to order at 1:00 PM on December 9, 2021. Roll was taken by Chairman Decerbo. Decerbo, Mark, Pharm.D. – Chair: Present ☒ Absent ☐ Adashek, Joseph, MD: Present ☐ Absent ☒ Crumby, Mark, Pharm.D.: Present ☒ Absent ☐ Hautekeet, Mike, R.Ph: Present ☒ Absent ☐ Khurana, Sapandeep, MD: Present ☒ Absent ☐ Passalacqua, Brian, MD: Present ☐ Absent ☒ Singh, Aditi, MD: Present ☒ Absent ☐ Ward, Kate, Pharm.D.: Present ☒ Absent ☐ A quorum was present.	**The DHCFP Staff Present were as follows:** Olsen, David, Social Services Chief III Gudino, Antonio, Social Services Program Specialist III Flowers, Ellen, Program Officer I Lither, Gabriel, Senior Deputy Attorney General (SDAG) **Gainwell Technologies Staff Present were as follows**: Leid, Jovanna, Pharm.D.

Agenda Item	Record	Notes
	Chairman Decerbo directed Kevin Whittington to proceed with the financial review of drug classes with proposed changes up for review during the fourth Quarter Silver State Scripts Board meeting. Mr. Whittington reminded the board members that the financial material presented is confidential and should not be discussed or disclosed outside of this closed session of the Silver States Scripts Board meeting. Mr. Whittington presented the financial review of the Cardiovascular Agents - Miscellaneous Cardiac Agents noting the products with proposed changes in PDL status. Mr. Whittington presented the financial review of the Electrolytic and Renal Agents – Potassium Removing Agents noting the products with proposed changes in PDL status. Mr. Whittington presented the financial review of the Neurological Agents – Movement Disorders class noting the products with proposed changes in PDL status. Mr. Whittington presented the financial review of the Genitourinary Agents – Bladder Antispasmodics class noting the products with proposed changes in PDL status. Mr. Whittington presented the financial review of the Hormones and Hormone Modifiers – Anti-Hypoglycemic Agents noting the products with proposed changes in PDL status. Mr. Whittington presented the financial review of the Neurological Agents – Anti-Migraine Agents – CGRP Receptor Antagonists class noting the products with proposed changes in PDL status. Mr. Whittington presented the financial review of the Ophthalmic Agents – Ophthalmic for Dry Eye Disease class, noting the products with proposed changes in PDL status.	**OptumRx Staff Present were as follows:** Whittington, Kevin, R.Ph. LeCheminant, Jill, Pharm.D. Chien, Michael, Pharm.D. Piccirilli, Annette Medina, Daniel

Agenda Item	Record	Notes
	Mr. Whittington presented the financial review of the Psychotropic Agents - Atypical Antipsychotics, Injectable class noting the products with proposed changes in PDL status. Mr. Whittington presented the financial review of the Psychotropic Agents - Atypical Antipsychotics, Oral/Topical class, noting the products with proposed changes in PDL status. Mr. Whittington presented the financial review of the Toxicology Agents - Opiate Antagonists noting the products with proposed changes in PDL status. Mr. Whittington presented the financial review of the Analgesics - Analgesic/Miscellaneous - Neuropathic Pain/Fibromyalgia Agents noting the products with proposed changes in PDL status. Mr. Whittington presented the financial review of the Cardiovascular Agents - Antihypertensive Agents - Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors), noting the products with proposed changes in PDL status. Mr. Whittington presented the financial review of the Hormones and Hormone Modifiers - Antidiabetic Agents - Incretin Mimetics noting the products with proposed changes in PDL status.	
Open Public Meeting		
1. Call to Order and Roll Call	Chairman Decerbo called the meeting to order at 1:50 PM on December 9, 2021. Roll was taken by Chairman Decerbo. Decerbo, Mark, Pharm.D. – Chair: Present ☒ Absent ☐ Adashek, Joseph, MD: Present ☐ Absent ☒ Crumby, Mark, Pharm.D.: Present ☒ Absent ☐ Hautekeet, Mike, R.Ph: Present ☒ Absent ☐ Khurana, Sapandeep, MD: Present ☒ Absent ☐	**The DHCFP Staff Present were as follows:** Olsen, David, Social Services Chief III Gudino, Antonio, Social Services Program Specialist III Flowers, Ellen, Program Officer I Lither, Gabriel, SDAG

Agenda Item	Record	Notes
	Passalacqua, Brian, MD ☐ ☒ Singh, Aditi, MD ☒ ☐ Ward, Kate, Pharm.D. ☒ ☐ A quorum was present.	**Gainwell Technologies 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. Chien, Michael, Pharm.D. Piccirilli, Annette Medina, Daniel **The public attendee list is included as Attachment A.** **Note**: Participants may not have chosen to reveal their identity. The accuracy of the attendee list is not assured.
2. Public Comment on Any Matter on the Agenda.	Telephonic and web comment was called for, and the phone lines were opened. Comment was provided by Ms. Robin Reedy from the mental health advocacy group National Alliance on Mental Illness (NAMI). Ms. Reedy noted that NAMI supports open access to all mental health agents by qualified health care professionals. She commented that they believe prescribers should be permitted to choose the most appropriate agent without prior authorization (PA) as it can worsen outcomes in patients. Comment was provided by Dr. Brian Wensel from Sanovi Pharmaceuticals. He requested Kynmobi be reviewed at the next Board meeting as it was not	

Agenda Item	Record	Notes
	included in this meeting for review. Chairman Decerbo commented that he would request OptumRx to include this in the next review.	
3. Administrative		
a. For Possible Action: Review and Approve Meeting Minutes from September 23, 2021.	No corrections were offered. 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).	Referenced web addresses: The Nevada Department of Health and Human Services, Division of Health Care Financing and Policy Provider Portal https://www.medicaid.nv.gov The Division of Health Care Financing and Policy http://dhcfp.nv.gov
4. Proposed New Drug Classes		
a. For Possible Action: Discussion and possible adoption of Cardiovascular Agents - Miscellaneous Cardiac Agents		
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened. Comment was made by Dr. Melissa Sommers with Novartis to discuss Entresto. She commented that pediatric patients were not included in the PA criteria during the Drug Utilization Review (DUR) Board meeting. Dr. Jill LeCheminant noted that the age limit would be updated in the PA criteria to meet the indication.	

Agenda Item		Record	
ii.	Drug class review presentation by OptumRx.	Dr. LeCheminant discussed the products within the drug class, including Entresto, Corlanor, and Verquvo. She provided indications for each agent. Dr. LeCheminant mentioned that Entresto and Corlanor are already managed via prior authorization. She noted that the criteria for Verquvo would be presented to the DUR Board. 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 noted that while these agents are not necessarily therapeutically equivalent, the class is miscellaneous cardiac agents, and it is helpful to have them grouped together. Chairman Decerbo asked Mr. Whittington to speak regarding the financial implications of separating the class. Mr. Whittington commented from a financial standpoint, separating the agents in the class would not impact the financials. Chairman Decerbo stated he did not have an issue with voting them as equivalent to keep them in one group. Board Member Ward commented that if in the future other agents are added to the class that is not used to treat heart failure, it may confuse as the agents would not treat the same disease state. Chairman Decerbo suggested renaming the class to Miscellaneous Heart Failure Agents. Chairman Decerbo moved to accept the class as clinically and therapeutically equivalent with a class name update to Miscellaneous Heart Failure Agents. Board Member Khurana seconded the motion. A vote was held: Yes ☒ No ☐ Abst. ☐ Decerbo, Mark, Pharm.D. – Chair Crumby, Mark, Pharm.D. Hautekeet, Mike, R.Ph	

Agenda Item	Record				Notes
	Khurana, Sapandeep, MD	☒	☐	☐	
	Singh, Aditi, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended adding Corlanor and Entresto as preferred and Verquvo as non-preferred.				
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Board Member Ward moved to accept the proposed changes. Board Member Khurana seconded the motion. A vote was held:				
		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Singh, Aditi, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
b. For Possible Action: Discussion and possible adoption of Electrolytic and Renal Agents – Potassium Removing Agents					
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened. No public comment was offered.				

Agenda Item		Record	Notes
ii.	Drug class review presentation by OptumRx.	Dr. LeCheminant cited that in this new class Lokelma, sodium polystyrene sulfonate, SPS, and Veltassa would be reviewed. She provided their clinical indications and the limitations of SPS. 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 list is clinically and therapeutically equivalent. Board Member Crumby seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Singh, Aditi, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
iv.	Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended the Board add Lokelma, sodium polystyrene sulfonate, and SPS as preferred. She recommended the Board add Veltassa as non-preferred.	
v.	Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Chairman Decerbo moved to accept the proposed updates as presented. Board Member Singh seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐	

Agenda Item	Record				Notes
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Singh, Aditi, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
c. For Possible Action: Discussion and possible adoption of Neurological Agents – Movement Disorders					
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened. Comment was provided by Ms. Reedy from the mental health advocacy group NAMI. She noted that NAMI supports open access to all mental health agents, including agents utilized to manage medication side effects such as tardive dyskinesia. She advocated for open access for agents that would prevent side effect issues. Comment was provided by Dr. Jennifer Shear from Teva Pharmaceuticals Medical Affairs. She wanted to clarify the boxed warning with Austedo and noted it was for patients with Huntington's Disease and not tardive dyskinesia. Comment was provided by Dr. Ed Paiewonsky from Neurocrine Biosciences. He made himself available for questions. Dr. LeCheminant notified the Board that a letter was provided for review requesting Ingrezza have preferred status.				
ii. Drug class review presentation by OptumRx.	Dr. LeCheminant discussed Austedo, Ingrezza, and tetrabenazine that would be added to this new class. She provided indications, actions, and dosing for the agents. Dr. LeCheminant noted that Ingrezza and Austedo already had prior authorization criteria placed from the DUR Board.				

<table>
<tr><th colspan="2">Agenda Item</th><th>Record</th><th>Notes</th></tr>
<tr><td colspan="2"></td><td>Dr. LeCheminant recommended the Board consider the class clinically and therapeutically equivalent.</td><td></td></tr>
<tr><td>iii.</td><td>Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.</td><td>Chairman Decerbo moved to accept the class as clinically and therapeutically equivalent.

Board Member Crumby seconded the motion.

Board Member Khurana inquired about the prior authorization criteria associated with Ingrezza and Austedo. Dr. LeCheminant displayed the criteria. Board Member Khurana asked how this Board might address the DUR Board if there are questions regarding the established criteria. He noted his concerns with delays in therapy regarding the criteria in place. Dr. LeCheminant noted that the criteria had not been reviewed since January of 2018 and stated she could bring the criteria back to the DUR Board for review and potential updating. Chairman Decerbo inquired how Board Member Khurana could relay his specific changes to the DUR Board. Mr. Gabriel Lither commented that Board Member Khurana could reach out directly to the DUR Board to provide thoughts as a prescriber providing feedback. Board Member Khurana noted that this Board has historically provided recommendations to the DUR Board. Mr. Lither stated that the Board can make a recommendation to the Board but may be difficult to relay to the Board depending on the number of changes recommended.

A vote was held:

<table>
<tr><th></th><th>Yes</th><th>No</th><th>Abst.</th></tr>
<tr><td>Decerbo, Mark, Pharm.D. – Chair</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Crumby, Mark, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Hautekeet, Mike, R.Ph</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Khurana, Sapandeep, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Singh, Aditi, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Ward, Kate, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
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Agenda Item		Record	Notes
		Board Member Khurana made a motion to provide recommendations to the DUR Board to allow access to these agents with appropriate FDA-approved diagnosis(es). Chairman Decerbo seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair ☒ Yes ☐ No ☐ Abst. Crumby, Mark, Pharm.D. ☒ Yes ☐ No ☐ Abst. Hautekeet, Mike, R.Ph ☒ Yes ☐ No ☐ Abst. Khurana, Sapandeep, MD ☒ Yes ☐ No ☐ Abst. Singh, Aditi, MD ☒ Yes ☐ No ☐ Abst. Ward, Kate, Pharm.D. ☒ Yes ☐ No ☐ Abst.	
iv.	Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended Ingrezza, Austedo, and tetrabenazine be added to the PDL as preferred and Xenazine be added as non-preferred.	
v.	Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Chairman Decerbo moved to accept the recommendation. Board Member Ward seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair ☒ Yes ☐ No ☐ Abst. Crumby, Mark, Pharm.D. ☒ Yes ☐ No ☐ Abst. Hautekeet, Mike, R.Ph ☒ Yes ☐ No ☐ Abst. Khurana, Sapandeep, MD ☒ Yes ☐ No ☐ Abst. Singh, Aditi, MD ☒ Yes ☐ No ☐ Abst. Ward, Kate, Pharm.D. ☒ Yes ☐ No ☐ Abst.	

Agenda Item	Record	Notes
5. Established Drug Classes Being Reviewed Due to the Release of New Drugs		
a. For Possible Action: Discussion and possible adoption of Genitourinary Agents - Bladder Antispasmodics		
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened.	
ii. Drug class review presentation by OptumRx.	Dr. LeCheminant discussed indications, treatment recommendations, and 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 Ward seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Singh, Aditi, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended adding Gemtesa as non-preferred and moving Detrol and Detrol LA to preferred status.	

Agenda Item	Record	Notes
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 Khurana seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: ☒ Yes ☐ No ☐ Abst. Crumby, Mark, Pharm.D.: ☒ Yes ☐ No ☐ Abst. Hautekeet, Mike, R.Ph: ☒ Yes ☐ No ☐ Abst. Khurana, Sapandeep, MD: ☒ Yes ☐ No ☐ Abst. Singh, Aditi, MD: ☒ Yes ☐ No ☐ Abst. Ward, Kate, Pharm.D.: ☒ Yes ☐ No ☐ Abst.	
b. For Possible Action: Discussion and possible adoption of Hormones and Hormone Modifiers - Anti-Hypoglycemic Agents		
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened. Comment was provided by Dr. Emily Smith from Zealand Pharma for Zegalogue. Dr. Smith made herself available for questions as Zegalogue is a new agent. Comment was provided by Dr. Lisa Renda from Eli Lilly for Baqsimi. She asked for any questions regarding Baqsimi. No questions were asked.	
ii. Drug class review presentation by OptumRx.	Dr. LeCheminant discussed Glucagen and Zegalogue. She noted indications, class overview, and routes of administration. Dr. LeCheminant recommended the Board consider the class clinically and therapeutically equivalent.	

Agenda Item	Record	Notes
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Chairman Decerbo moved to accept the class as clinically and therapeutically equivalent. Board Member Crumby seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Singh, Aditi, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended adding Zegalogue and Glucagen to preferred, moving Baqsimi to preferred, and moving Glucagon emergency kit to non-preferred.	
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Chairman Decerbo moved to accept the recommendation. Board Member Hautekeet seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Singh, Aditi, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
c. For Possible Action: Discussion and possible		

Agenda Item	Record	Notes
adoption of Neurological Agents - Anti-Migraine Agents - CGRP Receptor Antagonists		
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened. Public comment was provided by Dr. Renda from Eli Lilly supporting Emgality. She asked for any questions regarding the agent. None were asked at this time.	
ii. Drug class review presentation by OptumRx.	Dr. LeCheminant discussed indications, dosing, and efficacy of Qulipta. She noted that all agents in this class require prior authorization and that criteria for Qulipta would be presented to the DUR Board in January. Dr. LeCheminant recommended the Board consider the class clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Chairman Decerbo moved to accept the class as clinically and therapeutically equivalent. Board Member Crumby seconded the motion. A vote was held: Yes / No / Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Singh, Aditi, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
iv. Presentation of recommendations for	Dr. LeCheminant recommended Qulipta be added as preferred.	

Agenda Item	Record	Notes
PDL inclusion by OptumRx.		
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Chairman Decerbo noted that quantity limits would be presented to the DUR Board in January, which should help control utilization. Board member Ward motioned to accept the changes as presented. Board Member Khurana seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Singh, Aditi, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
d. For Possible Action: Discussion and possible adoption of Ophthalmic Agents - Ophthalmic for Dry Eye Disease		
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened. Comment was provided by Dr. Sommers from Novartis regarding Xiidra. She requested Xiidra be moved to preferred. She discussed the pathogenesis of dry eye disease and the mechanism of action of Xiidra. Dr. Sommers discussed Xiidra's side effect profile.	
ii. Drug class review presentation by OptumRx.	Dr. LeCheminant discussed Eysuvis. She noted the indication, dosing, and recommendations.	

Agenda Item	Record	Notes
	Dr. LeCheminant recommended the Board consider the class clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Chairman Decerbo moved to accept the class as clinically and therapeutically equivalent. Board Member Khurana seconded the motion. A vote was held: Yes / No / Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Singh, Aditi, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended adding Eysuvis to non-preferred.	
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Chairman Decerbo noted that he would consider adding Xiidra to preferred given utilization and pricing. Chairman Decerbo moved to accept the recommendation with the additional movement of Xiidra to preferred. Board Member Hautekeet seconded the motion. A vote was held: Yes / No / Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐	

Agenda Item	Record				Notes
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Singh, Aditi, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
e. For Possible Action: Discussion and possible adoption of Psychotropic Agents - Atypical Antipsychotics- Long Acting Injectable					
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened. Comment was provided by Ms. Reedy from the mental health advocacy group NAMI. She discussed the familial impact when patients cannot maintain therapy on antipsychotics. She noted NAMI's support for all agents to be preferred and that NAMI continues to recommend open access.				
ii. Drug class review presentation by OptumRx.	Dr. LeCheminant discussed Invega Hafyera. She provided indication, dosing, and administration. She noted the noninferiority to Invega Trinza. 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. Board Member Khurana inquired about the prior authorization for the use of Trinza prior to Hafyera. Chairman Decerbo noted package insert indications. A vote was held:				

Agenda Item	Record				Notes
		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Singh, Aditi, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended adding Invega Hafyera to preferred.				
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Board Member Ward moved to accept the recommendation. Board Member Crumby seconded the motion. A vote was held:				
		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Singh, Aditi, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
f. For Possible Action: Discussion and possible adoption of Psychotropic Agents - Atypical Antipsychotics - Oral/Topical					
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened. Dr. LeCheminant noted letters submitted in public comment.				

Agenda Item	Record	Notes
	Comment was provided by Dr. Phillip Rich, a psychiatrist from Reno with 41 years of experience. Dr. Rich discussed his utilization of Caplyta and the risk of weight gain with other agents. He requested Caplyta be moved to preferred. Comment was provided by Dr. Kenneth Berry from Alkermes to discuss Lybalvi. He noted indications, warnings, dosing, adverse events, and clinical efficacy data. He requested Lybalvi be moved to preferred. Comment was provided by Dr. Robert Lynn regarding the use of Caplyta. He noted that he has never been paid to use or speak for Caplyta. Due to drug interactions, once-daily dosing, and titration, he finds it useful in his patient population. Dr. Lynn requested Caplyta to be moved to preferred. Comment was provided by Dr. Jazmin Acosta from Intracellular Therapies for Caplyta. She provided clinical, safety, and tolerability of Caplyta.	
ii. Drug class review presentation by OptumRx.	Dr. LeCheminant discussed Lybalvi indications and clinical trial efficacy data. She noted Lybalvi's weight gain compared to olanzapine. She provided a summary of adverse events for the antipsychotic agents in this class. Dr. LeCheminant noted that the preferred agents do not require prior authorization unless the member is under 18 years of age. Non-preferred agents only require the failure of one preferred agent to receive. Six months of coverage of a non-preferred agent is permitted for those patients discharged from inpatient services to ensure time for stabilization with outpatient services. Dr. LeCheminant recommended the Board consider the class clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to approve clinical/therapeutic	Chairman Decerbo moved to accept the class as clinically and therapeutically equivalent. Board Member Ward seconded the motion.	

<table>
<tr><th colspan="2">Agenda Item</th><th>Record</th><th>Notes</th></tr>
<tr><td></td><td>equivalency of agents in class.</td><td>A vote was held:

<table>
<tr><th></th><th>Yes</th><th>No</th><th>Abst.</th></tr>
<tr><td>Decerbo, Mark, Pharm.D. – Chair</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Crumby, Mark, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Hautekeet, Mike, R.Ph</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Khurana, Sapandeep, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Singh, Aditi, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Ward, Kate, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
</table></td><td></td></tr>
<tr><td>iv.</td><td>Presentation of recommendations for PDL inclusion by OptumRx.</td><td>Dr. LeCheminant recommended adding Lybalvi to non-preferred, moving Geodon to preferred, and moving ziprasidone to non-preferred.</td><td></td></tr>
<tr><td>v.</td><td>Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.</td><td>Board Member Khurana discussed that no agent on the preferred side has a similar combination to Lybalvi. He noted that he supports being cost-effective while providing ample preferred agents.

Chairman Decerbo noted he appreciates that only one preferred agent is required for non-preferred utilization.

Chairman Decerbo moved to accept the recommendation.

Board Member Hautekeet seconded the motion.

A vote was held:

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

Agenda Item	Record	Notes
	Ward, Kate, Pharm.D. ☒ ☐ ☐ Board Member Khurana moved to move Lybalvi and Caplyta to preferred. Chairman Decerbo seconded the motion. Board Member Khurana noted his concerns regarding side effect profiles. Board Member Ward inquired if these would be agents that would be utilized first-line. Board Member Khurana stated that he would utilize these agents first-line as appropriate. Board Member Ward asked if prior authorization criteria from the DUR Board would control the utilization of these preferred products. Board Member Khurana noted that it would be a rational approach, but not necessarily something he would want to have in place. Mr. Lither inquired if prior authorization was required for these agents or not. Dr. LeCheminant noted that the non-preferred agents do have a medical justification component. Board Member Khurana commented that real-life processing does not occur in this fashion. A vote was held: Yes / No / Abst. Decerbo, Mark, Pharm.D. – Chair ☐ ☒ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☐ ☒ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Singh, Aditi, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
g. For Possible Action: Discussion and possible		

Agenda Item	Record	Notes
adoption of Toxicology Agents – Antidotes- Opiate Antagonists		
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 Kloxxado and provided an overview of dosing, formulations, and frequency. She noted Zimhi would be reviewed for placement at a future SSSB meeting. Dr. LeCheminant recommended the Board consider the class clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Chairperson Decerbo moved to accept the class as clinically and therapeutically equivalent. Board Member Khurana seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair ☒ Yes ☐ No ☐ Abst. Crumby, Mark, Pharm.D. ☒ Yes ☐ No ☐ Abst. Hautekeet, Mike, R.Ph ☒ Yes ☐ No ☐ Abst. Khurana, Sapandeep, MD ☒ Yes ☐ No ☐ Abst. Singh, Aditi, MD ☒ Yes ☐ No ☐ Abst. Ward, Kate, Pharm.D. ☒ Yes ☐ No ☐ Abst.	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended adding Kloxxado to preferred.	
v. Discussion by Board and action by Board	Chairman Decerbo moved to accept the recommendation.	

Agenda Item	Record	Notes
for approval of drugs for inclusion on the PDL.	Board Member Ward seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Singh, Aditi, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
6. Established Drug Classes Being Reviewed Due to the Release of New Generics		
a. For Possible Action: Discussion and possible adoption of Analgesics - Analgesic Miscellaneous - Neuropathic Pain/ Fibromyalgia Agents		
i. Public comment.	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 generic availability. Dr. LeCheminant recommended the Board consider the class clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to approve clinical/therapeutic	Chairman Decerbo moved to accept the class as clinically and therapeutically equivalent. Board Member Ward seconded the motion.	

Agenda Item	Record	Notes
equivalency of agents in class.	A vote was held: Decerbo, Mark, Pharm.D. – Chair ☒ Yes ☐ No ☐ Abst. Crumby, Mark, Pharm.D. ☒ Yes ☐ No ☐ Abst. Hautekeet, Mike, R.Ph ☒ Yes ☐ No ☐ Abst. Khurana, Sapandeep, MD ☒ Yes ☐ No ☐ Abst. Singh, Aditi, MD ☒ Yes ☐ No ☐ Abst. Ward, Kate, Pharm.D. ☒ Yes ☐ No ☐ Abst.	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended moving Lidoderm to preferred and pregabalin and pregabalin ER to non-preferred.	
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Chairman Decerbo moved to accept the recommendation. Board Member Ward seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair ☒ Yes ☐ No ☐ Abst. Crumby, Mark, Pharm.D. ☒ Yes ☐ No ☐ Abst. Hautekeet, Mike, R.Ph ☒ Yes ☐ No ☐ Abst. Khurana, Sapandeep, MD ☒ Yes ☐ No ☐ Abst. Singh, Aditi, MD ☒ Yes ☐ No ☐ Abst. Ward, Kate, Pharm.D. ☒ Yes ☐ No ☐ Abst.	
5. Established Drug Classes Being Reviewed Due to the Release of New Drugs		
b. For Possible Action: Discussion and possible adoption of Cardiovascular		

Agenda Item	Record	Notes
Agents – Antihypertensive Agents – Angiotensin-Converting Enzyme Inhibitors (ACE Inhibitors)		
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened. No public comment was offered.	
ii. Drug class review presentation by OptumRx.	Dr. LeCheminant discussed current generic availability within this drug class. Dr. LeCheminant recommended the Board consider the class clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Chairman Decerbo moved to accept the class as clinically and therapeutically equivalent. Board Member Ward seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Singh, Aditi, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended adding enalapril solution to non-preferred.	
v. Discussion by Board and action by Board for approval of drugs	Chairperson Decerbo moved to accept the recommendation. Board Member Crumby seconded the motion.	

Agenda Item	Record	Notes
for inclusion on the PDL.	A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Singh, Aditi, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
7. Established Drug Classes		
a. For Possible Action: Discussion and possible adoption of Hormone and Hormone Modifiers – Antidiabetic Agents – Incretin Mimetics Agents.		
i. Public comment.	Telephonic and web comment was called for, and the phone lines were opened. Comment was provided by Dr. Jonathan Delgado with Novo Nordisk asked for questions regarding Ozempic and Rybelsus. No questions were asked. Comment was provided by Dr. Renda with Eli Lilly asked for questions regarding Trulicity. No questions were asked.	
ii. Drug class review presentation by OptumRx.	Dr. LeCheminant discussed indications and current generic availability within this drug class. Dr. LeCheminant recommended the Board consider the class clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to approve	Chairperson Decerbo moved to accept the class as clinically and therapeutically equivalent.	

Agenda Item	Record	Notes
clinical/therapeutic equivalency of agents in class.	Board Member Ward seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair ☒ Yes ☐ No ☐ Abst. Crumby, Mark, Pharm.D. ☒ Yes ☐ No ☐ Abst. Hautekeet, Mike, R.Ph ☒ Yes ☐ No ☐ Abst. Khurana, Sapandeep, MD ☒ Yes ☐ No ☐ Abst. Singh, Aditi, MD ☒ Yes ☐ No ☐ Abst. Ward, Kate, Pharm.D. ☒ Yes ☐ No ☐ Abst.	
iv. Presentation of recommendations for PDL inclusion by OptumRx.	Dr. LeCheminant recommended moving Trulicity to preferred.	
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL.	Board Member Hautekeet moved to accept the recommendation. Board Member Singh seconded the motion. A vote was held: Decerbo, Mark, Pharm.D. – Chair ☒ Yes ☐ No ☐ Abst. Crumby, Mark, Pharm.D. ☒ Yes ☐ No ☐ Abst. Hautekeet, Mike, R.Ph ☒ Yes ☐ No ☐ Abst. Khurana, Sapandeep, MD ☒ Yes ☐ No ☐ Abst. Singh, Aditi, MD ☒ Yes ☐ No ☐ Abst. Ward, Kate, Pharm.D. ☒ Yes ☐ No ☐ Abst.	
8. OptumRx Reports: New Drugs to Market and New Line Extensions	Dr. LeCheminant reviewed tezepelumab, a new drug indicated for the treatment of severe asthma. Dr. LeCheminant reviewed levoketoconazole for the treatment of Cushing's syndrome. She reviewed antiretroviral agents cabotegravir, indicated for PrEP, and lenacapavir, indicated for the treatment of multidrug-resistant HIV-1 infection.	

Agenda Item	Record	Notes
9. Closing Discussion		
a. Public comments on any subject.	Telephonic and web comment was called for, and the phone lines were opened. No public comment was offered.	
b. Date and location of the next meeting.	Chairman Decerbo confirmed the next meeting is scheduled for March 24, 2022, and will be at the JW Marriott.	The meeting location has been moved to: Hampton Inn Tropicana. 4975 S. Dean Martin Dr. Las Vegas, Nevada, 89118
c. Adjournment.	Chairman Decerbo adjourned the meeting at 3:54 PM.	

Attachment A – Members of the Public in Attendance

Acosta, Jazmin, Intracellular Therapies
Alegria, Veronica, DHCFP
Ashton, Elisa, Johnson & Johnson
Belz, Jeanette, Belcase
Beranek, Thomas, Centene
Berry, Kenneth, Alkermes
Bitton, Ryan, HPN
Breen, A
Capen, Maribeth, WellPoint
Carter, Morgan, Artia Solutions
Colabianchi, Jeana, Sunovion
Cooper, Christa
Cummings, Sarah, Dungarvin
De Rosa, Regina, WellPoint
Delap, Terry, GSPNV
Delgado, Jonathan, Novo Nordisk
Diebes, Tressa, Takeda
Droese, Ben, Amgen
Duerre, Mark, Intercellular Therapies
Germain, Joe, Biogen
Gorzynski, Andy
Groppenbacher, Shannon, Johnson & Johnson
Grothe, Deron, Teva Pharma
Hartman, Nena, Neurocrine
Hawkins, Tina, Magellan
Horne, Dr. Robert
Kerr, Camille, Regeneron
Large, David
Leroue, Chelsea, Biohaven Pharma
Levin, Dr. Amy, WellPoint
Lim, Luke, WellPoint
Lovan, Charlie, AbbVie
Nguyen, Bao, Johnson & Johnson
Oliver, Carmen, Biohaven Pharma
Ou, Karen, Gilead
Paiewonsky, Ed, Neurocrine Biosciences
Pearce, Robert
Powell, Natasha, WellPoint
Reedy, Robin
Renda, Lisa, Lily
Rich, Dr. Phillip
Ritter, Jean
Roa, Ryan, Merck
Roy, Melissa
Shear, Jennifer, Teva Pharma
Smith, Emily, Zealand Pharma
Smith, Jason, Gilead
Sommers, Melissa, Novartis
Sullivan, Mike, Amgen
Thompson, La'Kendrick, Dungarvin
Walter, Lindsey, Novartis
Wensel, Brian, Sunovion
Willie, Brad, Neurocrine Biosciences
Yang, Rochelle, Teva Pharma
Zarob, Michael, Alkermes

Attendees with no last name available:
Amy
BN

Attachment B – Submitted Written Comment

- 11.29 Caplyta Dr Stoll
- 12.08 Nurtec Lisa Hammargen
- 12.09 Rachel Gardner Nurtec
- 1805_001
- caplyta letter
- caplyta letter of support to nevada medicaid committee, nov 2021
- Caplyta letter
- CCF_000282
- Dr. Paul Nguyen- Caplyta
- Dr. Sullivan
- Scan Dec 7, 2021
- SSSB_Public_Comment_Caplyta_Malinas
- SSSB_Public_Comment_Ingrezza_Malinas

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

Therapeutic Class Overview
Acne Agents

INTRODUCTION

- Acne vulgaris is a chronic inflammatory dermatosis characterized by open and/or closed comedones (blackheads and whiteheads) and inflammatory lesions including papules, pustules, or nodules (*Zaenglein et al 2016*). Four primary pathogenic factors interact in a complex manner to produce the different acne lesions. The four factors include sebum production by the sebaceous gland, Propionibacterium acnes (*P. acnes*) follicular colonization, alteration in the keratinization process, and the release of inflammatory mediators to the skin (*Thiboutot et al 2009*).
- Several options exist for the treatment of acne vulgaris including topical agents, systemic antibacterial agents, hormonal agents, isotretinoin, laser and light therapies, miscellaneous therapies, complementary and alternative therapies, and dietary restrictions. Topical therapy of acne vulgaris includes agents that are available over the counter or by prescription, and choice of therapy can be influenced by various factors including patient age, site of involvement, extent and severity of disease, and patient preference. Topical agents include antibiotics, benzoyl peroxide, retinoids, azelaic acid, dapsone, salicylic acid, and clascoterone, a topical androgen inhibitor approved by the Food and Drug Administration (FDA) in August 2020. (*Gollnick et al 2016, Zaenglein et al 2016, FDA summary [Winlevi] 2020*).
- Traditionally, the treatment of acne vulgaris has been directed toward controlling *P. acnes* and centered on the use of antibiotics. Current treatment modalities are directed toward as many pathogenic factors as possible. Combination treatment has the ability to target multiple pathogenic factors, including inflammatory and noninflammatory lesions (*Eichenfield et al 2013, Thiboutot et al 2009*). Data have shown that combination therapy results in faster and more complete clearing of acne vulgaris lesions compared with monotherapy (*Eichenfield et al 2013, Nast et al 2016, Thiboutot et al 2009*). Combination therapy should be used in the majority of patients with acne (*Gollnick et al 2016, Zaenglein et al 2016*). Additionally, antibiotics and benzoyl peroxide both target *P. acnes*; however, unlike antibiotics, benzoyl peroxide has not been associated with the development of bacterial resistance (*Zaenglein et al 2016*). The exact mechanism of clascoterone is unknown; the postulated mechanism is competition against dihydrotestosterone for binding to androgen receptors within the sebaceous gland and hair follicles (*Winlevi prescribing information 2020*, *Cassiopea press release 2019*).
- Topical retinoids are recommended as monotherapy in primarily mild, comedonal acne, or in combination with topical or oral antibiotics in patients with mixed or primarily inflammatory moderate acne vulgaris (*Gollnick et al 2016, Zaenglein et al 2016*). The comedolytic and anti-comedogenic properties associated with topical retinoids result in a reduction in the formation of microcomedones and comedones (*Zaenglein et al 2016*). For severe acne, oral antibiotics with topical therapy or oral isotretinoin is recommended for first-line treatment (*Zaenglein et al 2016*, *Zaenglein et al 2018*). Oral isotretinoin is one of several alternatives for treatment-resistant moderate acne. Clascoterone was primarily studied in patients with moderate to severe acne (*Hebert et al 2020*).
- The focus of this review will be the use of the topical agents and oral isotretinoin for the treatment of acne. Agents prescribed solely for rosacea and products combining hyaluronate, niacinamide, cholestryramine, aluminum oxide, or resorcinol will not be included in this review. The following table may not be all inclusive as products enter and leave the market frequently in this class.
- Medispan Class: Acne Products

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Antibiotics	
Aczone (dapsone) gel 5%, 7.5%	✔
Cleocin-T (clindamycin) lotion 1%	✔
Clindacin-P, Clindacin ETZ (clindamycin) swab 1%	✔
Clindacin Pac, Clindacin ETZ (clindamycin and cleanser kit) swab 1%	✔
Clindagel (clindamycin) gel 1%	✔
clindamycin solution 1%	✔

Drug	Generic Availability
Clindavix (clindamycin/dimethicone/zinc oxide) solution 1/1.8/2%	-
Evoclin (clindamycin) foam 1%	✔
NuCaraClinPAK (clindamycin and moisturizer kit) gel 1%	✔
Ery (erythromycin) pads 2%	-
Erygel (erythromycin) gel 2%	✔
erythromycin solution 2%	✔
Amzeeq (minocycline) topical foam 4%	-
Benzoyl Peroxide and Combinations	
benzoyl peroxide bar 10%; cream 2.5%, 10%; creamy wash 4%; cleanser ER 4.4%; external liquid 2.5%, 3.5%, 4%, 4.4%, 5%, 5.5%, 6%, 7%, 10%; external solution 5.5%; foaming cream 4%; foam 5.3%, 5.5%, 9.5%, 10%; gel 2.5%, 4%, 5%, 6.5%, 8%, 10%; foaming cloths 6%; lotion 5%, 8%, 10%	✔ †
Benzac AC (benzoyl peroxide) external liquid 5%	-
BenzePrO (benzoyl peroxide) foam 5.2%, 9.7%; external liquid 6.9%, 6.8%; foaming cloths 5.8%, 6%	-
PR (benzoyl peroxide) external liquid 6.9%	-
BenzePrO, BP, PR (benzoyl peroxide) external liquid 7%	-
Enzoclear, BenzePrO (benzoyl peroxide) foam 9.8%	-
Zaclir (benzoyl peroxide) lotion 8%	-
Vanoxide-HC (benzoyl peroxide/hydrocortisone) lotion 5/0.5%	✔
benzoyl peroxide/hydrocortisone lotion 7.5/1%	✔
Inova kit (benzoyl peroxide/vitamin E) pad/topical 4/5%, 8/5%	-
Inova 4/1, 8/2 kit (benzoyl peroxide/salicylic acid/vitamin E) pad/pad/topical 4/1/5%, 8/2/5%	-
Benzoyl Peroxide – Antibiotic Combinations	
Acanya (benzoyl peroxide/clindamycin) gel 2.5/1.2%	✔
BenzaClin (benzoyl peroxide/clindamycin) gel 5/1%	✔
Neuac (benzoyl peroxide/clindamycin) gel, kit 5/1.2%	✔
NuCaraRxPAK (benzoyl peroxide/clindamycin) kit 2.5/1%	✔
Onexton (benzoyl peroxide/clindamycin) gel 3.75/1.2%	-
Benzamycin (benzoyl peroxide/erythromycin) gel 5/3%	✔
Topical Retinoids – Single Entity	
adapalene external solution 0.1%, pad 0.1%	✔
Differin (adapalene) cream 0.1%; gel 0.1%†, 0.3%	✔
Differin (adapalene) lotion 0.1%	-
Arazlo (tazarotene) lotion 0.045%	-
Fabior (tazarotene) foam 0.1%	✔
Tazorac (tazarotene) gel and cream 0.05%, gel 0.1%	-
Tazorac (tazarotene) cream 0.1%	✔
Altreno (tretinoin) lotion 0.05%	-
Atralin (tretinoin) gel 0.05%	✔
Avita (tretinoin) cream 0.025%	✔
Avita (tretinoin) gel 0.025%	-§
Retin-A (tretinoin) cream 0.025%, 0.05%, 0.1%; gel 0.01%, 0.025%	✔
Retin-A Micro (tretinoin microsphere) gel 0.04%, 0.1%	✔

Drug	Generic Availability
Retin-A Micro (tretinoin microsphere) gel 0.06%, 0.08%	-
Aklief (trifarotene) cream 0.005%	-
Topical Retinoids – Combination	
Epiduo (adapalene/benzoyl peroxide) gel 0.1/2.5%	✔
Epiduo Forte (adapalene/benzoyl peroxide) gel 0.3/2.5%	-
Adainzde (adapalene/benzoyl peroxide/clindamycin) gel 0.3/2.5/1%	-
Twyneo (tretinoin/benzoyl peroxide) cream 0.1/3%	-
Veltin, Ziana (clindamycin phosphate/tretinoin) gel 1.2/0.025%	✔
Miscellaneous Topical Therapies	
Azelex (azelaic acid) cream 20%	-
Sulfacetamide/Sulfur and Combinations	
sodium sulfacetamide cream 10% (Ovace Plus); gel 10%; lotion 9.8% (Ovace Plus), 10% (Klaron); shampoo 10% (Ovace Plus); wash external liquid 10% (Ovace); wash external gel 10% (Ovace Plus); foam 9.8% (Ovace Plus)	✔
sulfacetamide with sulfur wash 9/4%, 9/4.5% (Sumadan); with sulfur cleanser 9.8/4.8% (Plexion), 10/2% (Avar LS), 10/5% (Avar); with sulfur emulsion 10/1% (BP 10-1, Sulfamez); with sulfur in urea emulsion 10/4%, 10/5%; with sulfur suspension 8/4% (SulfaCleanse), 9/4.25% (Clenia Plus), 10/5%; with sulfur cream 9.8/4.8% (Plexion), 10/2% (Avar-e LS), 10/5% (Avar-e Emollient, Avar-e Green, SSS 10-5); with sulfur foam 10/5% (SSS 10-5); with sulfur lotion 9.8/4.8% (Plexion), 10/5%; with sulfur pad 10/4% (Sumaxin); with sulfur cloths 9.8/4.8% (Plexion)	✔ †
Sumadan kit wash 9/4.5%, Sumaxin CP kit pad 10/4%, (sulfacetamide sodium/sulfur/skin cleanser)	-
Sumadan XLT kit wash 9/4.5% (sulfacetamide sodium/sulfur/sunscreen)	-
sulfur external bar 3%, 10%; lotion 5%	✔ *
SAStid (sulfur/salicylic acid) external bar 3/5%	✔ *
Draxace (sulfacetamide sodium/salicylic acid) external suspension 8/2%; lotion cleanser 8/2%	-
Drixece (sulfacetamide sodium/salicylic acid) external suspension 10/5%	-
Oral Retinoids	
Absorica (isotretinoin) oral capsule 10 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg	✔
Absorica LD (isotretinoin) oral capsule 8 mg, 16 mg, 24 mg, 32 mg	-
Accutane, Amnesteem, Claravis, Myorisan, Zenatane (isotretinoin) oral capsule 10 mg, 20 mg, 30 mg, 40 mg	✔ ‡
Androgen Receptor Inhibitor	
Winlevi (clascoterone) cream 1%	-

Abbreviation: ER = extended-release
*Over-the-counter (OTC) only product(s)
†Prescription and/or OTC product(s)
‡Claravis is the reference standard and other products are branded generics considered bioequivalent to Claravis
§Avita 0.025% gel is BT rated, considered to be not therapeutically equivalent to other pharmaceutically equivalent products.

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications*

Drug	Acne vulgaris	Inflammatory acne vulgaris	Adjunctive therapy for acne vulgaris, acne rosacea, and seborrheic dermatitis	Treatment and prevention of mild to moderate acne vulgaris	Treatment of severe recalcitrant nodular acne
Antibiotics					
Aczone (dapsone)	✔	-	-	-	-
Clindamycin	✔ ‡	-	-	-	-
Erythromycin	✔	-	-	-	-
Amzeeq (minocycline)	✔	-	-	-	-
Benzoyl Peroxide – Single Entity					
Benzoyl peroxide	✔	-	-	✔	
Benzoyl Peroxide – Antibiotic Combinations					
Benzoyl peroxide/clindamycin	✔ (Acanya, Benzaclin, Onexton)	✔ (Neuac)	-	-	-
Benzoyl peroxide/ erythromycin	✔ (Benzamycin)	-	-	-	-
Benzoyl Peroxide – Other Combinations					
Vanoxide-HC (benzoyl peroxide/hydrocortisone)	✔	-	-	-	-
Topical Retinoids – Single Entity					
Differin (adapalene)	✔	-	-	-	-
Arazlo (tazarotene)	✔ §	-	-	-	-
Fabior, Tazorac (tazarotene)†	✔ § (0.1% Tazorac strengths only)	-	-	-	-
Tretinoin	✔	-	-	-	-
Aklief (trifarotene)	✔	-	-	-	-
Topical Retinoids – Combination					
Epiduo, Epiduo Forte (adapalene/benzoyl peroxide)	✔	-	-	-	-
Twyneo (tretinoin/benzoyl peroxide)	✔	-	-	-	-
Veltin, Ziana (tretinoin/ clindamycin)	✔	-	-	-	-
Miscellaneous Topical Therapies					
Azelex (azelaic acid)	-	✔	-	-	-
Sulfacetamide/Sulfur and Combinations					
Sulfacetamide	✔ (gel, lotion)	-	-	-	-
Sulfacetamide/sulfur	-	-	✔	-	-
Oral Retinoids					
Absorica, Absorica LD, Accutane, Amnesteem, Claravis, Myorisan, Zenatane (isotretinoin)	-	-	-	-	✔
Androgen Receptor Inhibitor					

Drug	Acne vulgaris	Inflammatory acne vulgaris	Adjunctive therapy for acne vulgaris, acne rosacea, and seborrheic dermatitis	Treatment and prevention of mild to moderate acne vulgaris	Treatment of severe recalcitrant nodular acne
Winlevi (clascoterone)	✔	-	-	-	-

Note: OTC only products are not listed
*Approved ages vary by product.
†Tazorac is also approved for the treatment of psoriasis.
‡ Clindamycin has been associated with severe colitis (including death), diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis). The indication for Clindavix recommends physicians should consider whether other agents are more appropriate.
§Fabior is indicated in children aged ≥ 12 years. Arazlo is indicated in children aged ≥ 9 years.

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

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

CLINICAL EFFICACY SUMMARY

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

Dapsone

- Dapsone was shown to be effective in the management of acne. In a clinical trial comparing dapsone 5% gel to the combination of dapsone plus adapalene, dapsone plus benzoyl peroxide, or dapsone plus moisturizer, all treatment arms showed similar efficacy in reducing inflammatory lesions over 12 weeks (*Fleischer et al 2010*).
- The approval of dapsone 7.5% gel was based on 2 randomized, double-blind (DB), vehicle-controlled, multicenter (MC) studies. A total of 4,340 patients were randomized to receive dapsone 7.5% gel or vehicle once daily for 12 weeks. The primary endpoint was the percentage of patients with none (score of 0) or minimal (score of 1) on the 5-point Global Acne Assessment Score (GAAS) scale at week 12. The key secondary endpoints were mean absolute change from baseline in both inflammatory and non-inflammatory lesion counts (*Eichenfield et al 2016, Stein et al 2016*).
  - The majority of the subjects had moderate acne vulgaris, ie, 20 to 50 inflammatory and 30 to 100 non-inflammatory lesions at baseline.
  - In both studies, the GAAS success rate was approximately 30% in the dapsone arm and 21% in the vehicle arm.
  - In Study 1, the mean percent reduction in inflammatory lesions was 55.5% in the dapsone group and 49% in the vehicle group. In Study 2, it was 53.8% and 47.3%, respectively.
  - For the mean percent reduction in non-inflammatory lesions, 44.4% was reported in the dapsone group and 38.4% in the vehicle group in Study 1. In Study 2, it was 45.9% in the dapsone group and 40.4% in the vehicle group.

Benzoyl Peroxide

- There is limited evidence that differentiates the various formulations (gels, lotions, solutions, etc.) and strengths of the benzoyl peroxide and antibiotic combination agents. Clinical studies evaluating combination therapy with benzoyl peroxide and either clindamycin or erythromycin have consistently demonstrated that these agents are more effective compared to their respective monotherapies (*Chalker et al 1983, Cunliffe et al 2002, Leyden et al 2001, Lookingbill et al 1997, Thiboutot et al 2008b, Webster et al 2009, Xu et al 2016*).

- In a study by Leyden et al (n = 492), patients with moderate to severe acne vulgaris were randomized to receive benzoyl peroxide/clindamycin, benzoyl peroxide/erythromycin, or benzoyl peroxide alone for 10 weeks. The decrease in the number of inflammatory lesions from baseline, the primary endpoint, was significantly greater for those treated with benzoyl peroxide/clindamycin compared to benzoyl peroxide alone (p = 0.04). The average decrease in the number of inflammatory lesions was similar in patients treated with benzoyl peroxide/clindamycin and benzoyl peroxide/erythromycin (p = 0.4) (*Leyden et al 2001*).
- In a meta-analysis by *Seidler et al,* there was a significantly greater percent reduction in noninflammatory acne lesion count with benzoyl peroxide/clindamycin 2.5%/1.2% (-43.4%; 95% confidence interval [CI] depicted but not reported) compared to benzoyl peroxide/clindamycin 5%/1% (-38.2%; 95% CI depicted but not reported), benzoyl peroxide alone (-34.2%; 95% CI depicted but not reported), clindamycin alone (-27.9%; 95% CI depicted but not reported) and placebo (-14.9%; 95% CI depicted but not reported) over 10 to 12 weeks of treatment (*Seidler et al 2011*).
- Three clinical trials comparing benzoyl peroxide/clindamycin to adapalene monotherapy have reported consistently that the combination of benzoyl peroxide/clindamycin significantly reduces total lesion count over 12 weeks compared to adapalene. The combination of benzoyl peroxide/clindamycin in two trials also significantly reduced inflammatory lesion counts compared to baseline at week 12 to a greater extent than adapalene (*Langner et al 2008, Ko et al 2009*). For non-inflammatory lesion count, there were conflicting results among the studies (*Guerra-Tapia et al 2012, Ko et al 2009, Langner et al 2008*).

Topical Retinoids

- Several comparative studies have been conducted evaluating the topical retinoids. Efficacy results are mixed, with trials demonstrating:
  - Equivalent efficacy between tretinoin 0.04% microgel and tretinoin 0.1% microgel (*Berger et al 2007*)
  - Equivalent efficacy between adapalene 0.1% gel and tretinoin 0.025% gel (*Cunliffe et al 1997, Ellis et al 1998, Grosshans et al 1998*)
  - Equivalent efficacy between adapalene 0.1% gel and tretinoin 0.1% microgel (*Nyirady et al 2001*)
  - Equivalent efficacy between adapalene 0.1% gel and tazarotene 0.1% cream (*Pariser et al 2008*)
  - Equivalent efficacy between adapalene 0.3% gel and tazarotene 0.1% gel (*Thiboutot et al 2008a*)
  - Greater efficacy with tazarotene 0.1% plus clindamycin 1% gel over adapalene 0.1% plus clindamycin 1% gel (*Maiti et al 2017*).
  - Greater efficacy with tazarotene 0.1% cream over adapalene 0.3% gel (*Tanghetti et al 2010*)
  - Greater efficacy with tazarotene 0.1% cream over adapalene 0.1% cream (*Shalita et al 2005*)
  - Greater efficacy with tretinoin 0.05% gel over adapalene 0.1% gel (*Pierard-Franchimont et al 1999*)
  - Greater efficacy with adapalene 0.1% gel over tretinoin 0.025% gel (*Cunliffe et al 1997, Shalita et al 1996*)
- Two studies (n = 820 for each study) demonstrated that tretinoin 0.05% lotion was more effective than a vehicle in improving Evaluator's Global Severity Score (EGSS) and reducing the number of inflammatory and non-inflammatory facial lesions at week 12 in patients aged ≥ 9 years (all p < 0.001). Success rates were 9.6% higher in Study 1 and 7.3% higher in Study 2 compared to the vehicle (*Tyring et al 2018*).
- Two studies (n = 1614 total) found that tazarotene 0.045% lotion significantly improved EGSS and the number of inflammatory and non-inflammatory lesions compared to vehicle in patients aged ≥ 9 years with moderate to severe acne. Success rates were 12.3% to 12.5% higher compared to vehicle in Study 1 and 2, respectively (*Arazlo prescribing information 2021*).
- Two randomized studies (n = 2420 total) found that patients aged ≥ 9 years with moderate acne experienced greater improvement in Investigator's Global Assessment (IGA) of the face and the number of inflammatory and non-inflammatory lesions (all p < 0.001) with trifarotene 0.005% cream compared to vehicle (*Tan et al 2019*).
- A meta-analysis of 5 MC, investigator-blinded, randomized controlled trials (RCTs) compared the efficacy of adapalene 0.1% gel to tretinoin 0.025% gel in the treatment of patients with acne vulgaris (n = 900). Overall, adapalene demonstrated equivalent efficacy to tretinoin in terms of reducing inflammatory lesions (p = 0.51), non-inflammatory lesions (p = 0.38), and total lesion count (p = 0.48) at week 12, but demonstrated more rapid efficacy in reducing inflammatory and total lesions at week 1 compared to tretinoin (p < 0.05) (*Cunliffe et al 1998*).
- A systematic review of 54 clinical trials compared the efficacy and safety/tolerability of the topical retinoids for the treatment of acne vulgaris:

  - Of 5 studies that compared use of adapalene to tazarotene, 4 found no difference in the percent change of the total lesion count between the two treatments. One study, which combined both adapalene and tazarotene with clindamycin, found a significant change in lesion count with tazarotene plus clindamycin (17.54 vs 11.03; p = 0.007).
  - In one study comparing adapalene 0.3%, 0.1% to tretinoin 0.05%, a significantly greater reduction in total lesion count was found with tretinoin at week 12 (76.7% tretinoin vs 66.4% adapalene 0.3% vs 57.8% adapalene 0.1%; p < 0.001).
  - In a 12-week study of 40 patients, no difference in efficacy was found between tretinoin and tazarotene in the change in IGA, absolute change in inflammatory and noninflammatory lesion count, and total lesion count from baseline to week 12.
  - When comparing safety, 62% of patients receiving tretinoin 0.05% reported adverse effects (AE), compared to 19% and 40% with adapalene 0.1% and 0.3%, respectively. Treatment with tazarotene was associated with significantly more AE than treatment with adapalene (55.4 vs 24.4%; p < 0.0012) (*Kolli et al 2019*).
- A retrospective, investigator-blinded, vehicle-controlled, photographic assessment study was conducted to assess the efficacy of topical retinoids as monotherapy for the treatment of inflammatory acne. Five investigators rated pre- and post-treatment photographs of patients (n = 577) who had participated in 12- or 15-week, DB, RCTs of tazarotene 0.1% gel, adapalene 0.1% gel, tretinoin 0.1% microgel, tretinoin 0.025% gel, and tazarotene 0.1% cream (*Leyden et al 2005*).
  - Tazarotene, adapalene, and tretinoin were all superior to vehicle. Between-retinoid comparisons showed greater incidences of clinically significant improvements in overall acne severity in the tazarotene group compared with the groups receiving adapalene (p ≤ 0.001) or tretinoin (p ≤ 0.01).
- There are several limitations to these studies, including relatively small sample sizes (range, n = 25 to 323), short duration (typically 12 weeks), enrollment of patients with varying degrees of acne severity, and comparisons between different strengths and formulations of topical retinoids. In addition, most studies that showed greater efficacy data with adapalene were sponsored by Galderma, greater efficacy data with tretinoin were sponsored by Johnson and Johnson (Ortho Dermatologics), and greater efficacy data with tazarotene were sponsored by Allergan. Based on the varying efficacy results and study limitations, it is not clear whether one topical retinoid is more effective than another.
- Tazarotene foam led to greater decreases from baseline for all types of acne lesions compared to vehicle foam; direct comparisons to other forms of tazarotene and other therapies have not been completed (*Fabior prescribing information 2018, Feldman et al 2013*).
- For the combination products, several studies evaluated the effectiveness of the combination products compared to their individual components. The adapalene/benzoyl peroxide combination showed a statistically superior success rate compared to monotherapy with adapalene or benzoyl peroxide (*Gold et al 2009, Gollnick et al 2009, Pariser et al 2007, Thiboutot et al 2007*). In addition, the clindamycin/tretinoin combination had statistically significant superiority for all comparisons vs monotherapy with clindamycin or tretinoin (*Jarratt et al 2012, Leyden et al 2006, Schlessinger et al 2007*).
- Two multicenter, randomized, double-blind trials (n = 858) found that patients aged ≥ 9 years with moderate to severe acne vulgaris experienced greater IGA success and greater improvement in the number of inflammatory and non-inflammatory lesions with the tretinoin/benzoyl peroxide combination product compared to vehicle. Success rates were 25.7% and 11.6% higher compared to vehicle in Trial 1 and 2, respectively (*Twyneo prescribing information 2021*).
- A network meta-analysis of 40 trials (n = 18,089) compared various topical preparations for mild to moderate acne vulgaris. Compared to all comparators, benzoyl peroxide plus adapalene was ranked most effective, followed by benzoyl peroxide plus clindamycin, adapalene alone, tretinoin alone, benzoyl peroxide alone, clindamycin plus tretinoin, and clindamycin alone. Benzoyl peroxide plus adapalene was significantly more effective than all treatments except benzoyl peroxide plus clindamycin. Benzoyl peroxide plus clindamycin was significantly more effective than benzoyl peroxide or clindamycin alone. Those regimens which had lower discontinuation rates due to adverse events include clindamycin with lower odds of withdrawal, followed by clindamycin plus zinc, the vehicle, azelaic acid, clindamycin plus tretinoin, adapalene monotherapy, erythromycin plus zinc, tretinoin, clindamycin plus benzyl peroxide, benzyl peroxide monotherapy, erythromycin plus tretinoin, and then adapalene plus benzyl peroxide with the highest odds for discontinuation due to adverse events (*Stuart et al 2021*).

Oral retinoids

- A 2018 Cochrane review evaluated 31 RCTs of oral isotretinoin to assess its efficacy and safety for acne vulgaris. Included trials were comparisons to placebo, systemic antibiotics plus topical agents (combination therapy), or isotretinoin in various formulations or dose regimens. For the primary outcome of total inflammatory lesion count, oral isotretinoin did not produce a greater reduction in acne lesions compared to combination therapy after 20 to 24 weeks of

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

Androgen receptor inhibitor

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

Other products

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

CLINICAL GUIDELINES

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

- The 2013 recommendations from the American Acne and Rosacea Society (endorsed by the American Academy of Pediatrics) state that acne management of pediatric patients is similar to acne treatment in older adolescents and adults. For mild acne, benzoyl peroxide, a topical retinoid, or a combination of benzoyl peroxide with an antibiotic or retinoid is recommended. For moderate and severe acne, combination topical therapy with the possible addition of oral antibiotics may be considered. Oral isotretinoin may be considered for some patients with severe, refractory, and scarring acne (*Eichenfield et al 2013*).
- Androgen receptor inhibitors, like clascoterone, have yet to be incorporated into treatment guidelines.

SAFETY SUMMARY

- Oral isotretinoin carries a black box warning regarding its teratogenicity risk; therefore, its use is contraindicated in female patients who are or may become pregnant. If pregnancy does occur during treatment, the drug should be discontinued and the patient should be referred to a specialist in reproductive toxicity. The drug is available only through a restricted program call the iPLEDGE program, which requires enrollment by prescribers, patients, pharmacies, and distributors. The restricted program has very specific requirements regarding use of contraception if the drug is used in females with reproductive potential.
- Contraindications for the acne agents are primarily hypersensitivity to any component of the product. For clindamycin-containing products, clindamycin is contraindicated in patients with a history of regional enteritis, ulcerative colitis, antibiotic-associated colitis, or a hypersensitivity to lincomycin. Tazarotene (Arazlo, Fabior, Tazorac) is contraindicated in pregnant women.
- Warnings for antibiotics include the risk for superinfection and pseudomembranous colitis. Clindamycin has been associated with severe colitis (including death), diarrhea, bloody diarrhea, and colitis (including pseudomembranous colitis) have been reported with the use of topical and systemic formulations. Gels contain alcohol and may be flammable; use caution. Benzoyl peroxide-containing products may cause bleaching of fabric or hair; use care when applying. Retinoids and benzoyl peroxide-containing products may cause ultraviolet (UV) sensitivity; avoid exposure or limit exposure with sunscreen. Retinoids may cause local application site reactions such as erythema, scaling, and dryness especially for the first few weeks of use. Altreno and Atralin product labels recommend caution in patients with a fish allergy due to the potential for allergenicity to fish protein. Azelaic acid products may cause hypopigmentation, and can irritate the eyes and mucous membranes. Dapsone gel can cause methemoglobinemia resulting in hospitalization, particularly in patients with glucose-6 phosphate dehydrogenase deficiency or idiopathic methemoglobinemia.
- Warnings for oral isotretinoin include avoidance of micro-dosed progesterone preparations as contraception, risk of psychiatric disorders (depression, psychosis, suicidal behavior/thoughts), pseudotumor cerebri, Stevens-Johnson syndrome, acute pancreatitis, lipid abnormalities, hearing impairment, hepatotoxicity, inflammatory bowel disease, skeletal abnormalities, ocular abnormalities, and glucose and creatine phosphokinase abnormalities.
- Warnings for topical clascoterone include hypothalamic-pituitary-adrenal (HPA) axis suppression, greater susceptibility to systemic toxicity in pediatric patients, and hyperkalemia.
- Adverse events for topical acne agents are generally limited to local application site reactions including burning/stinging, erythema, scaling, and dryness.
- Common adverse reactions of oral isotretinoin include dryness in skin, lips, and eyes; arthralgia; headache; dermatitis; musculoskeletal discomfort; reduced visual acuity; and upper respiratory symptoms/infection.
- Avoid concurrent use of clindamycin with erythromycin due to possible antagonistic therapeutic effects based on *in vitro* data.
- In June 2014, the FDA warned that certain OTC topical acne products can cause rare but serious and potentially life-threatening allergic reactions or severe irritation. The hypersensitivity reactions may occur within minutes to a day or longer after product use.
  - The OTC topical acne products of concern are marketed under various brand names such as Proactiv, Neutrogena, MaxClarity, Oxy, Ambi, Aveeno, Clean & Clear, and as store brands. They are available as gels, lotions, face washes, solutions, cleansing pads, toners, face scrubs, and other products.
  - Based on the information reported to the FDA, it cannot be determined if the serious hypersensitivity reactions were triggered by the acne products' active ingredients, benzoyl peroxide or salicylic acid, the inactive ingredients, or by a combination of both. The FDA is continuing to monitor and evaluate this safety issue, and will work with manufacturers regarding any future label changes that would address the risk of severe hypersensitivity reactions. The hypersensitivity reactions may occur within minutes to a day or longer after product use. These serious hypersensitivity reactions differ from the local skin irritation that may occur at the product application site, such as

redness, burning, dryness, itching, peeling, or slight swelling, that are already included in the Drug Facts labels. (*Clinical Pharmacology 2021, FDA Drug Safety Communication 2014, Micromedex 2021*)

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Antibiotics				
Aczone (dapsone)	Gel	Topical	Apply once (7.5% dose) to twice daily (5% dose).	If no improvement in 12 weeks, treatment should be reassessed. The 7.5% gel is indicated in age ≥ 9 years. The 5% gel is indicated in age ≥ 12 years.
Clindagel, Cleocin T, Clindacin-P, Clindacin ETZ, Clindacin Pac, Evoclin, NuCaraClinPAK (clindamycin) Clindavix (clindamycin/ dimethicone/ zinc oxide)	Foam, gel, lotion, solution, swab, swab + cleanser kit, solution + skin protectant kit, gel kit	Topical	Foam and gel (Clindagel): Apply once daily. Gel (Cleocin T), lotion, solution, or swab: Apply twice daily. Solution (Clindavix): Apply twice daily.	If topical antibiotic therapy is longer than a few weeks, the addition of topical benzoyl peroxide is recommended.
Erygel, Ery (erythromycin)	Gel, pads, solution	Topical	Apply once to twice daily.	If no improvement after 6 to 8 weeks, or if the condition worsens, discontinue treatment. If topical antibiotic therapy is longer than a few weeks, the addition of topical benzoyl peroxide is recommended.
Amzeeq (minocycline)	Foam	Topical	Apply once daily.	Indicated in age ≥ 9 years.
Benzoyl Peroxide and Combinations				
Benzac AC, BenzePrO, BP, BPO, Enzoclear, PR, Riax, Zaclir (benzoyl peroxide)	Bar, cream, creamy wash, cleanser ER, external liquid, external solution, foaming cream, foam, gel, foaming cloths, lotion, wash + lotion kits	Topical	Cream, foam, gel, solution, lotion: Apply once daily. Foaming cloths, lotion, cleanser, bar, wash, liquid: Apply 1 to 3 times daily.	Improvement is usually noted in 3 to 4 weeks.
Vanoxide-HC (benzoyl peroxide/ hydrocortisone)	Lotion	Topical	Apply 1 to 3 times daily.	Product expires 3 months after dispensed.
Inova (benzoyl peroxide/ vitamin E)	Pad/topical kit	Topical	As directed.	
Inova 4/1, 8/2 kit (benzoyl peroxide/	Pad/pad/topical kit	Topical	As directed.	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
vitamin E/ ± salicylic acid)				
Benzoyl Peroxide – Antibiotic Combinations				
Acanya, Benzaclin, Neuac, NuCaraRxPAK, Onexton (benzoyl peroxide/clindamycin)	Gel, gel kit	Topical	Benzaclin: Apply twice daily. All other products: Apply once daily in the evening.	Indicated in age ≥ 12 years.
Benzamycin (benzoyl peroxide/erythromycin)	Gel	Topical	Apply twice daily.	Indicated in age ≥ 12 years.
Topical Retinoids – Single Entity				
Differin (adapalene)	Cream, gel, lotion, external solution, pad	Topical	Apply once daily in the evening.	Indicated in age ≥ 12 years.
Arazlo, Fabior, Tazorac (tazarotene)	Foam, gel, cream, lotion	Topical	Apply once daily in the evening.	Efficacy has not been established past 12 weeks. Fabior is indicated in age ≥ 12 years. Arazlo is indicated in age ≥ 9 years.
Altreno, Atralin, Avita, Retin-A, Retin-A Micro (tretinoin)	Lotion, cream, gel, microsphere gel	Topical	Apply once daily.	Altreno is indicated in age ≥ 9 years, Atralin is indicated in age ≥ 10 years, and all other products in age ≥ 12 years.
Aklief (trifarotene)	Cream	Topical	Apply once daily in the evening.	Indicated in age ≥ 9 years.
Topical Retinoids - Combination				
Epiduo, Epiduo Forte (adapalene/benzoyl peroxide)	Gel	Topical	Apply once daily.	Epiduo is indicated in age ≥ 9 years and Epiduo Forte in age ≥ 12 years.
Adainzde (adapalene/benzoyl peroxide/clindamycin)	Gel	Topical	Apply once daily.	
Twyneo (tretinoin/benzoyl peroxide)	Cream	Topical	Apply once daily.	Indicated in age ≥ 9 years.
Veltin, Ziana (clindamycin/tretinoin)	Gel	Topical	Apply once daily in the evening.	Indicated in age ≥ 12 years.
Miscellaneous Topical Therapies				
Azelex (azelaic acid)	Cream	Topical	Apply twice daily.	Indicated in age ≥ 12 years.
Sulfacetamide/Sulfur and Combinations				
Klaron, Ovace, Ovace Plus (sulfacetamide) Avar, Avar LS, Avar-e LS, Avar-e Emollient, Avar-e Green, BP 10-1, Clenia Plus, Plexion, SSS 10-5,	Monotherapy: Cream, foam, wash external gel, external liquid, gel, lotion, shampoo, wash With sulfur: cleanser, cloths, cream, emulsion,	Topical	Foam, cleanser cream, lotion, gel, bar, wash, kits: Apply 1 to 3 times daily.	Indicated in age ≥ 12 years.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
SulfaCleanse, Sulfamez, Sumadan, Sumadan XLT, Sumaxin, Sumaxin CP (sulfacetamide/sulfur)	foam, gel, lotion, pad, suspension, wash			
Sulfur SAStid (sulfur/salicylic acid)	Bar, lotion (sulfur only)	Topical	Apply 1 to 3 times daily.	
Draxace, Drixece (sulfacetamide sodium/salicylic acid)	External suspension, lotion cleanser	Topical	Apply as directed by physician	
Oral Retinoids				
Absorica, Absorica LD, Accutane, Amnesteem, Claravis, Myorisan, Zenatane (isotretinoin)	Capsule	Oral	Accutane, Amnesteem, Claravis, Myorisan, Zenatane: Twice daily with food. Absorica, Absorica LD: Twice daily with or without food.	Once daily dosing is not recommended. Duration of treatment: 15 to 20 weeks Pregnancy tests should be performed before prescribing, each month during therapy, and 1 month after discontinuation. Baseline lipids and liver function tests should be performed. Absorica and Absorica LD are indicated in age ≥ 12 years. The other oral isotretinoin products have not been studied in children < 12 years of age.
Androgen Receptor Inhibitor				
Winlevi (clascoterone)	Cream	Topical	Twice daily	Indicated in age ≥ 12 years.

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

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

CONCLUSION

- Current treatment of acne vulgaris is primarily topical agents. Guidelines suggest the use of combinations to treat acne (*Eichenfield et al 2013, Nast et al 2016, Thiboutot et al 2018, Zaenglein et al 2016*).
- Dapsone (Aczone), clindamycin, erythromycin, and minocycline (Amzeeq) are topical antibiotics for the treatment of acne vulgaris. Most agents have formulations available as generics (minocycline is brand-only). Antibiotics have a slow onset of action and may pose an increased risk for bacterial resistance. Antibiotics should be used in combination therapy if used for more than a few weeks (*Eichenfield et al 2013, Thiboutot et al 2009*).
- Topical benzoyl peroxide, available also as OTC, is often used for initial self-treatment of acne (*Medical Letter 2020*). Various dosage formulations and strengths are available. Benzoyl peroxide is used in combination with other topical

agents for acne. Excessive drying may occur with benzoyl peroxide use and may be observed as marked peeling, erythema, possible edema, and allergic contact sensitization. Additionally, benzoyl peroxide may bleach hair and/or fabric so care must be used to limit accidental exposure (*Lexi-comp 2021*). In 2014, the FDA warned that certain OTC topical acne products can cause rare but serious and potentially life-threatening allergic reactions or severe irritation. The hypersensitivity reactions may occur within minutes to a day or longer after product use. Based on the information reported to the FDA, it cannot be determined if the serious hypersensitivity reactions were triggered by the acne products' active ingredients, benzoyl peroxide or salicylic acid, the inactive ingredients, or by a combination of both (*FDA Drug Safety Communication 2014*).

- Topical retinoids, including adapalene (Differin), tazarotene (Arazlo, Fabior, Tazorac), tretinoin (Retin-A, Retin-A Micro, Altreno, Atralin, Avita), and Aklief (trifarotene) are effective in the treatment of acne vulgaris. Combinations of topical retinoids include adapalene/benzoyl peroxide (Epiduo, Epiduo Forte), adapalene/benzoyl peroxide/clindamycin (Adainzde), tretinoin/benzoyl peroxide (Twyneo), and clindamycin/tretinoin (Veltin, Ziana). In studies comparing the agents, no one agent was consistently more efficacious than another, and combination agents demonstrated greater efficacy when compared to monotherapy with their components. Guidelines do not recommend one retinoid over another (*Eichenfield et al 2013, Gollnick et al 2016, Thiboutot et al 2009, Zaenglein et al 2016*). A topical retinoid, alone or in combination with benzoyl peroxide and/or a topic antibiotic, is often used for first-line treatment of inflammatory and noninflammatory acne (*Medical Letter 2020*). Retinoid/antimicrobial combinations are more effective than either component alone, especially in patients with inflammatory acne. All topical retinoids normalize keratinization and appear to have anti-inflammatory effects.
- Most of the adverse reactions associated with retinoids are dermatological and may lessen with continued use. Retinoids cause increased sun sensitivity, and their use should be avoided with other agents that cause excessive drying. Differin gel is available as an OTC product.
- The topical benzoyl peroxide and antibiotic combination products include benzoyl peroxide/clindamycin (Acanya, Benzaclin, Neuac, NuCaraRxPAK, and Onexton) and benzoyl peroxide/erythromycin (Benzamycin). The benzoyl peroxide/clindamycin products primarily differ in their respective strengths. Acanya contains 2.5% benzoyl peroxide and 1.2% clindamycin, Benzaclin contains 5% benzoyl peroxide and 1% clindamycin, Neuac contains 5% benzoyl peroxide and 1.2% clindamycin, NuCaraRxPAK contains 2.5% benzoyl peroxide and 1% clindamycin, and Onexton contains 3.75% benzoyl peroxide and 1.2% clindamycin. The benzoyl peroxide and antibiotic combination agents are effective for the treatment of acne vulgaris. Combination treatment with benzoyl peroxide and either clindamycin or erythromycin has been shown to be more effective than treatment with each individual agent alone (*Lookingbill et al 1997, Webster et al 2009, Thiboutot et al 2008, Chalker et al 1983, Cunliffe et al 2002, Leyden et al 2001, Xu et al 2016*). Current clinical guidelines support the use of combination treatment in order to limit the development of bacterial resistance (*Eichenfield et al 2013, Gollnick et al 2016, Thiboutot et al 2009, Zaenglein et al 2016*).
- Oral isotretinoin is a recommended treatment option for severe nodular acne and treatment-resistant moderate acne. (*Eichenfield et al 2013, Gollnick et al 2016, Thiboutot et al 2018, Zaenglein et al 2016*). Isotretinoin has also been considered the most effective medication for treatment of inflammatory acne (*Medical Letter 2020*). Its efficacy was not found to be better than the combination of a systemic antibiotic with a topical agent (*Costa et al 2018*). It is available only through a restricted distribution program due to its teratogenic effects. If used in female patients, appropriate contraception is required. Additionally, the agent is associated with several other adverse events that require monitoring.
- Two other treatment options are sulfacetamide and azelaic acid (Azelex). Sulfacetamide is available in a variety of dosage forms and strengths and in combination with sulfur. Azelaic acid, a branded agent, is another topical treatment option for acne and is recommended by the guidelines for both mild acne as monotherapy and for moderate acne in combination with another class of topical acne agents (*Nast et al 2016, Gollnick et al 2016, Zaenglein et al 2016*).
- An androgen receptor inhibitor, clascoterone, is a newer treatment for acne with a unique mechanism of action. Phase 3 RCTs have demonstrated its superiority in efficacy over a vehicle cream (*Hebert et al 2020*). Common adverse events are application site reactions and nasal/respiratory symptoms (*Eichenfeld et al 2020, Hebert et al 2020, Winlevi prescribing information 2020*).

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INTRODUCTION

- Parkinson's disease (PD) is a neurodegenerative disorder caused by progressive dopamine depletion in the nigrostriatal pathway of the brain and characterized by the cardinal manifestations of tremor, bradykinesia, and rigidity. Although traditionally recognized as a motor disorder, PD is a complex multifactorial condition that also includes neuropsychiatric and other non-motor manifestations. Nearly 1 million people in the United States (US) have PD and an estimated 60,000 new cases are diagnosed annually *(Chou 2020, Jankovic 2020, Parkinson's Foundation 2018).*
  - Current treatment options for PD include levodopa, dopamine agonists (DAs) (eg, bromocriptine, pramipexole, ropinirole), monoamine oxidase (MAO)-B inhibitors, anticholinergic agents, amantadine, and catechol-O-methyl transferase (COMT) inhibitors. The dopamine precursor levodopa is the most effective drug for the symptomatic treatment of PD and is the first choice if symptoms, especially bradykinesia, become troublesome; however, levodopa-induced motor fluctuations develop within several years of starting therapy in a substantial number of patients *(Spindler et al 2021).*
  - DAs are commonly used as monotherapy in early PD, or in combination with other therapies in more advanced disease. DAs are ineffective in patients who show no response to levodopa, and while the DAs possibly delay the need to initiate levodopa therapy, their use is associated with adverse effects such as impulse control disorders. While PD symptoms can initially be controlled with DAs, few patients can be adequately maintained on monotherapy for more than a few years *(Spindler et al 2021).*
  - Amantadine is an N-methyl-D-aspartate (NMDA) receptor antagonist used for short-term monotherapy in mild PD. This drug has a low incidence of side effects compared to other therapies for early PD, but the treatment benefit may be transient. In advanced PD, it may be used to manage dyskinesia and motor fluctuations related to levodopa (*Spindler et al 2021*).
- Restless legs syndrome (RLS) is a neurological movement disorder characterized by an urge to move the legs, commonly in response to uncomfortable dysesthesia. Clinically important RLS affects around 2.5% of adults in the US and Northern Europe. There is higher prevalence in women and with increasing age *(Winkelman et al 2016).*
  - RLS is classified as primary or secondary in origin; secondary RLS may be attributed to comorbid iron deficiency, end-stage renal disease (ESRD), or pregnancy.
  - Consequences of RLS include impairment in sleep quantity and quality, mood and anxiety disorders, worsening of quality of life, and loss of work productivity.
  - Current guideline-recommended treatment options for RLS include DAs and gabapentin enacarbil.
- Tardive dyskinesia is an extrapyramidal side effect of long-term therapy with dopamine antagonists, particularly antipsychotics. The annual incidence of tardive dyskinesia is estimated to be 5 to 25% with first-generation antipsychotics; rates of tardive dyskinesia are thought to be lower with second-generation antipsychotics, but tardive dyskinesia has still been reported with these agents (*Deik 2020*).
  - Symptoms of tardive dyskinesia may include chorea, dystonia, akathisia, athetosis, and stereotyped behaviors (*Deik 2020*).
  - When tardive dyskinesia develops, common interventions include discontinuing the offending agent and switching from a first-generation antipsychotic to a second-generation antipsychotic, if applicable. Several agents have been studied for tardive dyskinesia treatment, but most produce only a slight to moderate benefit. Medications that have been studied include clonazepam, botulinum toxin, tetrabenazine, trihexyphenidyl, ginkgo biloba, and amantadine (*Liang et al 2021*).
- Pramipexole, ropinirole, and rotigotine are classified as non-ergot DAs; they have largely replaced ergot DAs (cabergoline, bromocriptine) in clinical use due to better safety and tolerability. Mirapex (pramipexole) tablets, Requip (ropinirole) tablets, and Neupro (rotigotine) transdermal patch are Food and Drug Administration (FDA)-approved for the treatment of PD and RLS. The pramipexole and ropinirole extended-release (ER) products are FDA-approved for PD.

- Rotigotine was originally approved in 2007 but was withdrawn from the US market in 2008 over concerns related to inconsistent absorption from the patch. Drug absorption issues were resolved by the manufacturer and a new formulation of rotigotine patch received FDA approval in 2012 *(Aurora et al 2012, Drugs@FDA 2021).*
- Apokyn (apomorphine) subcutaneous (SC) injection and Kynmobi (apomorphine) sublingual film are additional non-ergot DA approved for acute, intermittent hypomobility associated with PD.
- Horizant (gabapentin enacarbil) is indicated for moderate-to-severe primary RLS and for the management of postherpetic neuralgia in adults. Horizant will not be addressed in this class review but is included in the Neuropathic Pain and Fibromyalgia Therapeutic Class Overview.

- Amantadine is the only available anti-Parkinsonian NMDA antagonist. Amantadine immediate-release tablets, capsules, and oral solutions are FDA approved for PD, drug-induced extrapyramidal reactions, and influenza A prophylaxis and treatment. Gocovri (amantadine extended release [ER] capsule) is FDA approved for the treatment of dyskinesia in patients with PD receiving levodopa therapy, with or without concomitant dopaminergic medications. Osmolex ER (amantadine ER tablet) is FDA approved for PD and drug-induced extrapyramidal reactions.
- Levodopa and levodopa combinations are excluded from this review.
- Medispan class: Antiparkinson Dopaminergics - Nonergoline Dopamine Receptor Agonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
amantadine capsules	✔
amantadine tablets	✔
amantadine oral solution	✔
Apokyn (apomorphine) injection	-
Kynmobi (apomorphine) sublingual film	-
Cycloset (bromocriptine) tablets	-
Gocovri (amantadine) ER capsules	-
Mirapex (pramipexole) tablets	✔
Mirapex ER (pramipexole) extended-release tablets	✔
Neupro (rotigotine) transdermal patch	-
Osmolex ER (amantadine) ER tablets	-
Parlodel (bromocriptine) capsules	✔
Parlodel (bromocriptine) tablets	✔
Requip (ropinirole) tablets	✔
Requip XL (ropinirole) extended-release tablets	✔

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

INDICATIONS

Table 2. FDA-Approved Indications

Indication	amantadine	Gocovri (amantadine ER capsule)	Osmolex (amantadine ER tablet)	apomorphine	bromocriptine	Cycloset (bromocriptine tablet)	Kynmobi	pramipexole	pramipexole ER	ropinirole	Ropinirole ER	rotigotine
Acromegaly					✔							
Acute, intermittent treatment of hypomobility, "off" episodes ("end-of-dose wearing off" and unpredictable "on/off" episodes) associated with advanced PD				✔								

Indication	amantadine	Gocovri (amantadine ER capsule)	Osmolex (amantadine ER tablet)	apomorphine	bromocriptine	Cycloset (bromocriptine tablet)	Kynmobi	pramipexole	pramipexole ER	ropinirole	Ropinirole ER	rotigotine
Acute, intermittent treatment of "off" episodes in patients with PD.							✔					
Drug-induced extrapyramidal reactions	✔		✔									
Dyskinesia in patients with PD receiving levodopa-based therapy, with or without concomitant dopaminergic medications		✔										
Adjunctive treatment to levodopa/carbidopa in patients with PD experiencing "off" episodes		✔										
Hyperprolactinemia-associated dysfunctions					✔							
Moderate-to-severe primary RLS								✔		✔		✔
PD	✔		✔		✔			✔	✔	✔	✔	✔
Prophylaxis and treatment of uncomplicated influenza A virus illness	✔											
T2DM, as an adjunct to diet and exercise						✔						

Abbreviations: ER = extended release, PD = Parkinson's disease, RLS = restless leg syndrome, T2DM = type 2 diabetes mellitus

(*Prescribing information: Amantadine 2020, Apokyn 2020, Cycloset 2020, Gocovri 2021, Kynmobi 2020, Mirapex 2020, Mirapex ER 2020, Neupro 2020, Osmolex ER 2018, Parlodel 2019, Requip 2020, Requip XL 2017*)

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

CLINICAL EFFICACY SUMMARY

PD

- The efficacy of DAs for the symptomatic treatment of PD has been confirmed in meta-analyses of randomized controlled trials (RCTs) *(Baker et al 2009, Stowe et al 2008, Zhou et al 2014).*
  - A meta-analysis of 25 RCTs (N = 5185) in patients with early PD found that DAs were effective as monotherapy in PD symptom reduction based on the United Parkinson's Disease Rating Scale (UPDRS). When directly compared to levodopa as the initial therapy choice, DAs provided less symptom improvement than levodopa, but levodopa-treated patients were more likely to experience dyskinesias and wearing-off. Non-ergot DAs, when analyzed separately from ergot DAs, provided similar results. Overall, DA-treated patients experienced increased treatment discontinuation due to non-motor adverse effects *(Baker et al 2009).*
  - A Cochrane Review meta-analysis of 29 RCTs (N = 5247) in patients with early PD found that patients randomized to a DA were less likely to develop dyskinesias or motor fluctuations vs levodopa-treated patients; however, non-motor adverse effects such as edema, constipation, dizziness, hallucinations, and nausea were all increased in DA-treated patients. Additionally, symptomatic control of PD appeared to be better with levodopa, but data were reported inconsistently *(Stowe et al 2008).*
  - A meta-analysis of 9 RCTs (N = 2857) evaluated the efficacy of the long-acting DAs (rotigotine transdermal patch, pramipexole ER, and ropinirole ER) vs placebo in patients with PD. Patients treated with the long-acting DAs achieved greater reduction in symptoms, but with a higher incidence of adverse effects, especially in early PD patients *(Zhou et al 2014).*
- A Cochrane review meta-analysis of 3 RCTs (N = 482) in patients with PD who are receiving levodopa and suffering from motor complications compared bromocriptine and ropinirole as adjuvant therapies. Both agents demonstrated

similar outcomes for off-time reduction, dyskinesia as adverse event, motor impairment and disability, and dose reductions in levodopa (*Clarke et al 2001*).

- A Cochrane review including only 1 RCT (N = 163) concluded that the single trial lacked the necessary power to examine the comparative effectiveness between pramipexole and bromocriptine as adjuvant therapies in patients with PD who were receiving levodopa and suffering from motor complications. Compared with placebo, both agents improved off-time and reduced motor impairments and disability (*Clarke et al 2000*).
- In an evidence-based comparison of large, double-blind, RCTs of cabergoline, pramipexole, and ropinirole used as monotherapy in early PD, all agents were found similarly effective in reducing the risk of dyskinesia relative to levodopa. The risk reduction was slightly more evident for ropinirole and pramipexole. The mean change from baseline UPDRS score was comparable for pramipexole and ropinirole but was not evaluated for cabergoline. The proportion of withdrawals and AE profiles of the 3 agents were similar to each other, with the exception of edema, which was less in ropinirole-treated patients *(Inzelberg et al 2003)*.
- Transdermal rotigotine was compared to both pramipexole *(Poewe et al 2007)* and ropinirole *(Mizuno et al 2014)* in double-blind, RCTs in advanced stage PD. In the respective trials, rotigotine demonstrated noninferiority to pramipexole in the primary endpoint of change in absolute “off” time and noninferiority to ropinirole in the primary endpoint of change in UPDRS Part III (“on” state) from baseline. In both trials, rotigotine had a similar AE profile to the oral DAs, with the exception of higher rates of application site reactions.
- Several placebo-controlled RCTs have demonstrated the effectiveness of intermittent SC apomorphine for the treatment of “off” episodes in patients with advanced PD in whom conventional antiparkinson therapy had been optimized. Patients treated with apomorphine experienced improved mobility as measured by the UPDRS motor score 20 minutes after dosing. Patients previously unexposed to apomorphine were administered trimethobenzamide per labeled instructions to control nausea. Commonly reported adverse effects with apomorphine included yawning, nausea, dizziness, somnolence, and dyskinesias; most were considered mild to moderate in severity *(Apokyn prescribing information 2020, Dewey et al 2001, Pahwa et al 2007, Pfeiffer et al 2007).*
- A network meta-analysis of 21 studies evaluated the efficacy of ropinirole, rasagiline, rotigotine, entacapone, bromocriptine, apomorphine, pramipexole, sumanirole (not available in the US), and levodopa for PD treatment. In this study, apomorphine was found to be the most effective treatment for PD based on UPDRS III; it also had the highest efficacy for non-motor symptoms of PD (*Li et al 2018*).
- The efficacy of amantadine for treating dyskinesia in PD has been established in a meta-analysis of 11 RCTs (N = 356). Amantadine significantly improved UPDRS III, UPDRS IV, and Dyskinesia Rating Scale (DRS) scores compared to placebo (*Kong et al 2017*).
- The EASED and EASE LID studies support the efficacy of amantadine ER capsules (Gocovri) for the treatment of levodopa-induced dyskinesias in PD *(Pahwa et al 2017, Pahwa et al 2015)*. In the EASED study, amantadine ER capsules were superior to placebo in reduction of dyskinesia and increasing “on” time without troublesome dyskinesia (*Pahwa et al 2015)*. The EASE LID study found that amantadine ER capsules were superior to placebo for reducing Unified Dyskinesia Rating Scale (UDRS) scores and decreasing “off” time (*Pahwa et al 2017*).
- A pooled analysis of 2 identically designed Phase 3 studies (EASE LID and EASE LID 3) of amantadine ER capsules for dyskinesia in PD patients that were stable on 3 times a day levodopa therapy for at least 30 days (N=196) evaluated the change from baseline to 12 weeks in each patients UDRS scores. At 12 weeks the LS mean difference was -17.7 in the amantadine ER group (LS mean change in “off” time of 41.4%) vs -7.6 (LS mean change in “off” time of 13.9%) in the placebo group; demonstrating a percentage treatment difference of 27.3% (p < 0.0001) (*Elmer et al 2018).*
- A randomized, double-blind, placebo-controlled study evaluated apomorphine sublingual film (Kynmobi) in 109 patients with PD experiencing ≥ 2hours of “off” time per day, with predictable morning off periods, responsive to levodopa and on stable doses of PD medications. The primary endpoint was the in-clinic change from pre-dose to 30 min post-dose in the UPDRS motor score at 12 weeks. The change from pre-dose to 30 min post-dose in UPDRS motor score at week 12 was -11·1 (least mean square [SE], 1·46; 95% confidence interval [CI], -14·0 to -8·2) with apomorphine sublingual film and -3·5 (SE, 1·29; 95% CI, -6·1 to -0·9) with placebo (difference, -7·6; SE, 1·96; 95% CI, -11·5 to -3·7; p=0·0002). The most common side effects were oropharyngeal events (*Olanow et al 2020*).

RLS

- The efficacy of DAs for the treatment of RLS symptoms has been confirmed in meta-analyses and systematic reviews of RCTs *(Quilici et al 2008, Scholz et al 2011, Zintzaras et al 2010).*

- In a Cochrane Review of 38 RCTs (N = 7365) enrolling patients with moderate-to-severe RLS, the non-ergot DAs (lisuride [not currently approved in the US], pramipexole, rotigotine, and ropinirole) demonstrated superior efficacy vs placebo in improvement of the International RLS Severity Rating Scale (IRLS), decrease in periodic limb movements in sleep, and improved sleep efficiency. Compared to placebo, patients taking DAs experienced more adverse effects and were more likely to discontinue treatment *(Scholz et al 2011)*.
- A meta-analysis of 18 RCTs (N = 2848) in patients with RLS showed significant improvement in the IRLS with DAs (pramipexole, ropinirole, rotigotine, and cabergoline) vs placebo. The difference in IRLS score was statistically significantly better with pramipexole vs ropinirole; the difference between pramipexole and rotigotine was nonsignificant *(Zintzaras et al 2010)*.
- In a meta-analysis of 14 placebo controlled RCTs of pramipexole or ropinirole for RLS, superior efficacy was confirmed for both treatments' vs placebo based on improvement in the IRLS. An indirect comparison showed, with a probability of ≥ 95%, a superior reduction in the mean IRLS score and significantly lower rate of nausea, vomiting, and dizziness with pramipexole vs ropinirole. Head-to-head trials are needed to confirm these results *(Quilici et al 2008)*.

- A network meta-analysis of 35 studies examined the efficacy of DAs (pramipexole, ropinirole, and rotigotine), gabapentin enacarbil, and pregabalin in the treatment of RLS. All treatments were superior to placebo, but no difference in IRLS score reduction was seen between active treatments. Gabapentin enacarbil and rotigotine had the highest Clinical Global Impressions-Improvement (CGI-I) response rates among the studied treatments (*Iftikhar et al 2017*).

Drug-induced extrapyramidal reactions

- A Cochrane meta-analysis concluded that more studies are needed before amantadine, bromocriptine, or other therapies can be recommended for the treatment of antipsychotic-induced tardive dyskinesia (*El-Sayeh et al 2018*).
- One small crossover RCT (n=22) found that amantadine reduced Abnormal Involuntary Movements Scale (AIMS) scores in patients with drug-induced tardive dyskinesia, while placebo did not (*Pappa et al 2010)*.

CLINICAL GUIDELINES

PD

- The American Academy of Neurology (AAN) practice parameter on initiation of treatment for PD *(Miyasaki et al 2002)* recommends that in patients who require the initiation of dopaminergic treatment, levodopa or a DA may be used; the choice depends on the relative impact of improving motor disability (better with levodopa) compared with the lessening of motor complications (better with DAs).
  - Treatment of PD patients with cabergoline, ropinirole, and pramipexole results in fewer motor complications (wearing off, dyskinesias, "on/off" motor fluctuations) than levodopa, but is also associated with more frequent adverse events, including hallucinations, somnolence, and edema.
  - Amantadine is noted to have a modest effect on all features of PD with a mild adverse effect profile.

- **European Federation of Neurological Societies (EFNS) and Movement Disorders Society (MDS) - European Section (ES)** *(Oertel et al 2011a)*
  - This joint guideline outlines recommendations for treatment of late (complicated) PD, including treatment of motor complications and the nonmotor symptoms of PD. A summary of the treatment of motor complications is provided.
  - *Motor fluctuations: Wearing-"off" (end of dose akinesia, predictable "on"-"off")*
    - In the early phase, when motor fluctuations are just becoming apparent, adjustments in frequency of levodopa dosing during the day (4 to 6 daily doses) may attenuate wearing-"off".
    - COMT inhibitors or MAO-B inhibitors may be added: No recommendations can be made on which treatment should be chosen first. On average, all reduce "off" time by about 1 to 1.5 hours per day.
      - No difference has been demonstrated between entacapone and rasagiline. Tolcapone, although more effective than entacapone, is potentially hepatotoxic, and is only recommended in patients who have failed all other available medications.
      - Rasagiline should not be added to selegiline due to cardiovascular (CV) safety issues.
    - DAs may be added: efficacious in reducing "off" time in patients experiencing wearing-"off". Currently, no DA has proven better than another; switching from 1 DA to another can be helpful in some patients.
      - First line: Non-ergot DAs.
      - Second Line: Ergot DAs (association with lung, retroperitoneal, and heart valve fibrosis).
    - Standard levodopa can be switched to a CR formulation:
      - CR formulation of levodopa can improve wearing-"off".

- CR formulation of levodopa is useful for the treatment of night-time akinesia (nocturnal end-of-dose akinesia).
  - Amantadine or an anticholinergic may be added: In patients with disabling recurrent "off" symptoms that fail to improve further with the aforementioned strategies, the addition of an anticholinergic (in younger patients) or amantadine may improve symptoms in some cases.

- **The 2019 International Parkinson and Movement Disorder Society released an evidence-based review on treating the nonmotor symptoms of PD** (*Seppi et al 2019*). Pramipexole is clinically useful for treating depressive symptoms in PD, and rotigotine is possibly useful for treating sleep and wakefulness disorders in PD.

- **The 2018 International Parkinson and Movement Disorder Society released an evidence-based review on treating the motor symptoms of PD** (*Fox et al 2018*). Pramipexole, ropinirole, and rotigotine are DAs rated as clinically useful in patients requiring symptomatic therapy in early PD or requiring adjunct therapy to levodopa in early or stable PD. Bromocriptine and amantadine are listed as possibly useful in patients with early or stable PD requiring adjunct therapy to levodopa. Ropinirole ER is possibly useful in patients with early PD requiring symptomatic therapy. In patients with treated PD on optimized oral levodopa, pramipexole, ropinirole, rotigotine, apomorphine are clinically useful and bromocriptine and apomorphine are possibly useful for treating motor fluctuations. Amantadine is clinically useful for treating dyskinesia in patients with PD on optimized oral levodopa.

RLS

- In 2017, the International Parkinson and Movement Disorder Society updated the evidence-based review of treatment of RLS (*Winkelmann et al 2018*). The review considers ropinirole, rotigotine, pramipexole, and cabergoline to be efficacious for treating idiopathic RLS.
- In moderate-to-severe primary RLS, the AAN treatment guideline *(Winkelman et al 2016)* recommends clinicians consider prescribing medication to reduce RLS symptoms. Strong evidence supports pramipexole, rotigotine, cabergoline (rarely used due to cardiac valvulopathy risk), and gabapentin enacarbil use; moderate evidence supports ropinirole, pregabalin, and intravenous ferric carboxymaltose use. Few head-to-head comparisons exist to suggest agents preferentially.
- The American Academy of Sleep Medicine RLS practice parameter *(Aurora et al 2012)* recommends treatment of RLS with pramipexole or ropinirole, as the benefits clearly outweigh the harms. Gabapentin enacarbil or rotigotine can be utilized, but there is uncertainty in the balance between benefits and harms. Given the potential of side effects, including heart valve damage, cabergoline should only be used if other recommended agents have been tried first and failed. Other treatment options with low levels of evidence and unclear benefit/harm balance include gabapentin, pregabalin, carbamazepine, clonidine, and supplemental iron.

Drug-induced extrapyramidal reactions

- The AAN practice guideline on the treatment of tardive syndromes (*Bhidayasiri 2013*) recommends that amantadine may be considered for use with neuroleptics to treat tardive syndromes in the short term; however, the level of evidence for this recommendation is low. Other treatments that may be considered for treatment of tardive syndromes include tetrabenazine, clonazepam, and ginkgo biloba. Data are insufficient to support or refute the use of bromocriptine for the treatment of tardive syndromes.

SAFETY SUMMARY

Contraindications

- Concomitant use of apomorphine with 5HT3 antagonists, including antiemetics (ie, ondansetron, granisetron, dolasetron, palonosetron, alosetron).
- Hypersensitivity to sodium metabisulfite (in Kynmobi).
- Extended-release amantadine products (Gocovri and Osmolex ER) are contraindicated in patients with ESRD.
- Bromocriptine formulations (including Parlodel) are contraindicated in patients with uncontrolled hypertension.
- The bromocriptine brand formulation, Cycloset, is additionally contraindicated in patients with syncopal migraine, postpartum patients, and lactating patients.

Warnings and precautions

- All the non-ergot DAs have warnings for sudden onset of sleep and somnolence; syncope; hypotension, including orthostatic hypotension; hallucinations and psychotic-like behaviors; dyskinesia; and impulse control or compulsive behaviors.
- The rotigotine patch and apomorphine injection contain sodium metabisulfite that may cause allergic-type reactions in those with sulfite sensitivity.
- Application site reactions can occur with the rotigotine patch and may be severe.
- Apomorphine may cause coronary events, prolong QTc and cause torsades de pointes and sudden death. The injection is for SC use only; thrombus formation and pulmonary embolism have been observed following intravenous administration.
- Apomorphine sublingual film may cause nausea and vomiting, oral mucosal irritation, increase risk of falls, withdrawal emergent hyperpyrexia, or confusion.
- Based on animal data, the DAs may cause fetal harm and should only be used in pregnancy if the benefit justifies the potential risk to the fetus.
- Amantadine products have warnings for suicidal ideation; hallucinations and psychotic behavior; possible increased seizure activity in patients with a history of epilepsy; sudden onset of sleep and somnolence; withdrawal-emergent hyperpyrexia and confusion; and impulse control or compulsive behaviors.
- Extended-release amantadine products have additional warnings for dizziness and orthostatic hypotension. Concomitant use of alcohol is not recommended.
- Bromocriptine products have warnings for somnolence and sudden sleep onset; symptomatic hypotension, including orthostatic hypotension; impulse control or compulsive behaviors; and hallucinations and psychotic-like behaviors.
- When bromocriptine mesylate is being used to treat PD in patients who subsequently become pregnant, a decision should be made as to whether the therapy continues to be medically necessary or can be withdrawn. If it is continued, the drug should be withdrawn in those who may experience hypertensive disorders of pregnancy (including eclampsia, preeclampsia, or pregnancy-induced hypertension) unless withdrawal of bromocriptine mesylate is considered to be medically contraindicated.
- Bromocriptine should not be used during the postpartum period in women with a history of coronary artery disease and other severe cardiovascular conditions unless withdrawal is considered medically contraindicated. If the drug is used in the postpartum period, the patient should be observed with caution.
- Safety during long-term use of bromocriptine for more than 2 years at the doses required for PD has not been established.

Key adverse fffects

- All the non-ergot DAs may cause nausea, vomiting, drowsiness/somnolence, dizziness/hypotension, hallucinations, dyskinesia, and peripheral edema.
  - Apomorphine causes severe nausea and vomiting when administered at recommended doses; treatment with the concomitant antiemetic trimethobenzamide is recommended.
  - Apomorphine sublingual film may cause oral/pharyngeal soft tissue swelling or pain, and paresthesia.
  - Patients have reported postural deformities, including antecollis, camptocormia (Bent Spine Syndrome), and pleurothotonus (Pisa syndrome), after starting or increasing the dose of pramipexole. Postural deformity may occur several months after starting treatment or increasing the dose. Reducing the dose or discontinuation has been reported to improve postural deformity in some patients and should be considered if postural deformity occurs.
- Rotigotine may cause application site reactions and disturbances in initiating and maintaining sleep.
- Augmentation is an adverse effect related to long-term treatment of RLS with a dopaminergic medication and consists of iatrogenic worsening of RLS symptoms.
- Adverse reactions associated with amantadine include nausea, dizziness, insomnia, hallucination, depression, anxiety, dry mouth, peripheral edema, constipation, ataxia/falls, and orthostatic hypotension.
- Adverse reactions associated with bromocriptine use in PD include nausea, dyskinesia, hallucinations, confusion, “on-off” phenomenon, dizziness, drowsiness, faintness/fainting, vomiting, asthenia, abdominal discomfort, visual disturbance, ataxia, insomnia, depression, hypotension, shortness of breath, constipation, vertigo, dry mouth, peripheral edema, urinary frequency, incontinence, and retention, anxiety, blepharospasm, and dysphagia.

DOSING AND ADMINISTRATION

- Gradual dose titration during initiation and withdrawal of therapy is required with DAs. Titration schedules vary among products and indications.

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
amantadine	Tablet, capsule, oral solution	Oral	PD and influenza A prophylaxis and treatment: Once or twice daily Drug-induced extrapyramidal reactions: Twice daily	Dose adjustment required for renal impairment (CrCl <50 mL/min) and patients 65 years of age or older. Dose may need to be reduced for patients with heart failure, peripheral edema, or orthostatic hypotension. Use for influenza treatment/prophylaxis is not recommended due to high resistance rates (*CDC 2020*)
Apokyn (apomorphine)	Injection	SC	As needed	The first dose of apomorphine should be given under medical supervision; doses should be titrated to effect and tolerance and separated by at least 2 hours. Treatment with a concomitant antiemetic (eg, trimethobenzamide) is recommended, starting 3 days prior to the first dose of apomorphine. Treatment with trimethobenzamide should only be continued if necessary to control nausea and vomiting, and generally no longer than 2 months. The starting apomorphine dose should be reduced in patients with mild or moderate renal impairment; studies in patients with severe renal impairment have not been conducted.
Cycloset (bromocriptine)	Tablet	Oral	T2DM: Once daily within 2 hours after waking in the morning	Cycloset should be taken with food. The initial dose can be increased weekly by 1 tablet until maximal tolerated daily dose is achieved. Dose adjustments required during concomitant use of moderate CYP3A4 inhibitors. Avoid concomitant use with strong CYP3A4 inhibitors.
Gocovri (amantadine)	ER capsule	Oral	1 capsule once daily at bedtime for 1 week, then increase to 2 capsules daily at bedtime.	Do not crush or chew; capsules may be opened and sprinkled onto a teaspoonful of soft food (ie, applesauce). Avoid concomitant alcohol use.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Dose adjustment required for patients with moderate to severe renal impairment; contraindicated in patients with ESRD. Not interchangeable with other amantadine products
Kynmobi (apomorphine)	Sublingual film	Oral	As needed	10 to 30 mg per dose, separated by at least 2 hours. Treatment with a concomitant antiemetic (eg, trimethobenzamide) is recommended, beginning 3 days prior to initial dose.
Mirapex (pramipexole)	Tablet	Oral	PD: 3 times daily RLS: Once daily 2 to 3 hours before bedtime	Dosage reduction required in PD patients with renal impairment. In RLS patients with moderate and severe renal impairment, the duration between titration steps should be increased to 14 days.
Mirapex ER (pramipexole)	ER tablet	Oral	PD: Once daily	In patients with moderate renal impairment, pramipexole ER tablets should initially be taken every other day; pramipexole ER has not been studied in patients with severe renal impairment or patients on hemodialysis. Tablets must be swallowed whole and must not be chewed, crushed, or divided. Patients may be switched overnight from pramipexole IR tablets to ER tablets at the same daily dose.
Neupro (rotigotine)	Patch	TD	PD, RLS: Once daily	The patch should be applied once daily to a new site on the skin; the same site should not be used more than once every 14 days. Multiple patches may be used to achieve the prescribed dose.
Osmolex ER (amantadine)	ER tablet	Oral	PD, drug-induced extrapyramidal reactions: Once daily in the morning	Dose may be titrated in weekly intervals. When discontinuing the drug, reduce dose gradually for 1 to 2 weeks before discontinuation. Do not crush, chew, or divide tablets. Frequency of administration requires adjustment in patients with moderate to severe renal impairment; contraindicated in ESRD.
Parlodel (bromocriptine)	Tablets, capsules	Oral	Hyperprolactinemia-Associated Dysfunctions: Once daily Acromegaly: Once daily at bedtime	It is recommended that bromocriptine be taken with food. Patients should be evaluated frequently during dose escalation to determine the lowest dosage that produces a therapeutic response.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			PD: Twice daily	When being treated for acromegaly, patients should be reevaluated monthly and dosage adjusted based on reductions of growth hormone or clinical response.
Requip (ropinirole)	Tablet	Oral	PD: 3 times daily RLS: Once daily, 1 to 3 hours before bedtime	No dose adjustment is necessary in patients with moderate renal impairment; dosage adjustment required in patients with ESRD.
Requip XL (ropinirole)	ER tablet	Oral	PD: Once daily	In patients with ESRD on hemodialysis, dosage reduction is recommended. No dose adjustment necessary in patients with moderate renal impairment. Tablets must be swallowed whole and not be chewed, crushed, or divided. Patients may be switched directly from ropinirole IR to ropinirole ER with the initial switching dose approximately matching the total daily dose of ropinirole IR.

Abbreviations: CrCl = creatinine clearance; CYP3A4 = Cytochrome P450 3A4; ER = extended-release; ESRD = end-stage renal disease; IR = immediate release; PD = Parkinson's disease; RLS = Restless Legs Syndrome; SC = subcutaneous; TD = transdermal
See the current prescribing information for full details

CONCLUSION

- PD is a neurodegenerative disorder caused by progressive dopamine depletion in the brain and characterized by tremor, bradykinesia, and rigidity. Non-motor and neuropsychiatric symptoms also commonly occur. Current treatment options include levodopa, DAs, MAO-B inhibitors, anticholinergic agents, amantadine, and COMT inhibitors. DAs are commonly used as monotherapy in early PD, or in combination with other therapies in more advanced disease. While PD symptoms can initially be controlled with DAs, few patients can be adequately maintained on monotherapy for more than a few years before levodopa is needed. Amantadine is an NMDA receptor antagonist used for short-term monotherapy in mild PD. In advanced PD, it may be used to manage dyskinesia and motor fluctuations related to levodopa *(Chou 2020, Jankovic 2020, Spindler 2021).*
- RLS is a neurological movement disorder characterized by an urge to move the legs, commonly in response to uncomfortable dysesthesia. Consequences of RLS include impairment in sleep quantity and quality, mood and anxiety disorders, worsening of quality of life, and loss of work productivity. *(Winkelman et al 2016).*
- Tardive dyskinesia is an extrapyramidal side effect of long-term therapy with dopamine antagonists, particularly antipsychotics. Symptoms of tardive dyskinesia include chorea, dystonia, akathisia, athetosis, and stereotyped behaviors (*Deik 2020*). A number of agents have been studied for tardive dyskinesia treatment, but most produce only a slight to moderate benefit (*Liang 2021*). Treatments that may be considered according to current guidelines include clonazepam, tetrabenazine, amantadine, and gingko biloba (*Bhidayasiri 2013*).
- The non-ergot DAs Mirapex (pramipexole) tablets, Requip (ropinirole) tablets, and Neupro (rotigotine) transdermal patch are FDA-approved for the treatment of PD and RLS. The pramipexole and ropinirole ER products are FDA-approved for PD. Apokyn (apomorphine) is available as a SC injection for acute, intermittent hypomobility associated with advanced PD. Ergot DAs bromocriptine capsules and tablets (including brand name Parlodel) are FDA-approved for the treatment of PD, but are generally less preferred than non-ergot DAs due to adverse event profiles.
- Amantadine immediate-release tablets, capsules, and oral solutions are FDA approved for PD, drug-induced extrapyramidal reactions, and influenza A prophylaxis and treatment. Gocovri (amantadine ER capsule) is FDA approved for the treatment of dyskinesia in patients with PD receiving levodopa therapy, with or without concomitant

dopaminergic medications. Osmolex ER (amantadine ER tablet) is FDA approved for PD and drug-induced extrapyramidal reactions.

- The efficacy of DAs for the symptomatic treatment of PD has been confirmed in meta-analyses of RCTs. The DAs improved UPDRS motor scores vs placebo, but with increased incidence of adverse effects *(Baker et al 2009, Stowe et al 2008, Zhou et al 2014).*
- The efficacy of amantadine for treating dyskinesia in PD has been established in a meta-analysis of 11 RCTs (N = 356). Amantadine significantly improved UPDRS III, UPDRS IV, and Dyskinesia Rating Scale (DRS) scores compared to placebo (*Kong et al 2017*). The EASED and EASE LID studies support the efficacy of amantadine ER capsules (Gocovri) for the treatment of levodopa-induced dyskinesias in PD, showing reduction of dyskinesia and decreased "off" time vs placebo (*Pahwa et al 2017, Pahwa et al 2015)*.
- The efficacy of DAs for the treatment of moderate-to-severe RLS has been demonstrated in meta-analyses and systematic reviews of RCTs. DA-treated patients showed improvement in IRLS scores vs placebo *(Quilici et al 2008, Scholz et al 2011, Zintzaras et al 2010).*
  - Two meta-analyses suggest better efficacy with pramipexole vs ropinirole in RLS, although head-to-head trials are lacking *(Quilici et al 2008, Zintzaras et al 2010).*
- A Cochrane meta-analysis concluded that more studies are needed before amantadine or other therapies can be recommended for the treatment of antipsychotic-induced tardive dyskinesia (*El-Sayeh et al 2018*). One small crossover RCT (n=22) found that amantadine reduced Abnormal Involuntary Movements Scale (AIMS) scores in patients with drug-induced tardive dyskinesia, while placebo did not (*Pappa et al 2010)*.
- The AAN practice parameter on initiation of treatment for PD *(Miyasaki et al 2002)* suggests that levodopa or a DA may be used; the choice depends on the relative impact of improving motor disability (better with levodopa) compared with the lessening of motor complications (better with DAs). Amantadine is noted to have a modest effect on all features of PD with a mild adverse effect profile. The guidelines focused on PD from the International Parkinson and Movement Disorder Society (*Fox et al 2018, Seppi et al 2019)* consider pramipexole, ropinirole immediate-release, and rotigotine as clinically useful DAs in patients requiring symptomatic therapy in early PD or requiring adjunct therapy to levodopa in early or stable PD. Bromocriptine and amantadine are listed as possibly useful in patients with early or stable PD requiring adjunct therapy to levodopa. Ropinirole extended release is possibly useful in patients with early PD requiring symptomatic therapy. In patients with treated PD on optimized oral levodopa, pramipexole, ropinirole, rotigotine, apomorphine are clinically useful and bromocriptine and apomorphine are possibly useful for treating motor fluctuations. Amantadine is clinically useful for treating dyskinesia in patients with PD on optimized oral levodopa. Pramipexole is clinically useful for treating depressive symptoms in PD, and rotigotine is possible useful for treating sleep and wakefulness disorders in PD.
- Current RLS guidelines suggest that the DAs, specifically ropinirole, rotigotine, and pramipexole, be used for the treatment of primary moderate-to-severe RLS. Few head-to-head comparisons exist to suggest agents preferentially *(Aurora et al 2012, Winkelman et al 2016, Winkelmann et al 2018)*.
- The AAN practice guideline on the treatment of tardive syndromes (*Bhidayasiri 2013*) states that amantadine may be considered for use with neuroleptics to treat tardive syndromes in the short term.
- All of the DAs have warnings for sudden onset of sleep and somnolence; syncope; hypotension, including orthostatic hypotension; hallucinations and psychotic-like behaviors; dyskinesia; and impulse control or compulsive behaviors. The rotigotine patch may cause application site reactions.
- Amantadine products have warnings for suicidal ideation; hallucinations and psychotic behavior; sudden onset of sleep and somnolence; withdrawal-emergent hyperpyrexia and confusion; and impulse control or compulsive behaviors. Extended-release amantadine products have additional warnings for dizziness and orthostatic hypotension.
- Common adverse effects of the DAs include nausea, vomiting, drowsiness/somnolence, dizziness/hypotension, hallucinations, dyskinesia, and peripheral edema. Apomorphine causes severe nausea and vomiting when administered at recommended doses; concomitant treatment with the antiemetic trimethobenzamide is recommended.
- Additional adverse reactions associated with bromocriptine use in PD include confusion, "on-off" phenomenon, faintness/fainting, asthenia, abdominal discomfort, visual disturbance, ataxia, insomnia, depression, shortness of breath, constipation, vertigo, dry mouth, urinary frequency, incontinence, and retention, anxiety, blepharospasm, and dysphagia.
  - Bromocriptine should not be used during the postpartum period in women with a history of coronary artery disease and other severe cardiovascular conditions unless withdrawal is considered medically contraindicated. If the drug is used in the postpartum period, the patient should be observed with caution.

- Safety during long-term use of bromocriptine for more than 2 years at the doses required for PD has not been established.

- Adverse reactions associated with amantadine include nausea, dizziness, insomnia, hallucination, depression, anxiety, dry mouth, peripheral edema, constipation, ataxia/falls, and orthostatic hypotension.

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

INTRODUCTION

- Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder among children, with an estimated prevalence of up to 10% of school-age children in the United States (U.S.). It is more common in boys than girls and frequently persists into adulthood (*Centers for Disease Control and Prevention [CDC] 2021, Feldman et al 2014*). Epidemiologic studies of adult ADHD have estimated the current prevalence to be 4.4% in the U.S. (*Bukstein 2021*).
  - In children, this chronic disorder is characterized by symptoms of hyperactivity, impulsivity, and/or inattention. These symptoms affect cognitive, academic, behavioral, emotional, and social functioning (*Krull 2019*). Common comorbid psychiatric disorders include oppositional defiant disorder, conduct disorder, depression, anxiety disorder, and learning disabilities (*Krull 2021a*). Approximately 20% of children with ADHD develop chronic tic disorders and approximately 50% of children with chronic tics or Tourette syndrome have comorbid ADHD (*Krull 2021c*).
  - ADHD in adults is characterized by symptoms of inattention, impulsivity, and restlessness. Impairment in executive function and emotional dysregulation frequently occur. Common comorbid psychiatric disorders include mood and anxiety disorders, substance use disorder, and intermittent explosive disorder (*Bukstein 2021*).
- For children < 17 years of age, the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5) diagnosis of ADHD requires ≥ 6 symptoms of hyperactivity and impulsivity or ≥ 6 symptoms of inattention. For adolescents ≥ 17 years of age and adults, ≥ 5 symptoms of hyperactivity and impulsivity or ≥ 5 symptoms of inattention are required.
  - The symptoms of hyperactivity/impulsivity or inattention must occur often; be present in more than 1 setting; persist for at least 6 months; be present before the age of 12 years; impair function in academic, social, or occupational activities; and be excessive for the developmental level of the child.
  - Other physical, situational, or mental health conditions that could account for the symptoms must be excluded.
- Treatment of ADHD may involve behavioral/psychologic interventions, medication, and/or educational interventions, alone or in combination (*Krull 2020*).
  - For preschool children (age 4 through 5 years), behavioral therapy is considered the first-line treatment; when medication is necessary, methylphenidate is generally recommended.
  - For children and adolescents with moderate to severe ADHD, medication and behavioral therapy are recommended. In general, stimulants are the first-line agents; however, nonstimulant medications may be more appropriate for certain children.
    - About 30% of patients do not respond to or may not tolerate the initial stimulant treatment. At least one-half of children who do not respond to one type of stimulant will respond to the other. If there is still no improvement, consideration should be given to switching to or adding a nonstimulant ADHD medication (*Krull 2021b*).
- Multiple agents are currently approved by the Food and Drug Administration (FDA) for the treatment of ADHD. They include central nervous system (CNS) stimulants (amphetamine- and methylphenidate-based formulations), as well as nonstimulants: 2 selective norepinephrine reuptake inhibitors (SNRIs) atomoxetine and viloxazine extended-release (ER); and 2 alpha$_2$-adrenergic agonists clonidine ER, guanfacine ER.
  - Due to the potential for abuse, the stimulant agents are classified as Schedule II controlled substances.
  - Several stimulants are also approved for the treatment of narcolepsy and exogenous obesity; the use of stimulants for the treatment of obesity will not be covered in this review. Lisdexamfetamine dimesylate is the only FDA-approved drug for the treatment of binge eating disorder (BED).
- Medispan Classes: ADHD Agents – Amphetamines, Dexmethylphenidate, Methylphenidate, Selective Alpha-Adrenergic Agonists, Selective Norepinephrine Reuptake Inhibitor

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Stimulants	
Evekeo (amphetamine sulfate)	✔
Evekeo ODT (amphetamine sulfate)	-
Azstarys (serdexmethylphenidate/dexmethylphenidate)	-
Adderall (mixed amphetamine salts)	✔
Focalin (dexmethylphenidate hydrochloride [HCl])	✔
ProCentra (dextroamphetamine sulfate)	✔
Zenzedi (dextroamphetamine sulfate)	✔
Desoxyn (methamphetamine HCl)	✔
methylphenidate HCl chewable tablets	✔
Methylin Oral Solution (methylphenidate HCl)	✔
Ritalin (methylphenidate HCl)	✔
Dexedrine Spansule (dextroamphetamine sulfate sustained-release)	✔
Adzenys XR-ODT (amphetamine ER)	-
Dyanavel XR (amphetamine ER)	-
Adderall XR (mixed amphetamine salts ER)	✔
Mydayis (mixed amphetamine salts ER)	-
Focalin XR (dexmethylphenidate HCl ER)	✔
Vyvanse (lisdexamfetamine dimesylate)	-
Adhansia XR (methylphenidate HCl ER)	-
Aptensio XR (methylphenidate HCl ER)	✔
Concerta (methylphenidate HCl ER)	✔
Cotempla XR-ODT (methylphenidate ER)	-
Jornay PM (methylphenidate HCl ER)	-
methylphenidate HCl ER (CD)	✔
methylphenidate HCl ER	✔
QuilliChew ER (methylphenidate HCl ER)	-
Quillivant XR (methylphenidate HCl ER)	-
Relexxii (methylphenidate HCl ER) (72 mg)	✔
Ritalin LA (methylphenidate HCl ER)	✔
Daytrana (methylphenidate transdermal system)	-
Nonstimulants	
Strattera (atomoxetine HCl)	✔
Kapvay (clonidine HCl ER)	✔
Intuniv (guanfacine HCl ER)	✔
Qelbree (viloxazine ER)	-

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

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

Desoxyn (methamphetamine HCl)		✓				
Ritalin (methylphenidate HCl IR); methylphenidate HCl chewable tablets		✓		✓		
Methylin Oral Solution; methylphenidate ER tablets	✓			✓		
Adhansia XR, Aptensio XR, Concerta, Cotempla XR-ODT, Daytrana, Jornay PM, QuilliChew ER, Quillivant XR, Relexxii, Ritalin LA (methylphenidate ER)	✓					
Azstarys (serdexmethylphenidate/dexmethylphenidate)	✓					
Qelbree (viloxazine ER)	✓					

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

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

- Limitation of use:
  - Aptensio XR: Pediatric patients younger than 6 years of age experienced higher plasma exposure than patients 6 years and older at the same dose and high rates of AEs, most notably weight loss.
  - Lisdexamfetamine: Pediatric patients younger than 6 years of age experienced more long-term weight loss than patients 6 years and older. Lisdexamfetamine is not indicated or recommended for weight loss. Use of other sympathomimetic drugs for weight loss has been associated with serious cardiovascular (CV) adverse events (AEs). The safety and effectiveness of this drug for the treatment of obesity have not been established.
  - Mydayis: Pediatric patients 12 years and younger experienced higher plasma exposure than patients 13 years and older at the same dose and experienced higher rates of AEs, mainly insomnia and decreased appetite.

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

CLINICAL EFFICACY SUMMARY

- Randomized trials, systematic reviews, and meta-analyses have found stimulants, SNRIs (atomoxetine, viloxazine ER), and alpha$_2$-adrenergic agonists (clonidine ER, guanfacine ER) to be more efficacious than placebo in reducing the core symptoms of ADHD in children and adolescents.
  - Evekeo (amphetamine sulfate) was approved based on a randomized, double-blind (DB), multicenter (MC), placebo-controlled (PC) laboratory classroom study that was conducted in 107 children between the ages of 6 and 12 years (*Childress et al 2015*). The study found Evekeo to be associated with significant improvements in the average

Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) combined score compared to placebo (least squares [LS] mean difference -7.9; 95% CI, -10.1 to -5.6; p < 0.0001).
    - Evekeo ODT, an orally disintegrating amphetamine tablet, was approved under the 505(b)(2) regulatory pathway. The safety and effectiveness of Evekeo ODT for the treatment of ADHD was established based on an adequate and well-controlled study of Evekeo (*Childress et al 2015*).
- Cotempla XR-ODT, a new methylphenidate ER orally disintegrating tablet formulation, was approved based on a randomized, DB, MC, PC laboratory classroom study (*Childress et al 2017*) (N = 87) which found that the average SKAMP-combined score was significantly better for Cotempla XR-ODT than for placebo (LS mean 14.3 [95% CI, 12.2 to 16.4] vs 25.3 [9% CI, 23.0 to 27.6], respectively; p < 0.0001).
- Adhansia XR, a recently approved methylphenidate ER capsule, was approved via the 505(b)(2) regulatory pathway, and its efficacy was supported by 4 clinical studies in patients with ADHD including 2 studies conducted in adults, 1 study in adolescents 12 to 17 years of age, and 1 study in pediatric patients 6 to 12 years of age (*Adhansia XR FDA Clinical Review 2019):*
    - One randomized, DB, MC, PC 4-week study conducted in 368 adult patients with ADHD evaluated the safety and efficacy of 4 doses of Adhansia XR (25, 45, 70, and 100 mg) compared to placebo. The primary endpoint, change in the ADHD-Rating Scale (ADHD-RS)-5 total score from baseline to Week 5, was significantly improved compared to placebo in the Adhansia XR 45 mg group (LS mean difference, -6.9; 95% CI, -11.5 to -2.2; p = 0.0013), 100 mg group (LS mean difference, -8.1; 95% CI, -12.9 to -3.2; p = 0.0002), and when combining all dosage groups compared to placebo (LS mean difference, -4.7; 95% CI, -7.7 to -1.6; p = 0.0026). No significant difference was seen in the 25 mg or 70 mg groups compared to placebo.
- A second randomized, DB, crossover, PC study was conducted in 45 adults in an adult workplace environment (*Adhansia XR FDA Clinical Review 2019, Wigal et al 2020*). The study aimed to assess efficacy parameters for Adhansia XR vs placebo over 16 hours post-dose. Patients were titrated to an optimal dose of Adhansia XR (either 25, 35, 45, 55, 70, 85, or 100 mg) during an open-label (OL) treatment period between 2 and 7 weeks, then entered into a 1-week PC, DB treatment phase prior to the adult workplace environment session, followed by a 7-day washout period between crossover periods, then another 1-week treatment phase followed by another adult workplace environment session. The primary endpoint was the average Permanent Product Measure of Performance (PERMP) score for various time points up to 16 hours post-dose. When combining data from all time points, patients treated with Adhansia XR had significant improvements in the PERMP score compared to placebo (LS mean difference, 13.05; 95% CI, 3.88 to 22.23; p = 0.0064).
- A 4-week randomized, DB, PC trial assessed efficacy of Adhansia XR in 354 adolescent patients 12 to 17 years of age (*Adhansia XR FDA Clinical Review 2019)*. The study compared Adhansia XR 25, 45, 70, and 85 mg to placebo and found significant improvements in the ADHD-5-RS score from baseline to Week 5 in adolescents treated with Adhansia XR 45 mg (LS mean difference, -5.4; 95% CI, -9.2 to -1.6; p = 0.0052), 70 mg (LS mean difference, -5.2; 95% CI, -9.0 to -1.4; p = 0.0069), and when combining all dosage groups compared to placebo (LS mean difference, -4.3; 95% CI, -7.3 to -1.3; p = 0.0049). Adolescents treated with Adhansia XR 25 or 85 mg did not achieve significant improvements in the ADHD-5-RS score compared to placebo.
    - A fourth study, which included a 6-week OL dose optimization period (majority of patients received between 45 and 55 mg of Adhansia XR) followed by a 1- week DB, PC study, was conducted to assess the efficacy of Adhansia XR in 147 children 6 to 12 years of age in an analog classroom setting. The primary endpoint, average SKAMP-C score (taken at various time points up to 13 hours post-dose), was significantly improved in children treated with Adhansia XR compared to placebo (LS mean difference, -8.6; 95% CI, -10.6 to -6.6).
- Jornay PM, an ER methylphenidate capsule formulation, was approved based on the results of 2 clinical studies conducted in patients 6 to 12 years of age with ADHD:
    - The first study was a 6-week OL dose-optimization study, followed by a 1-week DB, PC withdrawal phase where patients were randomized to continue treatment with Jornay PM or switch to placebo (*Childress et al 2020, Jornay PM Prescribing Information 2021*). The study, which was conducted in an analog classroom setting and included 117 children aged 6 to 12 years, found that Jornay PM was associated with a significant reduction in the SKAMP symptom score over a 12-hour period (LS mean difference, -5.9; 95% CI, -9.1 to -2.7).
    - A randomized, DB, MC, PC, parallel group, forced-dose titration trial was conducted over 3 weeks in 161 children 6 to 12 years of age with ADHD (*Pliszka et al 2017*). The study found that 40 to 80 mg/day of Jornay PM achieved significant improvements vs placebo in ADHD symptoms (LS mean ADHD rating scale-IV, 24.1 vs 31.2; p = 0.002) at 3 weeks. Significant improvements were also seen vs placebo in key secondary outcomes including at-home

early morning and late afternoon/evening functional impairment at 3 weeks. The most commonly reported treatment-emergent AEs were insomnia and decreased appetite.

- Mydayis, a mixed amphetamine salts product, was approved for the treatment of ADHD based on the results of 5 MC, DB, PC, randomized controlled trials (RCTs): 3 in adults and 2 in pediatric patients 13 to 17 years of age. The studies found that Mydayis demonstrated a statistically significant treatment effect compared with placebo on various ADHD outcomes measures (eg, ADHD-RS score, PERMP score) (*Mydayis Prescribing Information 2020, Weisler et al 2017, Wigal et al 2018a, Wigal et al 2018b, Wigal et al 2019*) (see results below in Table 3 below). An additional 6-week, randomized, PC, DB, forced dose titration trial in 411 adults with ADHD similarly found that Mydayis significantly improved ADHD-RS-IV scores compared to placebo (LS mean treatment difference for all Mydayis doses combined vs placebo, -10.6; 95% CI, -13.2 to -8.0; p < 0.0001) (*Frick et al 2020*).

Table 3. Summary of Primary Efficacy Results for Mydayis

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

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

- Azstarys, a combination of serdexmethylphenidate and dexmethylphenidate, was approved based on results from a randomized, DB, PC analog classroom study *(Azstarys Prescribing Information 2021).* A total of 150 patients aged 6 to 12 years were enrolled. Following an OL, 3-week dose titration phase, patients were randomly assigned during a 1-week parallel treatment period to either the optimized dose Azstarys or placebo. After 1 week, evaluations were done using the SKAMP rating scale over 13 hours in a classroom setting. Mean change in SKAMP from baseline (primary outcome) was significantly greater with Azstarys compared with placebo (placebo-subtracted difference -5.4; 95% CI, -7.1 to -3.7). The efficacy of Azstarys in adults and pediatric patients 13 to 17 years of age was established by pharmacokinetic bridging between Azstarys and Focalin XR (dexmethylphenidate ER) capsules.
- Qelbree (viloxazine ER), an SNRI, was shown to be superior to placebo in 3 DB, MC, randomized, PC trials in patients with ADHD.
  - Trial 1 enrolled 313 patients aged 6 to 11 years who were randomized to treatment with viloxazine ER 200 or 400 mg or placebo once daily for 8 weeks (*Nasser 2021b*). Improvements in ADHD-RS-5 total scores were reported, with LS mean changes from baseline of -17.6, -17.5 and -11.7 for viloxazine ER 200 mg, 400 mg, and placebo, respectively (p < 0.05 for both comparisons to placebo).
  - Trial 2 enrolled 477 patients aged 6 to 11 years who were randomized to either viloxazine ER 100 mg or 200 mg or placebo once daily for 6 weeks (*Nasser 2020*). LS mean changes from baseline in ADHD-RS-5 total scores were

-16.6, -17.7, and -10.9 for viloxazine ER 100 mg, 200 mg, and placebo, respectively ($p < 0.05$ and $p < 0.0001$ for viloxazine ER 100 mg and 200 mg vs placebo, respectively).
    - A third trial evaluated viloxazine ER in 310 patients aged 12 to 17 years of age who were randomized to viloxazine ER 200 mg, 400 mg, or placebo (*Nasser 2021a*). After 6 weeks of treatment, viloxazine ER 200 mg and 400 mg resulted in LS mean changes from baseline in ADHD-RS-5 total scores of -16.0, -16.5, and -11.4 for viloxazine ER 200 mg, 400 mg, and placebo, respectively ($p < 0.05$ vs placebo for both comparisons).
  - A systematic (Cochrane) review of 185 RCTs (*Storebø et al 2015*) (N = 12,245) in children and adolescents with ADHD found that methylphenidate may improve teacher-rated ADHD symptoms, teacher-reported general behavior, and parent-reported quality of life (QOL) vs placebo. However, the evidence was of low quality.
  - An RCT called the Preschool ADHD Treatment Study (PATS) (*Greenhill et al 2006*) evaluated the efficacy of methylphenidate immediate-release (IR) in 303 preschool children with ADHD and found that it demonstrated significant reductions on ADHD symptom scales; however, the effect sizes (0.4 to 0.8) were smaller than those generally reported for school-age children.
  - A systematic (Cochrane) review of 23 PC, RCTs (*Punja et al 2016*) (N = 2675) found that amphetamines were effective at improving the core symptoms of ADHD, but they were also associated with a higher risk of AEs compared to placebo. There was no evidence that one kind of amphetamine was better than another and there was no difference between short-acting and long-acting formulations.
  - A meta-analysis of 25 DB, PC, RCTs (*Schwartz et al 2014*) (N = 3928) in children and adolescents with ADHD found atomoxetine to be superior to placebo for overall ADHD symptoms, with a medium effect size (-0.64).
  - A meta-analysis of 25 RCTs (all rated as low or very low quality evidence) in children with autism and concurrent ADHD symptoms concluded that methylphenidate and atomoxetine both reduced parent-rated hyperactivity and inattention (*Rodrigues et al 2021*). Methylphenidate also reduced teacher-rated hyperactivity and inattention, but atomoxetine only reduced teacher-rated inattention.
  - A meta-analysis of 12 RCTs (*Hirota et al 2014*) (N = 2276) in pediatric patients with ADHD found that alpha$_2$-adrenergic agonists were significantly superior to placebo for overall ADHD symptoms both as monotherapy and, to a lesser extent, as augmentation therapy to stimulants.
    - Meta-analytic results failed to demonstrate a significant difference in efficacy between alpha$_2$-adrenergic agonists. In sub-analyses of individual formulations, the ER formulations separated robustly from placebo whereas the IR formulations did not separate from placebo.
  - A systematic review of 16 RCTs and 1 meta-analysis (*Chan et al 2016*) (N = 2668) found evidence supporting the use of methylphenidate ER and amphetamine ER formulations, atomoxetine, and guanfacine ER for the treatment of ADHD in adolescents. For the primary outcome measure of mean change in ADHD-RS total symptom score, both stimulant and nonstimulant medications led to clinically significant reductions of 14.93 to 24.60 points.
- For the treatment of ADHD in children and adolescents, stimulants typically have a slightly larger treatment effect size (standardized mean difference [SMD]) than nonstimulants (approximately 1.0 vs approximately 0.7 for both atomoxetine and alpha$_2$-adrenergic agonists). However, there is insufficient evidence to definitively conclude that one stimulant is more efficacious than another (*Krull 2021b*, (*Wolraich et al 2019).*
  - An Agency for Healthcare Research and Quality (AHRQ) review of 78 studies (*Jadad et al 1999*) evaluating the efficacy of various interventions for the treatment of ADHD in children and adults found few, if any, differences between methylphenidate and dextroamphetamine.
  - A meta-analysis of 23 DB, PC trials (*Faraone 2010a*) comparing the efficacy of methylphenidate and amphetamine formulations found that amphetamine products may be moderately more efficacious than methylphenidate products.
  - A DB, PC, RCT (*Newcorn et al 2008*) (N = 516) comparing the efficacy of atomoxetine vs methylphenidate ER (osmotic-release formulation) in patients 6 to 16 years of age with ADHD found that both drugs were superior to placebo in terms of response rate, and that methylphenidate ER was superior to atomoxetine.
  - A meta-analysis of 29 DB, PC trials (*Faraone et al 2006*) evaluated the efficacy of various medications (methylphenidate and amphetamine compounds, atomoxetine, pemoline [no longer available in the U.S.], bupropion, and modafinil) for the treatment of ADHD. The effect sizes for nonstimulant medications were significantly less than those for IR stimulants or long-acting stimulants. The 2 classes of stimulant medications did not differ significantly from one another.
  - A meta-analysis of 28 DB, PC, RCTs (*Stuhec et al 2015*) (N = 4699) compared the efficacy of various medications for the treatment of ADHD in children and adolescents. Efficacy in reducing ADHD symptoms compared to placebo was small for bupropion (SMD, -0.32; 95% CI, -0.69 to 0.05), modest for atomoxetine (SMD, -0.68; 95% CI, -0.76 to -0.59)

and methylphenidate (SMD, -0.75; 95% CI, -0.98 to -0.52), and highest for lisdexamfetamine (SMD, -1.28; 95% CI, -1.84 to -0.71).
  - A network meta-analysis and mixed treatment comparison of 36 RCTs (*Joseph et al 2017*) evaluating the comparative efficacy and safety of ADHD pharmacotherapies in children and adolescents found that lisdexamfetamine had greater efficacy than guanfacine ER, atomoxetine, and methylphenidate ER. Guanfacine ER had a high posterior probability of being more efficacious than atomoxetine, but their credible intervals overlapped.
  - A network meta-analysis of 48 DB, RCTs (*Padilha et al 2018*) compared the safety and efficacy of various ADHD medications in children and adolescents. Of the 12 trials that were evaluated for efficacy, analysis was performed using the Clinical Global Impression Improvement (CGI-I) scale for 3 drugs, which showed that methylphenidate was more effective than atomoxetine (MD, 3.15; 95% CI, 0.75 to 13.71) and guanfacine (MD, 1.92; 95% CI, 0.64 to 5.94). Thirty-three trials were evaluated for safety. Ranking of AEs showed that lisdexamfetamine was more likely to cause sleep disorders, loss of appetite, and behavior problems compared to other treatments.
- Alpha$_2$-adrenergic agonists have been associated with improvements in ADHD symptoms and comorbid tics.
  - A meta-analysis of 9 DB, PC, RCTs (*Bloch et al 2009*) (N = 477) was conducted to determine the relative efficacy of different medications in treating ADHD and tic symptoms in children with both Tourette syndrome and ADHD.
  - Methylphenidate seemed to offer the greatest improvement of ADHD symptoms and did not seem to worsen tic symptoms.
  - Alpha$_2$-adrenergic agonists offered the best combined improvement in both tic and ADHD symptoms.
  - Atomoxetine significantly improved both tic and ADHD severity compared to placebo.
  - One small study found that tic severity was significantly increased with higher doses of dextroamphetamine treatment.
  - A Cochrane review of 8 RCTs (*Osland et al 2018*) including 510 children with both ADHD and a chronic tic disorder found low-quality evidence for improvement of ADHD symptoms with methylphenidate, atomoxetine, and clonidine, and very low-quality evidence for desipramine, dextroamphetamine, guanfacine, and deprenyl. Tic symptoms improved with guanfacine, desipramine, methylphenidate, clonidine, and a combination of methylphenidate and clonidine. The authors noted that in 1 study with a short duration (3 weeks), high doses of dextroamphetamine worsened tics.
- There are limited efficacy data regarding the treatment of ADHD in the adult population. Comparison of effect sizes in clinical trials suggests that stimulant medications are more efficacious in adult ADHD than nonstimulants.
  - In a meta-analysis of 12 clinical trials (*Cunill et al 2013*) (N = 3375) comparing atomoxetine with placebo in adult ADHD, atomoxetine led to a modestly greater reduction in ADHD symptom severity, but was associated with higher all-cause discontinuation.
  - A meta-analysis (*Faraone 2010b*) of 19 randomized trials of 13 medications for adult ADHD found a greater average effect size for reduction in ADHD symptoms in patients receiving short- and long-acting stimulant medications (vs placebo; 0.86 and 0.73, respectively) compared with patients receiving nonstimulant medication (vs placebo; 0.39). No difference in effect size was found between short- and long-acting stimulants.
  - A meta-analysis of 20 randomized trials (*Stuhec et al 2019*) compared the efficacy, acceptability, and tolerability of lisdexamfetamine, mixed amphetamine salts, methylphenidate, and modafinil in the treatment of ADHD in adults. The highest effect size in reducing ADHD symptoms was found with lisdexamfetamine (SMD -0.89; 95% CI, -1.09 to -0.70), while moderate reductions in symptoms were seen with mixed amphetamine salts (SMD -0.64; 95% CI, -0.83 to -0.45) and methylphenidate (SMD -0.50; 95% CI, -0.58 to -0.41). No efficacy was reported with modafinil.
  - A Cochrane review of 19 studies (*Castells et al 2018*, N = 2521) comparing dextroamphetamine, lisdexamfetamine, and mixed amphetamine salts for the treatment of ADHD in adults found that overall, amphetamines reduced the patient- and clinician-rated severity of ADHD symptoms compared to placebo; however, they did not improve retention in treatment. Amphetamines were associated with an increased proportion of patients who withdrew because of AEs. When comparing different types of amphetamines, lisdexamfetamine and mixed amphetamine salts reduced the severity of ADHD symptoms as rated by clinicians, but dextroamphetamine did not. No differences in any outcome were found when comparing immediate- and sustained-release formulations.
  - A systematic review and network meta-analysis (*Elliot et al 2020*) of 81 RCTs compared methylphenidate, atomoxetine, dexamfetamine, lisdexamfetamine, guanfacine, mixed amphetamine salts, modafinil, and bupropion for the treatment of ADHD in adults. Treatment with any ADHD pharmacotherapy was associated with statistically significant improvement in patient-reported clinical response vs placebo. When drugs were analyzed individually, only atomoxetine was found to significantly improve patient-reported clinical response compared to placebo (mean difference [MD], -5.9; 95% CI, -12.6 to -0.4). Atomoxetine (MD, -3.7; 95% CI, -6.7 to -0.9), sustained-release methylphenidate (MD, -5.7; 95% CI, -11.2 to -0.3), and low-dose methylphenidate (MD, -10.4; 95% CI, -19.0 to -2.1)

were found to improve clinician-assessed clinical response compared to placebo. No significant differences were observed between individual medications when response was considered as a continuous outcome.
  - Another meta-analysis (*Cortese et al 2018*) of 133 RCTs comparing the use of amphetamines, atomoxetine, bupropion, clonidine, guanfacine, methylphenidate, and modafinil for the treatment of ADHD found that all drugs were superior to placebo for ADHD core symptoms as rated by clinicians in children and adolescents, and all drugs except for modafinil were more efficacious than placebo in adults.
    - When comparing the various drugs based on teachers' ratings in children and adolescents, only methylphenidate and modafinil were found to be more efficacious than placebo.
    - In head-to-head comparisons, differences in efficacy based on clinicians' ratings were found, favoring amphetamines over modafinil (SMD, -0.39; 95% CI -0.67 to -0.12), atomoxetine (SMD, -0.46; 95% CI, -0.65 to -0.27), and methylphenidate (SMD, -0.24; 95% CI, -0.44 to -0.05) in children and adolescents. Efficacy results based on clinicians' ratings were similar for adults, and favored amphetamines over modafinil (SMD, -0.94; 95% CI -1.43 to -0.46), atomoxetine (SMD, -0.34; 95% CI, -0.58 to -0.10), and methylphenidate (SMD, -0.29; 95% CI, -0.54 to -0.05).
- Lisdexamfetamine dimesylate has demonstrated efficacy in the treatment of BED. Direct comparison trials between lisdexamfetamine and other drugs used off-label to treat BED are lacking.
  - In 2 Phase 3, 12-week, randomized, DB, PC trials (*McElroy et al 2016*) (N = 773) in patients with moderate to severe BED, lisdexamfetamine-treated patients had a statistically significantly greater reduction from baseline in mean number of binge days per week at week 12 vs placebo (treatment difference in study 1: -1.35; 95% confidence interval [CI], -1.70 to -1.01; study 2: -1.66; 95% CI, -2.04 to -1.28; both $p < 0.001$).
    - A 12-month, OL extension study (*Gasior et al 2017*) (N = 599) in adults with BED found that the long-term safety and tolerability of lisdexamfetamine were generally consistent with the safety profile observed in 3 previous short-term trials in BED as well as its established profile for ADHD. Common treatment-emergent AEs included dry mouth, headache, insomnia, and upper respiratory tract infection. Weight loss and increases in blood pressure and pulse rate were also observed.
  - In a phase 3, DB, randomized, PC, withdrawal study (*Hudson et al 2017*) (N = 418) in adults with moderate to severe BED, responders to lisdexamfetamine during a 12-week OL phase were randomized to placebo or continued lisdexamfetamine during a 26-week, DB phase. The percentage of patients meeting relapse criteria was 3.7% with lisdexamfetamine vs 32.1% with placebo; time to relapse statistically favored lisdexamfetamine ($p < 0.001$). The hazard ratio (HR) was 0.09 (95% CI, 0.04 to 0.23).
  - A systematic review and meta-analysis of 14 clinical and 7 preclinical trials concluded that lisdexamfetamine effectively treats BED and reduces both symptoms (MD, 0.93; 95% CI, 0.74 to 1.12) and body weight (based on systematic review only) (*Schneider et al 2021*).
  - A systematic review and meta-analysis of 9 waitlist-controlled psychological trials and 25 PC trials evaluating pharmacologic (n = 19) or combination (n = 6) treatment for BED (*Brownley et al 2016*) found that therapist-led cognitive behavioral therapy (CBT), lisdexamfetamine, and second-generation antidepressants (SGAs) increased binge-eating abstinence (relative risk [RR], 4.95 [95% CI, 3.06 to 8.00], 2.61 [95% CI, 2.04 to 3.33], and 1.67 [95% CI, 1.24 to 2.26], respectively), while lisdexamfetamine and SGAs decreased binge-eating frequency (MD in days/week, -1.35 [95% CI, -1.77 to -0.93] and -0.67 [95% CI, -1.26 to -0.09], respectively). Topiramate and other forms of CBT also increased abstinence and reduced binge-eating frequency.
  - A 2018 systematic review and meta-analysis of 45 RCTs (*Ghaderi et al 2018*) compared various psychological, pharmacological, and combined treatments for BED, and found moderate support for the efficacy of CBT and CBT-guided self-help (moderate quality of evidence), and low-quality evidence to support interpersonal psychotherapy, selective serotonin reuptake inhibitors (SSRIs), and lisdexamfetamine for the cessation of or reduction in the frequency of binge eating. Only lisdexamfetamine showed a modest effect on weight loss (SMD for body mass index -5.23; 95% CI, -6.52 to -3.94).

CLINICAL GUIDELINES

ADHD

- Several clinical guidelines have provided recommendations on the treatment of ADHD in children and adolescents.
  - According to the American Academy of Pediatrics (AAP) guidelines (*Wolraich et al 2019*), the evidence is particularly strong for stimulant medications, and sufficient but less strong for atomoxetine, guanfacine ER, and clonidine ER (in that order; newer agents such as serdexmethylphenidate/dexmethylphenidate [Azstarys] and viloxazine [Qelbree] are

not addressed in the current guidelines). Guanfacine ER and clonidine ER have evidence to support their use as adjunctive therapy with stimulant medications. Methylphenidate is recommended for preschool-aged children who have had an inadequate response to behavioral interventions.
  - The Society for Developmental and Behavioral Pediatrics guideline on assessment and treatment of children and adolescents with complex ADHD states that treatment should aim to improve functional impairment and include skill development in self-management strategies (*Barbaresi et al 2020*). Multimodal treatment with both behavioral and pharmacologic therapies may be needed. Specific pharmacologic classes are discussed in the context of learning disorder, for which the guideline recommends both stimulants and atomoxetine, with stimulants having a greater strength of evidence, and autism, for which a stimulant is recommended first followed by an alpha$_2$-adrenergic agonist or atomoxetine. Stimulant use is also endorsed in children with intellectual disability, tics, anxiety or depression, and disruptive behavior disorders.
  - The Medical Letter recommends that treatment of ADHD in school-age children or adults should begin with a stimulant, either a methylphenidate- or amphetamine-based formulation (*Med Lett Drugs Ther 2020*). Mixing short- and long-acting stimulants can be helpful to achieve an immediate effect for early-morning school classes or for reducing rebound irritability or overactivity, especially in the evening. Nonstimulants can be used in combination with stimulants or when stimulants are contraindicated, ineffective, or not tolerated.
  - According to the American Academy of Neurology guidelines for treatment of tics (*Pringsheim et al 2019*), physicians should counsel individuals with tics and comorbid ADHD that alpha$_2$-adrenergic agonists may provide benefit for both conditions. Alpha$_2$-adrenergic agonists and topiramate should be prescribed for the treatment of tics when the benefits of treatment outweigh the risks, while antipsychotics and botulinum toxin may be prescribed when the benefits outweigh the risks.
  - The American Academy of Child and Adolescent Psychiatry (AACAP) practice parameter for the treatment of children and adolescents with tic disorders (*Murphy et al 2013*) states that alpha$_2$-adrenergic agonists have demonstrated an effect size of 0.5 for the amelioration of tics and may be preferred by some prescribers over antipsychotics due to their relatively favorable AE profile.

Narcolepsy

- The American Academy of Sleep Medicine (AASM) practice parameters (*Maski et al 2021*) recommend various drugs for the treatment of daytime sleepiness in adults due to narcolepsy including modafinil, pitolisant, sodium oxybate, solriamfetol (strongly recommended), and armodafinil, dextroamphetamine, and methylphenidate (conditionally recommended). Idiopathic hypersomnia in adults should be treated with modafinil (strongly recommended), clarithromycin, methylphenidate, pitolisant, or sodium oxybate (conditionally recommended). Recommended therapies for children with narcolepsy include modafinil and sodium oxybate (both conditionally recommended),

BED

- According to the American Psychiatric Association (APA) practice guidelines on eating disorders (*Yager et al 2006*, *Yager et al 2012* [guideline watch update], now categorized as a legacy guideline), treatment of BED may include the following:
  - Nutritional rehabilitation and counseling
  - Psychosocial treatment
    - CBT, behavior therapy, dialectical behavior therapy (DBT), and interpersonal therapy (IPT) have all been associated with binge frequency reduction rates of 67% or more and significant abstinence rates during active treatment.
    - Self-help programs using self-guided, professionally designed manuals have been effective in reducing the symptoms of BED in the short-run for some patients and may have long-term benefit.
  - Medications
    - Antidepressant treatment is associated with short-term reductions in binge-eating but generally does not result in substantial weight loss. SSRIs have the fewest difficulties with AEs and the most evidence for efficacy when used at the high end of the recommended dose range.
    - Topiramate can reduce bingeing and decrease weight, but its use may be limited by AEs.
  - Combination psychotherapy and pharmacotherapy
    - For most patients, adding antidepressant therapy to a behavioral weight control and/or CBT regimen does not have a significant effect on binge suppression.
    - Although limited evidence is available, combined treatment is frequently used in clinical practice.

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

SAFETY SUMMARY

- Due to the potential for abuse, the stimulants are classified as Schedule II controlled substances. Atomoxetine, clonidine ER, guanfacine ER, and viloxazine ER are not classified as controlled substances.
- Various stimulants are contraindicated for use in patients with advanced arteriosclerosis, symptomatic CV disease, moderate to severe hypertension, hyperthyroidism, hypersensitivity to sympathomimetic amines, glaucoma, agitated states, history of drug abuse, tics, and in those using monoamine oxidase inhibitors (MAOIs). The stimulants carry a boxed warning for potential drug abuse and dependence. They also have warnings for increased risks of serious CV reactions, psychiatric AEs, suppression of growth, seizures, visual disturbance, peripheral vasculopathy, and priapism. Amphetamines have a warning for risk of serotonin syndrome when used in combination with other drugs affecting the serotonergic neurotransmitter systems.
  - Common AEs of stimulants include anorexia, decreased weight, tachycardia, anxiety, irritability, and insomnia.
  - Refer to the prescribing information for details on warnings, precautions, and AEs for individual products. For example:
    - QuilliChew ER can be harmful to patients with phenylketonuria (PKU) since it contains phenylalanine.
    - Because Concerta and Relexxii tablets are nondeformable and do not appreciably change in shape in the gastrointestinal tract, they should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing.
    - The use of Daytrana may result in chemical leukoderma and contact sensitization; in addition, exposure of the application site to external heat sources should be avoided due to increased absorption of the drug.
    - Adhansia XR capsules contain FD&C yellow No. 5 dye (tartrazine), which may cause allergic-type reactions in susceptible patients.
- Atomoxetine is contraindicated for use in patients with narrow angle glaucoma, pheochromocytoma, severe CV disorders, hypersensitivity to any component of the product, and in those taking MAOIs. It carries a boxed warning for a rare increased risk of suicidal ideation in children and adolescents. It also has warnings for serious CV events, effects on blood pressure and heart rate, effects on growth, psychiatric AEs, rare cases of severe liver injury, urinary retention, and priapism.
  - Common AEs associated with atomoxetine include somnolence, nausea, and vomiting.
- Viloxazine ER is contraindicated with concurrent use of MAOIs and sensitive CYP1A2 substrates or CYP1A2 substrates with a narrow therapeutic index. Viloxazine ER carries a boxed warning for suicidal thoughts and behavior in children and adolescents. It also has warnings for effects on heart rate and blood pressure and the potential for somnolence and fatigue. Patients should be screened for bipolar disorder prior to use of viloxazine ER due to the risk of activation of mania or hypomania.
  - Common AEs associated with viloxazine ER include somnolence, nausea, and vomiting.
- The alpha$_2$-adrenergic agonists are contraindicated in patients known to be hypersensitive to any constituent of the product. They carry warnings for increased risk of hypotension, bradycardia, and syncope; sedation and somnolence; rebound hypertension; and cardiac conduction abnormalities.
  - Common AEs associated with clonidine ER include somnolence, fatigue, and irritability while common AEs with guanfacine ER include somnolence, fatigue, and hypotension.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Stimulants					
Evekeo (amphetamine)	4 to 6 h	Tablets	Oral	*ADHD, narcolepsy*: Daily up to divided doses daily *Exogenous obesity*: Divided doses daily	*ADHD and narcolepsy* The first dose should be given upon awakening; additional doses at intervals of 4 to 6 hours.
Evekeo ODT (amphetamine)	4 to 6 h	Orally disintegrating tablets	Oral	Once or twice daily in the morning	As soon as the blister pack is opened, the tablet should be placed on the patient's tongue and allowed to disintegrate without chewing or crushing. The tablet will disintegrate in saliva so that it can be swallowed.
Adzenys XR-ODT (amphetamine ER)	10 to 12 h	Orally disintegrating tablets	Oral	Daily in the morning	As soon as the blister pack is opened, the tablet should be placed on the patient's tongue and allowed to disintegrate without chewing or crushing. The tablet will disintegrate in saliva so that it can be swallowed.
Dyanavel XR (amphetamine ER)	Up to 13 h	Suspension, ER tablets	Oral	Daily in the morning	The bottle should be shaken before administration. ER tablets may be chewed or swallowed whole. The 5 mg tablet may be split along the score line.
Adderall (mixed amphetamine salts)	4 to 6 h	Tablets	Oral	*ADHD, narcolepsy*: Daily up to divided doses daily	The first dose should be given on awakening, then additional doses at intervals of 4 to 6 hours.

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Adderall XR (mixed amphetamine salts ER)	10 to 12 h	Capsules	Oral	Daily in the morning	Capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce and consumed immediately. The dose of a single capsule should not be divided.
Mydayis (mixed amphetamine salts ER)	16 h	Capsules	Oral	Daily in the morning	Dosage adjustment is needed for severe renal impairment. Use in end stage renal disease (ESRD) is not recommended. Capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce and consumed immediately in its entirety without chewing. The dose of a single capsule should not be divided.
Focalin (dexmethylphenidate)	3 to 5 h	Tablets	Oral	Twice daily	Separate doses by at least 4 hours.
Focalin XR (dexmethylphenidate ER)	8 to 12 h	Capsules	Oral	Daily in the morning	ER capsules may be taken whole, or the capsule may be opened and the entire contents sprinkled on applesauce and consumed immediately in its entirety without chewing. The dose of a single capsule should not be divided.

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
ProCentra, Zenzedi (dextroamphetamine)	4 to 6 h	Solution (ProCentra) Tablets (Zenzedi)	Oral	*ADHD, narcolepsy*: Daily up to divided doses daily	The first dose should be given upon awakening; additional doses at intervals of 4 to 6 hours
Dexedrine Spansule (dextroamphetamine SR)	6 to 8 h	Capsules	Oral	*ADHD* Daily or twice daily Narcolepsy Daily	
Vyvanse (lisdexamfetamine)	10 to 12 h	Capsules, chewable tablets	Oral	*ADHD, BED*: Daily in the morning	Dosage adjustment is needed for renal impairment/ESRD. The capsules may be swallowed whole or can be opened, emptied, and mixed with yogurt, water, or orange juice and consumed immediately. A single capsule should not be divided. The chewable tablets must be chewed thoroughly before swallowing. A single dose should not be divided.
Desoxyn (methamphetamine)	4 to 5 h	Tablets	Oral	Daily to twice daily	
Methylin, Ritalin (methylphenidate)	3 to 5 h	Chewable tablets, tablets (Ritalin), solution (Methylin)	Oral	Twice daily to 3 times daily	The chewable tablets should be taken with at least 8 ounces (a full glass) of water or other fluid. The liquid and chewable tablets

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Methylphenidate ER	8 h	Tablets			should be given 30 to 45 minutes before meals. The ER tablets may be used in place of the IR tablets when the 8-hour dosage of the ER product corresponds to the titrated 8-hour dosage of the IR products. The ER tablets must be swallowed whole and never crushed or chewed.
Adhansia XR (methylphenidate ER)	13 h	Capsules	Oral	Daily in the morning	The capsules may be taken whole or they can be opened and sprinkled onto applesauce or yogurt; the entire contents of the mixture should be consumed within 10 minutes, and should not be chewed. The dose of a single capsule should not be divided.
Aptensio XR (methylphenidate ER)	12 h	Capsules	Oral	Daily in the morning	The capsules may be taken whole or they can be opened and sprinkled onto applesauce; the applesauce should be consumed immediately and it should not be chewed. The dose of a single capsule should not be divided.

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Concerta (methylphenidate ER)	12 h	Tablets	Oral	Daily in the morning	The tablets should not be chewed or crushed. Note: An FDA analysis of methylphenidate ER products manufactured by UCB/Kremers (formerly Kudco) and Mallinckrodt indicated that in some individuals, they may deliver the drug in the body at a slower rate during the 7- to 12-hour range. As a result, the FDA changed the therapeutic equivalence of these products from AB to BX. Because these manufacturers have subsequently failed to demonstrate that their products are bioequivalent to the brand-name reference drug, the FDA proposed to withdraw their approval (*FDA 2016*).
Methylphenidate ER					
Cotempla XR-ODT (methylphenidate ER)	12 h	Orally disintegrating tablets	Oral	Daily in the morning	As soon as the blister pack is opened, the tablet should be placed on the patient's tongue and allowed to disintegrate without chewing or crushing. The tablet will disintegrate in saliva so that it can be swallowed.
Jornay PM (methylphenidate ER)	10 h	Capsules	Oral	Daily in the evening	The capsule may be swallowed whole

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
					or it may be opened and the contents sprinkled onto applesauce and given immediately. The capsule contents must not be crushed or chewed, the dose of a single capsule should not be divided, and the contents of the entire capsule should be taken at the same time.
Methylphenidate ER (CD)	6 to 9 h	Capsules	Oral	Daily in the morning	The capsule may be swallowed whole or it may be opened and the contents sprinkled onto a small amount (one tablespoon) of applesauce and given immediately, followed by some fluids. The capsule contents must not be crushed or chewed.
QuilliChew ER (methylphenidate ER)	8 h	Chewable tablets	Oral	Daily in the morning	A 10 mg or 15 mg dose can be achieved by breaking in half the functionally scored 20 mg and 30 mg tablets, respectively.
Quillivant XR (methylphenidate ER)	12 h	Suspension	Oral	Daily in the morning	The bottle of Quillivant XR should be shaken vigorously for 10 seconds prior to administration. The suspension is stable for up to 4 months once reconstituted.

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
Relexxii (methylphenidate ER 72 mg)	12 h	Tablet	Oral	Daily in the morning	The tablet must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed.
Ritalin LA (methylphenidate ER)	6 to 9 h	Capsules	Oral	Daily in the morning	The capsule may be swallowed whole or may be administered by sprinkling the capsule contents on a small amount of applesauce; the contents should not be crushed, chewed, or divided. The mixture should be consumed immediately.
Daytrana (methylphenidate transdermal system)	12 h	Transdermal system	Transdermal	The patch should be applied 2 hours before an effect is needed and removed within 9 hours. It may be removed earlier than 9 hours if a shorter duration of effect is desired or late day side effects appear.	
Azstarys (serdexmethylphenidate/ dexmethylphenidate)	10 to 13 h	Capsules	Oral	Daily in the morning	The capsule may be swallowed whole or may be administered by sprinkling the capsule contents over 2 tablespoons of applesauce or 50 mL of water. The mixture should be consumed immediately.
Non-stimulants					
Strattera (atomoxetine)	At least 10 to 12 h	Capsules	Oral	Daily in the morning or divided dose in the morning and	Dosage adjustment is recommended for patients with moderate or severe

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
				late afternoon/ early evening	hepatic insufficiency, for use with strong CYP2D6 inhibitors, and for patients known to be CYP2D6 poor metabolizers. The capsules are not intended to be opened and should be taken whole.
Kapvay (clonidine ER)	At least 10 to 12 h	Tablets	Oral	Daily at bedtime or twice daily divided doses	With twice daily dosing, either an equal or higher split dosage should be given at bedtime. The tablets should not be crushed, chewed, or broken prior to swallowing. The initial dosage should be based on the degree of renal impairment.
Intuniv (guanfacine ER)	At least 8 to 12 h	Tablets	Oral	Daily in the morning or evening	The tablets should not be crushed, chewed, or broken prior to swallowing; they should not be administered with high fat meals, due to increased exposure. It may be necessary to reduce the dosage in patients with significant renal and hepatic impairment.
Qelbree (viloxazine ER)	Throughout the day (specific duration not reported)	Capsule	Oral	Daily	The capsule may be swallowed whole or may be administered by sprinkling the capsule contents

Drug	Duration of action*	Available Formulations	Route	Usual Recommended Frequency	Comments
					over a teaspoon of applesauce. The mixture should be consumed within 2 hours, without chewing.

See the current prescribing information for full details
*References: Prescribing information for individual products, *Medical Letter 2020, Pharmacist's Letter 2021, Krull 2020.*

CONCLUSION

- Both CNS stimulants and nonstimulants may be used for the treatment of ADHD. In general, stimulants are first-line treatment due to their superior efficacy. Clinical evidence suggests that methylphenidate and amphetamines are equally efficacious, but some patients may respond to one stimulant and not the other. Various short-, intermediate- and long-acting formulations (eg, tablets/capsules, chewable/orally disintegrating tablets, solution/suspension, transdermal patch) are available to provide a range of dosing options. Although nonstimulants such as atomoxetine and alpha$_2$-adrenergic agonists have smaller effect sizes, they may be used in patients who have failed or are intolerant to stimulants or when there is concern about possible abuse or diversion. The efficacy of the nonstimulant viloxazine ER in comparison to other nonstimulants is unknown. The alpha$_2$-adrenergic agonists are approved both as monotherapy and as adjunctive therapy to stimulants, and they have been shown to improve both tic and ADHD symptoms in patients with comorbid tic disorder.
  - Current consensus clinical guidelines for the treatment of children and adolescents with ADHD recommend that stimulants are highly effective for reducing core symptoms of ADHD in children (*Wolraich et al 2019*).
- Ultimately, the choice of the initial agent for treatment of ADHD depends upon various factors such as: duration of desired coverage; ability of the child to swallow pills; coexisting tic disorder (use of alpha$_2$-adrenergic agonists may be warranted); potential AEs, history of substance abuse in the patient or household member (eg, avoid stimulants or use stimulants with less potential for abuse [eg, lisdexamfetamine, osmotic-release preparation, methylphenidate patch]); and preference of the patient and parent/guardian (*Krull 2021a*).
- Various stimulants are indicated for treatment of narcolepsy and are generally considered to be second-line agents after modafinil/armodafinil due to their sympathomimetic AEs (*Scammell 2021*).
- Lisdexamfetamine is the only FDA-approved drug indicated for the treatment of moderate to severe BED, with demonstrated efficacy in reduction of mean binge days per week vs placebo. Direct comparison trials between lisdexamfetamine and other drugs used off-label to treat BED are lacking.

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

Therapeutic Class Overview
Ophthalmic Anti-Allergy

INTRODUCTION

- Conjunctivitis can be classified as noninfectious or infectious, and as acute, chronic, or recurrent. Types of noninfectious conjunctivitis are allergic, mechanical/irritative/toxic, immune-mediated, and neoplastic. Causes of infectious conjunctivitis are viruses and bacteria *(American Academy of Ophthalmology [AAO] 2018)*.
- Types of allergic conjunctivitis include atopic keratoconjunctivitis, seasonal or perennial conjunctivitis, vernal conjunctivitis, and giant papillary conjunctivitis. Atopic keratoconjunctivitis is a severe, chronic, external ocular inflammation associated with atopic dermatitis. Vernal keratoconjunctivitis is a severe form of allergic conjunctivitis that may involve the cornea *(AAO 2018, Bielory et al 2020)*.
- Allergic conjunctivitis results from classic Type I immunoglobulin E (IgE)-mediated hypersensitivity, where the immediate response to allergens is mediated predominantly by mast cells. The mast cells are present in the conjunctiva in high concentrations and release chemical mediators when activated by allergen-IgE cross-linkage. During the early response, histamine is the main mediator, and it causes itching, vasodilation, and vasopermeability. During the late phase of the allergic reaction, mast cells release chemokines and cytokines, which results in the influx of other inflammatory cells and continued inflammation (*Bielory et al 2020, Bielory et al 2012*). Symptoms of allergic conjunctivitis include itching, tearing, mucoid discharge, chemosis, hyperemia, and redness. Most commonly, symptoms are present in both eyes, but they may also occur unilaterally *(Hamrah and Dana 2020, Bielory et al 2012)*.
- The ophthalmic anti-allergy therapeutic class overview details the efficacy and safety of the ophthalmic antihistamines and ophthalmic mast cell stabilizers.
  - The ophthalmic antihistamines are Food and Drug Administration (FDA)-approved for the management of the signs and symptoms associated with allergic conjunctivitis *(Micromedex 2.0 2021, Facts & Comparisons 2021)*.
    - All ophthalmic antihistamines are available by prescription with the exception of ketotifen. OTC products include ketotifen and olopatadine which are indicated for the temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair, and dander.
  - The ophthalmic mast cell stabilizers include cromolyn sodium (previously marketed under the brand name, Opticrom), Alomide (lodoxamide) and Alocril (nedocromil). Nedocromil is approved for the treatment of itching associated with allergic conjunctivitis while cromolyn and lodoxamide are the only agents in this review that are FDA-approved for the treatment of vernal keratoconjunctivitis (*Drugs@FDA 2021, Hamrah and Dana 2021*).
  - Alrex (loteprednol etabonate 0.2%) ophthalmic suspension, an ophthalmic corticosteroid, is also indicated for the temporary relief of the signs and symptoms of seasonal allergic conjunctivitis in adults. Acular (ketorolac 0.5%) ophthalmic solution, an ophthalmic non-steroid anti-inflammatory drug (NSAID), is also FDA-approved for the treatment of ocular pruritus due to seasonal allergic conjunctivitis (ages ≥ 2 years) (*Micromedex 2.0 2021*). These 2 agents are reviewed in separate class reviews.
- Medispan Therapeutic Class: Ophthalmic Antiallergic

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Ophthalmic Antihistamines	
Alaway†, Alaway Preservative-Free†, Zaditor† (ketotifen 0.025% ophthalmic solution)	✔
Bepreve (bepotastine besilate 1.5% ophthalmic solution)	✔
Elestat* (epinastine HCl 0.05% ophthalmic solution)	✔
Lastacaft (alcaftadine 0.25% ophthalmic solution)	-
Optivar* (azelastine HCl 0.05% ophthalmic solution)	✔
Pataday† (olopatadine HCl 0.2% ophthalmic solution)	✔
Pataday† (olopatadine HCl 0.7%** ophthalmic solution)	-
olopatadine HCl 0.1% ophthalmic solution* †	✔

Drug	Generic Availability
Zerviate (cetirizine 0.24% ophthalmic solution)	-
Ophthalmic Mast Cell Stabilizers	
Alocril (nedocromil 2% ophthalmic solution)	-§
Alomide (lodoxamide 0.1% ophthalmic solution)	-
cromolyn sodium 4% ophthalmic solution	✔

Key: HCl = hydrochloride
* Brand name has been discontinued; generics are available.
† Available over-the-counter.
** This prescription brand, Pazeo, has been discontinued; olopatadine HCl 0.7% became available over-the-counter as Pataday Once Daily Relief Extra Strength in September 2020.

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications – Ophthalmic Antihistamines

Indication	**Alaway, Alaway Preservative-Free, and Zaditor** (ketotifen)	**Bepreve** (bepotastine)	**Elestat** (epinastine)	**Lastacaft** (alcaftadine)	**Optivar** (azelastine)	olopatadine prescription	(olopatadine) OTC	**Zerviate** (cetirizine)
Prevention of ocular itching associated with allergic conjunctivitis			✔	✔				
Treatment of ocular itching associated with allergic conjunctivitis		✔			✔	✔ (0.2%)		✔
Treatment of signs and symptoms of allergic conjunctivitis						✔ (0.1%)		
Temporary relief of itchy eyes due to pollen, ragweed, grass, animal hair, and dander	✔						✔	

(Prescribing information: Alaway 2020, Alaway Preservative-Free 2020, Azelastine 2019, Bepreve 2019, Epinastine ophthalmic solution 2021, Lastacaft 2020, Olopatadine ophthalmic solution 2019, Pataday Once Daily Relief 2020, Pataday Once Daily Relief Extra Strength 2020, Pataday Twice Daily Relief 2020, Zaditor 2020, Zerviate 2020)

Table 3. Food and Drug Administration Approved Indications – Ophthalmic Mast Cell Stabilizers

Indication	Alocril (nedocromil)	Alomide (lodoxamide)	cromolyn sodium
Treatment of itching associated with allergic conjunctivitis	✔		
Treatment of vernal keratoconjunctivitis, vernal conjunctivitis, and vernal keratitis		✔	✔

(*Prescribing information: Alocril 2018, Alomide 2020, cromolyn sodium ophthalmic solution 2016*)

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

CLINICAL EFFICACY SUMMARY

Ophthalmic Antihistamines

- Due to the rapid onset of action of the ophthalmic antihistamines, most trials used the conjunctival allergen challenge model to establish the relative efficacy of these formulations compared to placebo. The results of these trials demonstrated improvements in symptoms, especially for itching, in those treated with ophthalmic antihistamines and antihistamines/mast cell stabilizers compared to placebo.
- Several studies have been conducted to directly compare ophthalmic ketotifen and ophthalmic olopatadine. These studies have produced mixed results, generally demonstrating no difference between the agents. Results of some studies suggest that ophthalmic olopatadine may be preferred and better tolerated by patients *(Avunduk et al 2005, Berdy et al 2000, Borazan et al 2009, Ganz et al 2003, Leonardi et al 2004)*. There are limited head-to-head studies that compare the clinical efficacy of the other ophthalmic antihistamines to one another, and all are considered equally efficacious at improving ocular allergy symptoms. While some studies reported statistically significant differences in symptom scores, the overall clinical significance of these differences is not known, as many of these trials were conducted using single doses of study medication (in the conjunctival allergen challenge model) and generally enrolled a small number of patients. A Cochrane review of topical antihistamines for treatment of allergic conjunctivitis concluded that topical antihistamines and mast cell stabilizers reduce symptoms temporarily. Data for the long-term use of topical antihistamines are lacking *(Castillo et al 2015)*.
- A study compared efficacy of daily use of alcaftadine (n = 60), olopatadine (n = 60), and bepotastine (n = 60) for 14 days in 180 patients with mild-to-moderate allergic conjunctivitis. At day 14, the total ocular symptom score (TOSS) had significantly reduced from baseline scores in all 3 groups. Although the authors describe a statistically significant difference between groups in mean TOSS score at day 14, this was a post hoc assessment and the clinical significance of this difference is unclear. No significant differences in adverse events were observed between the 3 groups (*Ayyappanavar et al 2021*).
- Clinical data supporting the FDA approval of cetirizine ophthalmic solution were from two Phase 3 studies that evaluated the efficacy and safety of the drug compared with vehicle in the treatment of allergen-induced conjunctivitis using a conjunctival allergen challenge model (*Malhotra et al 2019, Meier et al 2018*). Approximately 100 subjects were randomized in each study. Results revealed that ophthalmic cetirizine administered 15 minutes or 8 hours before the challenge results in significantly reduced ocular itching at all time points post-challenge ($p < 0.0001$) compared to vehicle in both studies. Additionally, significant improvement in chemosis, eyelid swelling, tearing, ciliary redness, episcleral redness, and nasal symptoms were observed with cetirizine. The ophthalmic solution was well-tolerated and was associated with a low incidence of mild adverse events.

Ophthalmic Mast Cell Stabilizers

- Clinical studies have demonstrated that ophthalmic mast cell stabilizers are safe and effective for their FDA-approved indications.
- Ophthalmic formulations of cromolyn and lodoxamide are FDA-approved for the treatment of vernal keratoconjunctivitis, which is a severe form of allergic keratoconjunctivitis that may involve the cornea. A study confirmed that ophthalmic cromolyn 4% was significantly more effective than placebo in treating the signs and symptoms of vernal keratoconjunctivitis, such as conjunctival and limbal injection, limbal edema, and tearing (n = 65) (*Foster et al 1988*). In a few small studies (N = 30 to 120) conducted over 10 to 28 days, ophthalmic lodoxamide was reported to be more effective than ophthalmic cromolyn 4% in improving clinical signs and symptoms of vernal keratoconjunctivitis (*Avunduk et al 2000, Caldwell et al 1992, Leonardi et al 1997*).
- Clinical studies have shown that ophthalmic formulations of cromolyn, lodoxamide, azelastine, and nedocromil were more effective than placebo for managing symptoms of seasonal and perennial allergic conjunctivitis (*James et al 2003, Kjellman et al 1995, Leino et al 1992, Orfeo et al 2002, Owen et al 2004*). Pooled data showed that patients using ophthalmic mast-cell stabilizers were 4.9 times more likely to perceive benefit than those using placebo (*Owen et al 2004*).
- A meta-analysis of 4 trials found that patients were 1.3 times more likely to perceive their treatment response as “good” with ophthalmic antihistamines and ophthalmic antihistamines/mast-cell stabilizers compared to patients receiving pure ophthalmic mast-cell stabilizers. However, this difference in response failed to reach statistical significance (*Owen et al 2004*).
- Single-acting mast cell stabilizers are now rarely used in the treatment of acute allergic conjunctivitis because of their slow onset of action (ie, 3 to 5 days may be required for symptom abatement). Dual-acting antihistamine/mast cell

stabilizers reduce allergic inflammation by preventing mast cell release of inflammatory mediators and by selectively blocking the H_1-receptor, thus countering the effects of histamine that has already been released and enabling a relatively rapid onset of action and an effect on the late-phase response (*Bielory et al 2013*).

CLINICAL GUIDELINES

- According to the AAO, mild allergic conjunctivitis may be treated with an OTC antihistamine/vasoconstrictor or with the more effective second-generation topical histamine H_1 receptor antagonists (*AAO 2018*). Because ophthalmic vasoconstrictors have a short duration of action and may cause rebound hyperemia and conjunctivitis medicamentosa, they should only be used short-term. Ophthalmic mast-cell stabilizers can be utilized if the condition is recurrent or persistent. Newer medications that combine antihistamine activity with mast cell stabilizing properties can be utilized for either acute or chronic disease. If symptoms are not adequately controlled, a brief course of low-potency topical corticosteroids can be added. Additional measures include artificial tears, cool compresses, and allergen avoidance. Oral antihistamines are commonly used as well but may induce or worsen dry eye syndrome, impair the tear film's protective barrier, and worsen allergic conjunctivitis.
- For vernal/atopic conjunctivitis, general treatment measures include minimizing exposure to allergens or irritants and using cool compresses and ocular lubricants. Topical and oral antihistamines and topical mast cell stabilizers can be used to maintain comfort. For acute exacerbations of vernal or atopic keratoconjunctivitis, topical corticosteroids are usually necessary to control severe symptoms (*AAO 2018*).
- The guideline does not recommend one specific ophthalmic antihistamine or mast cell stabilizer over another (*AAO 2018*). There are limited head-to-head trials comparing the agents in these classes to each other. While a few studies reported some differences, the overall clinical significance of these differences is not known since many trials were conducted using single doses of study medication (conjunctival allergen challenge model), in a small number of patients, and/or with comparisons to products that are no longer commercially available.

SAFETY SUMMARY

Ophthalmic Antihistamines

- Contact lens use: patients should not wear a contact lens when using formulations containing benzalkonium chloride (all products in this review except the preservative-free form of Alaway) if the eye is red; remove contact lenses prior to instilling this product, as the preservative, benzalkonium chloride, may be absorbed by soft contact lenses. Some manufacturers state that contact lenses may be reinserted 10 minutes after administering a formulation that contains benzalkonium chloride.
- Contamination of tip and solution: do not touch eyelids or surrounding areas with the dropper tip of the bottle.
- Solutions that change color or become cloudy should not be used.
- Single-use applicators should be stored in the original container until they are ready to be used and discarded after being used in each eye. One single-use container can be used to place medication into both eyes.
- Products are for ophthalmic use only.
- Adverse events are primarily ocular in nature with burning/stinging upon instillation, ocular irritation, ocular pruritus, and redness. Systemic adverse events include mild taste upon instillation, headache, rhinitis, and potential hypersensitivity reactions.
- Due to the topical application of the ophthalmic antihistamines, drug interactions have not been reported.

Ophthalmic Mast Cell Stabilizers

- Contraindications to these products include hypersensitivity to any component of the medications.
- Contact lenses should not be worn during use of these medications.
- Contact of dropper tip to any surface should be avoided to minimize risk of contamination and ocular infection.
- Products are for ophthalmic use only.
- The most common adverse effects of the ophthalmic mast cell stabilizers are ocular burning, stinging, taste disturbances, and headache.
- In general, drug interactions are limited due to low systemic bioavailability by the ocular route.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ophthalmic Antihistamines				
Alaway, Alaway Preservative-Free and Zaditor (ketotifen)	Ophthalmic solution	Ophthalmic	Twice daily	Instill 1 drop into affected eye(s) twice daily, every 8 to 12 hours, no more than twice per day. For children ≥ 3 years of age, refer to adult dose; safety and effectiveness in children < 3 years of age have not been established. Not studied in pregnancy.
Bepreve (bepotastine)	Ophthalmic solution	Ophthalmic	Twice daily	Instill 1 drop into affected eye(s) twice daily. For children ≥ 2 years of age, refer to adult dose; safety and effectiveness in children < 2 years of age have not been established. Pregnancy: Unclassified†
Elestat (epinastine)	Ophthalmic solution	Ophthalmic	Twice daily	Instill 1 drop in each eye twice daily. Treatment should be continued throughout the period of exposure (ie, until the pollen season is over or until exposure to the offending allergen is terminated), even when symptoms are absent. For children ≥ 2 years of age, refer to adult dose; safety and effectiveness in children < 2 years of age have not been established. Pregnancy Category C*
Lastacaft (alcaftadine)	Ophthalmic solution	Ophthalmic	Once daily	Instill 1 drop in each eye once daily. If more than 1 topical ophthalmic medicinal product is being used, each one should be administered at least 5 minutes apart. For children ≥ 2 years of age, refer to adult dose; safety and effectiveness in children < 2 years of age have not been established.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Pregnancy: Unclassified†
Optivar (azelastine)	Ophthalmic solution	Ophthalmic	Twice daily	Instill 1 drop into affected eye(s) twice daily. For children ≥ 3 years of age, refer to adult dose; safety and effectiveness in children < 3 years of age have not been established. Pregnancy Category C*
Olopatadine (prescription)	Ophthalmic solution	Ophthalmic	Once daily	Instill 1 drop into affected eye(s) once daily. For children ≥ 2 years of age, refer to adult dose; safety and effectiveness in children < 3 years of age have not been established.
Pataday Once Daily Relief, Pataday Once Daily Relief Extra Strength, and Pataday Twice Daily Relief (olopatadine)	Ophthalmic solution	Ophthalmic	Once or twice daily (varies by product)	Pataday Twice Daily Relief 0.1%: Instill 1 drop into affected eye(s) twice daily at an interval of 6 to 8 hours, no more than twice per day Pataday Once Daily Relief 0.2%: Instill 1 drop into affected eye(s) once daily, no more than once daily Pataday Once Daily Relief Extra Strength 0.7%: Instill no more than 1 drop into affected eye(s) once daily For aged ≥ 2 years, use adult dosage for all OTC Pataday products. Not studied in pregnancy.
Zerviate (cetirizine)	Ophthalmic solution	Ophthalmic	Twice daily	Instill 1 drop into affected eye(s) twice daily. For children ≥ 2 years of age, refer to adult dose; safety and effectiveness in children < 2 years of age have not been established.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Pregnancy: Unclassified†
Ophthalmic Mast Cell Stabilizers				
Alocril (nedocromil)	Ophthalmic Solution	Ophthalmic	Twice daily	Instill 1 or 2 drops into affected eye(s) twice daily. Use at regular intervals. Treatment should be continued throughout the period of exposure, even when symptoms are absent. For children ≥ 3 years of age, refer to adult dose; safety and effectiveness in children < 3 years of age have not been established. Pregnancy: Unclassified†
Alomide (lodoxamide)	Ophthalmic solution	Ophthalmic	4 times a day for up to 3 months	Instill 1 to 2 drops into affected eye(s) four times daily for up to 3 months. For children > 2 years of age, refer to adult dose; safety and effectiveness in children ≤ 2 years of age have not been established. Pregnancy: Unclassified†
cromolyn sodium	Ophthalmic solution	Ophthalmic	4 to 6 times daily	Instill 1 or 2 drops into affected eye(s) 4 to 6 times daily at regular intervals. Symptomatic response is usually evident within a few days, but up to 6 weeks may be required; therapy should be continued if needed to sustain improvement. For children ≥ 4 years of age, refer to adult dose; safety and effectiveness in children < 4 years of age have not been established. Pregnancy Category B*.

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

*Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women. Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

See the current prescribing information for full details.

CONCLUSION

- The most common form of ocular allergy is allergic conjunctivitis (*Bielory et al 2012, Hamrah and Dana 2020*). Ophthalmic mast cell stabilizers and antihistamines are FDA-approved for the management of signs and symptoms associated with allergic conjunctivitis. The ophthalmic mast cell stabilizers cromolyn and lodoxamide are the only agents in this class that are FDA-approved for the treatment of vernal conjunctivitis.
- Few distinguishing characteristics exist among the available ophthalmic antihistamines, but alcaftadine and olopatadine 0.2% and 0.7% may be administered once daily, while the remaining ophthalmic antihistamines are administered 2 to 4 times daily. Currently, ophthalmic formulations of azelastine, bepotastine, epinastine, ketotifen, and olopatadine are available generically. Ophthalmic formulations of ketotifen and olopatadine are also available in OTC formulations. Due to the ophthalmic administration of these agents, relatively few adverse effects have been reported; the most common adverse reactions are ocular burning and stinging and headache.
- Regarding the ophthalmic mast cell stabilizers, all are approved for use in children (> 2 to 4 years of age depending on the product). The most common adverse effects of these agents are ocular burning, stinging, and headache. The administration schedule of these ophthalmic products ranges from twice daily to 6 times daily. Ophthalmic cromolyn is the only mast cell stabilizer currently available as a generic formulation.
- The AAO conjunctivitis guideline does not recommend one specific ophthalmic antihistamine or mast cell stabilizer over another (*AAO 2018*). There are limited head-to-head trials comparing the agents in these classes to each other. While a few studies reported some differences, the overall clinical significance of these differences is not known since many trials were conducted using single doses of study medication (conjunctival allergen challenge model), in a small number of patients, and/or with comparisons to products that are no longer commercially available.

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OPTUMRx®

Established Drug Classes

Therapeutic Class Overview
Multiple Sclerosis Agents

INTRODUCTION

Multiple Sclerosis

- Multiple Sclerosis (MS), a chronic, immune-mediated disease of the central nervous system (CNS), is among the most common causes of neurological disability in young adults *(MS Coalition 2019, National Institutes of Health MS 2021)*. Multiple sclerosis is characterized by inflammation, demyelination, and degenerative changes in the CNS. Most patients with MS experience relapses and remissions of neurological symptoms, usually early in the disease process, with clinical events that are generally associated with CNS inflammation. There are 4 clinical subtypes of MS:
  - Relapsing-remitting MS (RRMS), which is characterized by acute attacks followed by partial or full recovery. This is the most common form of MS, accounting for an estimated 85% of cases.
  - Secondary progressive MS (SPMS) begins as RRMS; however, the attack rate declines over time. Patients experience a gradual deterioration. Patients with RRMS for more than 10 years may transition to SPMS.
  - Primary progressive MS (PPMS) occurs in approximately 15% of patients with MS. Patients have a continuous and gradual decline in function without evidence of acute attacks.
  - Clinically isolated syndrome (CIS) refers to the first episode of neurologic symptoms that lasts at least 24 hours and is caused by inflammation or demyelination in the CNS. Patients who experience a CIS may or may not develop MS *(Sanvito et al 2011, National MS Society 2020[a])*.
- An estimated 1 million adults in the United States (U.S.) are affected by MS. Most patients are diagnosed between the ages of 20 and 50 years, and MS is at least 2 to 3 times more common in women than in men *(National MS Society 2020[b])*.
- Diagnosis of MS requires evidence that demonstrates lesions in the CNS showing “dissemination in space” (ie, suggestions of damage in > 1 place in the nervous system) and “dissemination in time” (ie, suggestions that damage has occurred more than once). It is a diagnosis of exclusion, after consideration of and elimination of more likely diagnoses *(Thompson et al 2018)*.
- The patient evaluation includes an extensive history, neurological examination, laboratory tests to rule out other possible causes, magnetic resonance imaging (MRI) to evaluate for new disease and signs of more chronic damage, and possibly lumbar puncture (*Thompson et al 2018*).
- Exacerbations, also known as flares, relapses, or attacks of MS, are caused by inflammation in the CNS that leads to damage to the myelin and slowing or blocking of transmission of nerve impulses. A true MS exacerbation must last at least 24 hours and be separated from a previous exacerbation by at least 30 days. Exacerbations can be mild or severe. Intravenous (IV) corticosteroids may be used to treat severe exacerbations of MS. Corticosteroids decrease acute inflammation in the CNS but do not provide any long-term benefits *(Frohman et al 2007)*.
- The approach to treating MS includes the management of symptoms, treatment of acute relapses, and utilization of disease-modifying therapies (DMTs) to reduce the frequency and severity of relapses, reduce lesions on MRI scans, and possibly delay disease and disability progression *(Rae-Grant et al 2018)*. The American Academy of Neurology (AAN), the European Committee for Research and Treatment of Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) guidelines recommend initiation of DMTs early in the patient’s disease course (*Montalban et al 2018, Rae-Grant et al 2018*). These therapies may delay the progression from CIS to clinically definite MS (CDMS) *(Armoiry et al 2018, Miller et al 2012)*. The MS Coalition, the AAN, and the Association of British Neurologists guidelines support access to available DMTs for patients with MS. While there are no precise algorithms to determine the order of product selection, therapy should be individualized and patients’ clinical response and tolerability to medications should be monitored (*MS Coalition 2019, Rae-Grant et al 2018, Scolding et al 2015*).
- Pediatric-onset MS is rare, with the vast majority of cases demonstrating a relapsing-remitting disease course (*Otallah et al 2018*). Gilenya (fingolimod) is the first FDA-approved agent for pediatric patients with MS. Its approval was based on the PARADIGMS trial (*Chitnis et al 2018*).

- Vumerity (diroximel fumarate) is rapidly converted to monomethyl fumarate (MMF), which also is the active metabolite of Tecfidera (dimethyl fumarate). Diroximel fumarate may offer improved gastrointestinal (GI) tolerability as compared to dimethyl fumarate (*Naismith et al 2019, Selmaj et al 2019*). In April 2020, the FDA approved another agent in this class, Bafiertam (monomethyl fumarate). This drug is considered a "bioequivalent alternative" to dimethyl fumarate since dimethyl fumarate is a prodrug, and monomethyl fumarate is its active ingredient. Since the drug is already in its active form, it is administered at a lower dose than dimethyl fumarate, and it is thought that it may lead to fewer GI adverse effects (*Bafiertam prescribing information 2021*).

- Agents for the treatment of MS also have been developed for use in GI disorders.
- Ulcerative Colitis (UC)
  - UC is a form of inflammatory bowel disease (IBD) that is characterized by recurrent episodes of inflammation of the mucosal layer of the colon. The inflammation, limited to the mucosa, commonly involves the rectum and may extend in a proximal and continuous fashion to affect other parts of the colon. The hallmark clinical symptom is an inflamed rectum with symptoms of urgency, bleeding, and tenesmus *(Peppercorn and Kane 2020[a], Rubin et al 2019).*
  - Precise incidence and prevalence estimates of UC have been limited by a lack of gold standard criteria for diagnosis, inconsistent case ascertainment, and disease misclassification. The existing data suggest that the U.S. incidence rate of UC varies between 2.2 to 19.2 per 100,000 person-years. As many as 3 million persons in the U.S. suffer from IBD *(Molodecky et al 2012, Shivashankar et al 2017, Centers for Disease Control and Prevention [CDC] 2020).*
  - Current pharmacotherapy for UC includes 5-aminosalicylic acid (5-ASA) derivatives, glucocorticoids, immunomodulators (azathioprine, 6-mercaptopurine [6-MP], and methotrexate), and biologic agents (eg, infliximab, Humira [adalimumab]) *(Micromedex 2021, Bernstein et al 2015).* These agents are discussed in separate class reviews.
  - Zeposia (ozanimod) is the first sphingosine 1-phosphate (S1P) receptor modulator that is approved for moderate to severe UC in adults in addition to its approval for MS *(Zeposia prescribing information 2021).*
- Crohn's Disease
  - Crohn's disease (CD) is a form of IBD that can involve any part of the GI tract and is characterized by transmural inflammation and "skip areas." Transmural inflammation may lead to fibrosis, strictures, sinus tracts, and fistulae *(Peppercorn and Kane 2020[b]).*
  - Precise incidence and prevalence of CD have been limited by a lack of gold standard criteria for diagnosis, inconsistent case ascertainment, and disease misclassification. The existing data suggest that the U.S. incidence rate of CD varies from 3.1 to 20.2 per 100,000 person-years. *(Molodecky et al 2012, Shivashankar et al 2017)*
  - Current pharmacotherapy for the treatment of CD includes the use of 5-ASA derivatives, biologic agents (eg, infliximab, adalimumab, certolizumab pegol, ustekinumab, and vedolizumab), glucocorticoids, locally active steroids (eg, budesonide) methotrexate, and thiopurines (eg, azathioprine and 6-MP) (*Torres et al 2020, Lichtenstein et al 2018, Feuerstein et al 2021*). These agents are discussed in separate class reviews.
  - Tysabri (natalizumab) is approved for inducing and maintaining clinical response and remission in adults with moderate to severe active CD with evidence of inflammation, who have had an inadequate response to conventional therapies or tumor necrosis factor (TNF) blockers. Natalizumab should not be used in combination with other immunosuppressants or inhibitors of TNF (*Tysabri prescribing information 2020*).
- All agents in this class review are listed as Multiple Sclerosis Agents in Medispan; the exceptions are mitoxantrone (listed as an antineoplastic antibiotic) and Ampyra (dalfampridine) (listed as a potassium channel blocker).

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Ampyra (dalfampridine)	✔
Aubagio (teriflunomide)	-
Avonex (interferon β-1a)	-
Bafiertam (monomethyl fumarate)	-
Betaseron (interferon β-1b)	-
Copaxone, Glatopa† (glatiramer acetate)	✔
Extavia (interferon β-1b)	-
Gilenya (fingolimod)	-

Drug	Generic Availability
Kesimpta (ofatumumab)§	-
Lemtrada (alemtuzumab)	-
Mavenclad (cladribine)‖	-
Mayzent (siponimod)	-
mitoxantrone	✔ ‡
Ocrevus (ocrelizumab)	-
Plegridy (peginterferon β-1a)	-
Ponvory (ponesimod)	-
Rebif (interferon β-1a)	-
Tecfidera (dimethyl fumarate)	✔
Tysabri (natalizumab)	-
Vumerity (diroximel fumarate)	-
Zeposia (ozanimod)	-

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

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Drug	Improve walking in MS	Relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease in adults	Relapsing forms of MS, to include relapsing-remitting disease and active secondary progressive disease in adults	Primary Progressive MS in adults	Reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary progressive, progressive relapsing, or worsening relapsing-remitting MS	Moderately to severely active ulcerative colitis in adults	Moderately to severely active Crohn's disease in adults
Ampyra (dalfampridine)	✔ *	-	-	-	-	-	-
Aubagio (teriflunomide)	-	✔	-	-	-	-	-
Avonex (interferon β-1a)	-	✔	-	-	-	-	-
Bafiertam (monomethyl fumarate)	-	✔	-	-	-	-	-
Betaseron/Extavia (interferon β-1b)	-	✔	-	-	-	-	-

Drug	Improve walking in MS	Relapsing forms of MS, to include CIS, relapsing-remitting disease, and active secondary progressive disease in adults	Relapsing forms of MS, to include relapsing-remitting disease and active secondary progressive disease in adults	Primary Progressive MS in adults	Reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary progressive, progressive relapsing, or worsening relapsing-remitting MS	Moderately to severely active ulcerative colitis in adults	Moderately to severely active Crohn's disease in adults
Copaxone (glatiramer acetate)	-	✔	-	-	-	-	-
Gilenya (fingolimod)	-	✔ †	-	-	-	-	-
Kesimpta (ofatumumab)		✔					
Lemtrada (alemtuzumab)	-	-	✔ ‡	-	-	-	-
Mavenclad (cladribine)	-	-	✔ §	-	-	-	-
Mayzent (siponimod)	-	✔	-	-	-	-	-
mitoxantrone	-	-	-	-	✔ ‖	-	-
Ocrevus (ocrelizumab)	-	✔	-	✔	-	-	-
Plegridy (peginterferon β-1a)	-	✔	-	-	-	-	-
Ponvory (ponesimod)	-	✔	-	-	-	-	-
Rebif (interferon β-1a)	-	✔	-	-	-	-	-
Tecfidera (dimethyl fumarate)	-	✔	-	-	-	-	-
Tysabri (natalizumab)	-	✔ ¶	-	-	-	-	✔ #
Vumerity (diroximel fumarate)	-	✔	-	-	-	-	-
Zeposia (ozanimod)	-	✔	-	-	-	✔	-

*Ampyra is indicated as a treatment to improve walking in adult patients with MS. This was demonstrated by an increase in walking speed.
†Approved in patients 10 years of age and older.
‡Because of its safety profile, Lemtrada should generally be reserved for patients who have had an inadequate response to 2 or more drugs indicated for the treatment of MS. Lemtrada is not recommended for use in patients with CIS because of its safety profile.
§ Because of its safety profile, use of Mavenclad is generally recommended for patients who have had an inadequate response, or are unable to tolerate, an alternate drug indicated for the treatment of MS. Mavenclad is not recommended for use in patients with CIS because of its safety profile.
‖Mitoxantrone is indicated for reducing neurologic disability and/or the frequency of clinical relapses in patients with secondary (chronic) progressive, progressive relapsing, or worsening RRMS (ie, patients whose neurologic status is significantly abnormal between relapses). Mitoxantrone is not

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

(Prescribing information: Ampyra 2021, Aubagio 2021, Avonex 2021, Bafiertam 2021, Betaseron 2021, Copaxone 2020, Extavia 2021, Gilenya 2019, Glatopa 2020, Kesimpta 2020, Lemtrada 2021, Mavenclad 2019, Mayzent 2021, mitoxantrone 2018, Ocrevus 2021, Plegridy 2021, Ponvory 2021, Rebif 2021, Tecfidera 2021, Tysabri 2020, Vumerity 2021, Zeposia 2021)

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

CLINICAL EFFICACY SUMMARY

Multiple Sclerosis

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

Interferons and glatiramer acetate

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

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

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

patients; placebo, 2 patients) *(Calabresi et al 2014[b])*. Preliminary data on NAb development to peginterferon β-1a over 2 years showed < 1% for all groups *(White et al 2014)*.

- The ADVANCE study continued into a second year. Patients originally randomized to placebo were re-randomized to peginterferon β-1a (the "placebo-switch group"). Peginterferon β-1a patients were continued on their original assigned therapy. A total of 1332 patients entered the second year of the study. After 96 weeks, the ARR was significantly lower in the peginterferon β-1a SC every 2 weeks group (ARR, 0.221; p = 0.0001 vs placebo-switch group; p = 0.0209 vs every 4 week regimen) compared to both the placebo-switch group (ARR, 0.351) and the peginterferon β-1a SC every 4 week group (ARR, 0.291). The peginterferon β-1a SC every 4 week group (ARR, 0.291; p = not significant [NS] vs placebo-switch group) was not significantly different from the placebo-switch group (ARR, 0.351) after 96 weeks based on the intent-to-treat (ITT) analysis. Peginterferon β-1a SC every 2 weeks was also associated with a lower proportion of patients who had relapse and a lower proportion of patients who had disability progression. Mean number of new or newly enlarging T2-weighted hyperintense MRI lesions over 2 years was numerically lower with the peginterferon β-1a SC every 2 weeks group compared to the placebo-switch group *(Calabresi et al 2014[b], Kieseier et al 2015)*.
- The ATTAIN study was an open-label extension of the ADVANCE study, where patients were followed for an additional 2 years (*Newsome et al 2018*). Of the original ADVANCE patients, 71% continued into the ATTAIN study, and 78% of those patients completed the extension study. The primary objective of the study was to evaluate the long-term safety of peginterferon β-1a SC. During the study, the common adverse events were influenza-like illness (43%), injection site erythema (41%), and headache (29%). The rate of treatment-related serious adverse events was 1%. The adjusted ARR and risk of relapse were reduced significantly with the every 2 weeks compared to the every 4 weeks dosing group (0.188 vs 0.263 and 36% vs 49%, respectively).
- Bioequivalency was demonstrated for Plegridy administered by IM and SC injection in an unpublished, open-label, crossover, single-dose, Phase 1 study of 136 healthy volunteers; this study was the basis for the FDA approval of the IM route of administration for Plegridy (*Zhao et al 2020*). Injection site reactions were reported less frequently after IM dosing (14.4%) than after SC dosing (32.1%).

ORAL AGENTS

Aubagio (teriflunomide)

- Efficacy and safety of Aubagio (teriflunomide) were evaluated in two Phase 3, double-blind, placebo-controlled, RCTs – the TEMSO trial (*O'Connor et al, 2011*) and the TOWER trial *(Confavreux et al 2014)*. In the TEMSO trial, 1088 patients with relapsing MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for a total of 108 weeks. Results demonstrated that compared to placebo, teriflunomide, at both doses, reduced the ARR.
  - The percentage of patients with confirmed disability progression (CDP) at 12 weeks was significantly lower only in the teriflunomide 14 mg group (20.2%) compared to placebo (27.3%; p = 0.03) *(O'Connor et al 2011)*.
- Teriflunomide has demonstrated beneficial effects on MRI scans in a Phase 2, double-blind, RCT. A total of 179 patients with MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for 36 weeks and were followed every 6 weeks with MRI scans during the treatment period. The teriflunomide groups had significant reductions in the average number of unique active lesions per MRI scan *(O'Connor et al 2006)*.
- In the TOWER trial, 1165 patients with relapsing MS were randomized to teriflunomide 7 mg or 14 mg daily or placebo for at least 48 weeks of therapy. The study ended 48 weeks after the last patient was randomized. Results demonstrated that, compared to placebo, teriflunomide 14 mg significantly reduced the ARR and the risk of sustained accumulation of disability at 12 weeks *(Confavreux et al 2014)*.
- Teriflunomide and Rebif (IFNβ-1a SC) were compared in the 48-week TENERE study evaluating 324 patients with relapsing MS. The primary outcome, time to failure defined as a confirmed relapse or permanent discontinuation for any cause, was comparable for teriflunomide 7 mg and 14 mg and Rebif *(Vermersch et al 2014)*.

Mavenclad (cladribine)

- The 96-week Phase 3 trial, CLARITY, was a double-blind, 3-arm, placebo-controlled, multicenter RCT to evaluate the safety and efficacy of oral cladribine in 1326 patients with RRMS (*Giovannoni et al 2010*, *Giovannoni 2017*).
  - Patients were required to have at least 1 relapse in the previous 12 months. The median patient age was 39 years and the female-to-male ratio was 2:1. The mean duration of MS prior to study enrollment was 8.7 years.
  - Patients were randomized to receive either placebo (n = 437), or a cumulative oral dose of cladribine 3.5 mg/kg (n = 433) or 5.25 mg/kg (n = 456) over the 96-week study period in 2 treatment courses.

- ARRs at 96 weeks, the primary outcome, were reduced in both cladribine treatment groups vs placebo (0.14, 0.15, and 0.33 in the 3.5 mg/kg, 5.25 mg/kg and placebo groups, respectively; each p < 0.001).
- A significantly higher percentage of patients remained relapse-free at 96 weeks in both cladribine treatment groups vs placebo; a total of 79.7% and 78.9% of patients in the 3.5 mg/kg and 5.25 mg/kg groups, respectively, were relapse free vs 60.9% in the placebo group (each p < 0.001 vs placebo).
- Cladribine 3.5 mg/kg group had a lower risk of 3-month CDP vs placebo (hazard ratio [HR], 0.67; 95% CI, 0.48 to 0.93; p = 0.02). Lesions on MRI were significantly lower in the cladribine 3.5 mg/kg group vs placebo (p < 0.001 for all comparisons).

Oral sphingosine-1-phosphate (S1P) receptor modulators

Gilenya (fingolimod)

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

Mayzent (siponimod)

- The Phase 3 EXPAND trial was a double-blind, parallel-group, placebo-controlled, time-to-event RCT in patients with SPMS who had evidence of disability progression in the previous 2 years (*Kappos et al 2018*). A total of 1651 patients were randomized to treatment with either siponimod 2 mg (n = 1105) or placebo (n = 546). A total of 82% of the siponimod-treated patients and 78% of placebo-treated patients completed the study. The median age of patients was 49.0 years, 95% of patients were White, and 60% were female.
  - For the primary endpoint, 288 (26%) of 1096 patients receiving siponimod and 173 (32%) of 545 patients receiving placebo had a 3-month CDP (HR, 0.79; 95% CI, 0.65 to 0.95; p = 0.013).
  - Key secondary endpoints included time to 3-month confirmed worsening of at least 20% from baseline in timed 25-foot walk (T25FW) and change from baseline in T2 lesion volume on MRI. Siponimod did not show a significant difference in T25FW.
  - Patients treated with siponimod had a 55% relative reduction in ARR (0.071 vs 0.16), compared to placebo (nominal p < 0.01). The absolute reduction in the ARR was 0.089 with siponimod.
- A Cochrane Review evaluated the safety and efficacy of siponimod 2 mg daily vs placebo for the treatment of MS (*Cao et al 2021*). A total of 1948 patients with SPMS and RRMS were evaluated from the 2 RCTs included in the analysis. Siponimod was associated with a reduction in disability compared to placebo at 6 months (RR, 0.78; 95% CI, 0.65 to

0.94; low-certainty evidence), a slight reduction in relapses at 6 months (RR, 0.38; 95% CI, 0.15 to 1.00; very low-certainty evidence), and a reduction in ARR (RR, 0.43; 95% CI, 0.34 to 0.56; low-certainty evidence). The mean number of Gd-enhancing lesions on MRI was also lowered at 6 months vs placebo (RR, 0.14; 95% CI, 0.10 to 0.19; very low-certainty evidence). No significant differences were found for serious adverse event rates between siponimod and placebo groups at 6 months. No data was available on cardiac adverse events.

Zeposia (ozanimod)

- The efficacy and safety of ozanimod were compared to Avonex (IFNβ-1a IM) in two multicenter, Phase 3, double-blind, double-dummy RCTs in patients with relapsing forms of MS– SUNBEAM and RADIANCE (*Comi et al 2019, Cohen et al 2019)*. In the studies, which were conducted over a minimum of 12 months, patients were randomized 1:1:1 to oral ozanimod 0.5 mg daily, oral ozanimod 1 mg daily, or Avonex (IFNβ-1a) 30 mcg IM once weekly. All patients received an initial 7-day dose escalation of ozanimod or placebo prior to receiving their assigned dose on day 8. Prophylactic administration of acetaminophen or ibuprofen was recommended 1 hour before each IFN or placebo injection and every 6 hours for 24 hours after the injection. Patients in both trials (n = 1346 for SUNBEAM and n = 1320 for RADIANCE) had an EDSS score of ≤ 5, and a history of at least 1 relapse within 12 months prior to screening or 1 relapse within 24 months in addition to at least 1 Gd-enhancing lesion on MRI within 12 months prior to screening. The primary endpoint in both trials was the ARR.
  - In the SUNBEAM, the ARR was 0.18 (95% CI, 0.14 to 0.24) for ozanimod 1 mg, 0.24 (95% CI, 0.19 to 0.31) for ozanimod 0.5 mg, and 0.35 (95% CI, 0.28 to 0.44) for IFNβ-1a IM. Significant reductions in ARR were observed compared to IFNβ-1a IM with both ozanimod 1 mg (rate ratio, 0.52; 95% CI, 0.41 to 0.66; p < 0.0001) and ozanimod 0.5 mg (rate ratio, 0.69; 95% CI, 0.55 to 0.86; p = 0.0013).
  - In the RADIANCE trial, adjusted ARRs were found to be 0.17 (95% CI, 0.14 to 0.21) for ozanimod 1 mg, 0.22 (95% CI, 0.18 to 0.26) for ozanimod 0.5 mg, and 0.28 (95% CI, 0.23 to 0.32) for IFNβ-1a IM. The rate ratios were significant when comparing ozanimod 1 mg (rate ratio, 0.62; 95% CI, 0.51 to 0.77; p < 0.0001) and ozanimod 0.5 mg (rate ratio, 0.79; 95% CI, 0.65 to 0.96; p = 0.0167) to IFNβ-1a IM.
  - Clinically significant evidence of bradycardia, second-, or third-degree heart block was not noted after administration of the first dose in either trial.

Ponvory (ponesimod)

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

Oral Fumarates

Tecfidera (dimethyl fumarate)

- Tecfidera (dimethyl fumarate) was evaluated in two Phase 3 studies: DEFINE and CONFIRM *(Fox et al 2012, Gold et al 2012, Xu et al 2015)*. DEFINE was a multicenter RCT that compared 2 dosing regimens of dimethyl fumarate (240 mg twice daily and 240 mg 3 times daily) to placebo in 1237 patients with RRMS over 96 weeks. Results demonstrated that, compared to placebo, treatment with both doses of dimethyl fumarate reduced the proportion of patients with a relapse within 2 years, the ARR, the number of lesions on MRI, and the proportion of patients with disability progression at 12 weeks *(Gold et al 2012)*.
- CONFIRM was a multicenter RCT that compared 2 dosing regimens of dimethyl fumarate (240 mg twice daily and 240 mg 3 times daily) to placebo, with an additional, open-label study arm evaluating glatiramer acetate 20 mg SC daily. Glatiramer acetate was included as a reference comparator, but the study was not designed to test the superiority or non-inferiority of dimethyl fumarate vs glatiramer acetate. There were 1430 patients enrolled, and the trial duration was 96 weeks. Results of CONFIRM were similar to DEFINE, with the exception that there was no significant difference between groups in the likelihood of CDP at 12 weeks. The CONFIRM trial demonstrated that, compared to placebo, treatment with both doses of dimethyl fumarate reduced the proportion of patients with a relapse within 2 years, the ARR, and the number of lesions on MRI *(Fox et al 2012)*.

Vumerity (diroximel fumarate)

- The efficacy of diroximel fumarate was established through bioavailability studies in patients with relapsing forms of MS and healthy subjects comparing oral dimethyl fumarate to diroximel fumarate (*Vumerity Prescribing Information 2021*).
- In a Phase 3, open-label, long-term safety study, 696 patients with RRMS (EVOLVE-MS-1) were administered diroximel fumarate 462 mg twice daily for up to 96 weeks (*Palte et al 2019*). Interim results revealed that GI treatment-emergent adverse events occurred in 215 (30.9%) patients; the vast majority of these events (207 [96%]) were mild or moderate in severity. Gastrointestinal events occurred early in therapy, resolved (88.8%; 191/215), and were of short duration (median 7.5 days) in most patients. Discontinuation of treatment due to a GI treatment-emergent adverse event occurred in < 1% of patients.
- Topline results from the randomized, double-blind, 5-week, Phase 3, EVOLVE-MS-2 study also demonstrated significantly improved GI tolerability with diroximel fumarate vs dimethyl fumarate in 506 patients with RRMS (*Selmaj et al 2019*). Patients were randomized to diroximel fumarate 462 mg twice daily or dimethyl fumarate 240 mg twice daily. The primary endpoint was the number of days patients reported GI symptoms with a symptom intensity score ≥ 2 on the Individual Gastrointestinal Symptom and Impact Scale (IGISIS) rating scale. Results revealed that patients treated with diroximel fumarate self-reported significantly fewer days of key GI symptoms with intensity scores ≥ 2 as compared to dimethyl fumarate (p = 0.0003). The most commonly reported adverse events for both groups were flushing, diarrhea, and nausea.

Bafiertam (monomethyl fumarate)

- The efficacy of monomethyl fumarate, the active moiety of dimethyl fumarate, is based on bioavailability studies in healthy patients comparing oral dimethyl fumarate delayed-release capsules to monomethyl fumarate delayed-release capsules. Analyses compared the blood levels of monomethyl fumarate to establish bioequivalency and support the FDA approval (*Bafiertam Prescribing Information 2021*).

High Efficacy Infusibles and Injectables

Tysabri (natalizumab)

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

Lemtrada (alemtuzumab)

- The efficacy and safety of alemtuzumab were compared to Rebif (IFNβ-1a SC) in two Phase 3, open-label RCTs in patients with relapsing forms of MS – CARE-MS I and CARE-MS II (*Cohen et al 2012, Coles et al 2012)*. In the 2-year studies, patients were randomized to alemtuzumab infused for 5 consecutive days followed by a 3 consecutive day treatment course 12 months later or to Rebif (IFNβ-1a SC) 44 mcg 3 times weekly after an initial dosage titration. All patients received methylprednisolone 1 g IV for 3 consecutive days at the initiation of treatment and at month 12.
  - The CARE-MS I trial enrolled treatment-naïve patients with MS (n = 581) who were high functioning based on the requirement of a score of 3 or lower on the EDSS.
  - Patients (n = 840) enrolled in the CARE-MS II trial had experienced at least 1 relapse while on IFNβ or glatiramer acetate after at least 6 months of treatment. Patients were required to have an EDSS score of ≤ 5.
  - The co-primary endpoints for both trials were the relapse rate and the time to 6-month sustained accumulation of disability.
  - In the CARE-MS I trial, alemtuzumab reduced the risk of relapse by 55% compared to IFNβ-1a SC (p < 0.0001). Relapses were reported in 22% of alemtuzumab-treated patients and 40% of IFNβ-1a SC patients over 2 years. The

proportion of patients having sustained accumulation of disability over 6 months was not significantly different between alemtuzumab (8%) vs IFNβ-1a SC (11%) (p = 0.22).
  - In the CARE-MS II trial, alemtuzumab significantly reduced the relapse rate and sustained accumulation of disability compared to IFNβ-1a SC. The relapse rate at 2 years was reduced by 49% with alemtuzumab (p < 0.0001). The percent of patients with sustained accumulation of disability confirmed over 6 months was 13% with alemtuzumab and 20% with IFNβ-1a SC, representing a 42% risk reduction with alemtuzumab (p = 0.0084).
  - Both studies evaluated MRI outcomes, specifically the median percent change in T2 hyperintense lesion volume from baseline. Neither study found a significant difference between the 2 drugs for this measure.
  - During extension studies of CARE-MS I and CARE-MS II, approximately 80% of patients previously treated with alemtuzumab did not require additional treatment during the first year of the extension study *(Garnock-Jones 2014)*.
- A Cochrane review by Zhang et al (2017) that compared the efficacy, tolerability, and safety of alemtuzumab vs IFNβ-1a in the treatment of RRMS identified 3 RCTs in 1694 total patients from the CARE-MS I, CARE-MS II, and CAMMS223 studies. In the alemtuzumab 12 mg/day group, the results showed statistically significant differences in reducing relapses (RR, 0.60; 95% CI, 0.52 to 0.70); preventing disease progression (RR, 0.60; 95% CI, 0.45 to 0.79); and developing new T2-weighted lesions on MRI (RR, 0.75; 95% CI, 0.61 to 0.93) after 24 and 36 months' follow-up, but found no statistically significant difference in the changes of EDSS score (MD, -0.35; 95% CI, -0.73 to 0.03). The most frequently reported adverse effects with alemtuzumab were infusion-associated reactions, infections, and autoimmune events.

Kesimpta (ofatumumab)
- The two Phase 3, double-blind, double-dummy, active-controlled, multicenter RCTs, the ASCLEPIOS I and II trials, included 1882 patients with relapsing MS who were treated with ofatumumab 20 mg SC every 4 weeks or teriflunomide 14 mg daily for up to 30 months. Approximately 40% of the patients in each group had no prior exposure to DMTs. Ofatumumab significantly reduced the ARR, the primary endpoint, compared with teriflunomide.
  - ASCLEPIOS I: ARR: 0.11 vs 0.22; difference, -0.11; 95% CI, -0.16 to -0.06; p < 0.001; RR, 0.49; 95% CI, 0.37 to 0.65; p < 0.001.
  - ASCLEPIOS II: ARR: 0.10 vs 0.25; difference, -0.15; 95% CI, -0.20 to -0.09; p < 0.001; RR, 0.42; 95% CI, 0.31 to 0.56; p < 0.001.
  - Pooled data demonstrated that the percentage of patients with confirmed disability worsening at 3 months was 10.9% vs 15.0% for ofatumumab vs teriflunomide, respectively (HR, 0.66; 95% CI, 0.50 to 0.86; p = 0.002). For the confirmed disability worsening at 6 months, the percentage was also lower in the ofatumumab group (8.1% vs 12.0%; HR, 0.68; 95% CI, 0.50 to 0.92; p = 0.01). There was no significant difference between the groups for disability improvement.
  - For the MRI endpoints, the ofatumumab group had significantly fewer mean number of Gd-enhancing lesions and mean number of new or enlarging lesions per year on T2-weighted MRI (all p < 0.001). Brain volume loss did not differ significantly between groups in either trial *(Hauser et al 2020[a])*.

Ocrevus (ocrelizumab)
- The Phase 3 clinical development program for ocrelizumab (ORCHESTRA) included 3 studies: OPERA I, OPERA II, and ORATORIO *(Hauser et al 2017, Montalban et al 2017)*.
  - OPERA I and OPERA II were 2 identically-designed, 96-week, Phase 3, active-controlled, double-blind, double-dummy, multicenter, parallel-group RCTs that evaluated the efficacy and safety of ocrelizumab (600 mg administered as an IV infusion given as 2-300 mg infusions separated by 2 weeks for dose 1 and then as a single 600 mg infusion every 6 months for subsequent doses) compared with Rebif (IFNβ-1a 44 mcg SC 3 times weekly) in 1656 patients with relapsing MS *(Hauser et al 2017, ClinicalTrials.gov Web site, Ocrevus Formulary Submission Dossier 2017)*.
    - Across both studies, the majority of patients had not been treated with a DMT in the 2 years before screening (range: 71.4% to 75.3%); of those patients that had received a previous DMT as allowed by the protocol, most received IFN (18.0% to 21.0%) or glatiramer acetate (9.0% to 10.6%).
    - Ocrelizumab achieved statistically significant reductions in the ARR vs Rebif (IFNβ-1a SC) across both trials (primary endpoint).
      - OPERA I (0.16 vs 0.29; 46% lower rate with ocrelizumab; p < 0.001)
      - OPERA II (0.16 vs 0.29; 47% lower rate; p < 0.001)

- In pre-specified pooled analyses (secondary endpoints), the percentage of patients with disability progression confirmed at 12 weeks was statistically significantly lower with ocrelizumab vs Rebif (9.1% vs 13.6%; HR, 0.60; 95% CI, 0.45 to 0.81; p < 0.001). The results were similar for disability progression confirmed at 24 weeks (6.9% vs 10.5%; HR, 0.60; 95% CI, 0.43 to 0.84; p = 0.003). The percentages of patients with disability improvement confirmed at 12 weeks were 20.7% in the ocrelizumab group vs 15.6% in the Rebif group (33% higher rate of improvement with ocrelizumab; p = 0.02).
- The mean numbers of Gd-enhancing lesions per T1-weighted MRI scan were statistically significantly reduced with ocrelizumab vs Rebif (secondary endpoint).
  - OPERA I: 0.02 vs 0.29 (rate ratio = 0.06; 95% CI, 0.03 to 0.10; 94% lower number of lesions with ocrelizumab; p < 0.001)
  - OPERA II: 0.02 vs 0.42 (rate ratio = 0.05; 95% CI, 0.03 to 0.09; 95% lower number of lesions; p < 0.001)
- The most common adverse events were infusion-related reactions and infections.

○ No opportunistic infections, including PML, were reported in any group over the duration of either trial.
- An imbalance of malignancies was observed with ocrelizumab; across both studies and through 96 weeks, neoplasms occurred in 0.5% (4/825) of ocrelizumab-treated patients vs 0.2% (2/826) of Rebif-treated patients.
- Among the ocrelizumab-treated patients that developed neoplasms, there were 2 cases of invasive ductal breast carcinoma, 1 case of renal-cell carcinoma, and 1 case of malignant melanoma. Rebif-treated patients with neoplasms included 1 case of mantle-cell lymphoma and 1 case of squamous-cell carcinoma in the chest.
  - Between the clinical cutoff dates of the 2 trials (April 2, 2015 [OPERA I] and May 12, 2015 [OPERA II]) and June 30, 2016, 5 additional cases of neoplasm (2 cases of breast cancer, 2 cases of basal-cell skin carcinoma, and 1 case of malignant melanoma) were observed during the open-label extension phase in which all continuing patients received ocrelizumab.
  - As of February 2018, the overall crude incidence rate of malignancies among patients from OPERA I and II who received ocrelizumab in the double-blind period or open-label extension was 0.40 per 100 patient-years of exposure to ocrelizumab. The incidence rate as of the data cutoff of May 2015 after the completion of the double-blind period was 0.28 for the ocrelizumab group and 0.14 for the IFN β-1a SC group (*Hauser et al 2020[b]*).
  - As of January 2019, the age- and sex-standardized incidence rate of all malignancies in the ocrelizumab all-exposure (all Phase 2 and 3 studies, plus 4 other trials) (0.22 per 100 patient-years; 95% CI, 0.16 to 0.33), remained stable over time, with confidence intervals overlapping and within epidemiological references from the Surveillance, Epidemiology, and End Results [SEER] Program of the National Cancer Institute, which reports data on cancer incidence in approximately 28% of the general U.S. population (0.31 per 100 patient-years) (*Genentech 2020[a]*).
  - Since breast cancer occurred in 6 out of 781 females treated with ocrelizumab (vs in none of 668 females treated with IFN β-1a SC or placebo), the labeling of ocrelizumab recommends that patients follow standard breast cancer screening guidelines (*Genentech 2020[b]*). In an analysis of the all-exposure ocrelizumab population from the trials through January 2019, the incidence rate of female breast cancer using age at event onset methodology was 0.15 (95% CI, 0.08 to 0.27) per 100 patient-years compared to 0.14 per 100 patient-years (95% CI, 0.14 to 0.14) based on SEER (*Genentech 2020[a]*).

○ ORATORIO was an event-driven, Phase 3, double-blind, multicenter, placebo-controlled, RCT evaluating the efficacy and safety of ocrelizumab (600 mg administered by IV infusion every 6 months; given as 2-300 mg infusions 2 weeks apart for each dose) compared with placebo in 732 people with PPMS *(Montalban et al 2017, ClinicalTrials.gov Web site, Ocrevus Formulary Submission Dossier 2017)*. Double-blind treatment was administered for a minimum of 5 doses (120 weeks) until the occurrence of ~253 events of disability progression in the trial cohort that was confirmed for at least 12 weeks.
- The majority of patients (~88%) reported no previous use of DMTs within 2 years of trial entry. The proportion of patients with Gd-enhancing lesions was similar (27.5% in the ocrelizumab group vs 24.7% in the placebo group); however, there was an imbalance in the mean number of Gd-enhancing lesions at baseline, with nearly 50% fewer lesions in the placebo group (1.21 vs 0.6) (*Ocrevus FDA Medical and Summary Reviews 2017*).
- For the primary endpoint, the percentages of patients with 12-week CDP were 32.9% with ocrelizumab vs 39.3% with placebo (HR, 0.76; 95% CI, 0.59 to 0.98; p = 0.03).
- The percentages of patients with 24-week CDP, a secondary endpoint, were 29.6% with ocrelizumab vs 35.7% with placebo (HR, 0.75; 95% CI, 0.58 to 0.98; p = 0.04).

- Additional secondary endpoints included changes in the T25FW, the total volume of hyperintense brain lesions on T2-weighted MRI, and brain volume loss.
  - The proportion of patients with 20% worsening of the T25FW confirmed at 12 weeks was 49% in ocrelizumab-treated patients compared to 59% in placebo-treated patients (25% risk reduction).
  - From baseline to Week 120, the total volume of hyperintense brain lesions on T2-weighted MRI decreased by 3.37% in ocrelizumab-treated patients and increased by 7.43% in placebo-treated patients ($p < 0.001$).
  - From Weeks 24 to 120, the percentage of brain volume loss was 0.90% with ocrelizumab vs 1.09% with placebo ($p = 0.02$).
- Infusion-related reactions, upper respiratory tract infections, and oral herpes infections occurred more frequently with ocrelizumab vs placebo.
- Neoplasms occurred in 2.3% (11/486) of patients treated with ocrelizumab vs 0.8% (2/239) of patients who received placebo. Among the ocrelizumab-treated patients that developed neoplasms, there were 4 cases of breast cancer, 3 cases of basal-cell carcinoma, and 1 case in each of the following: endometrial adenocarcinoma, anaplastic large-cell lymphoma (mainly T cells), malignant fibrous histiocytoma, and pancreatic carcinoma. In the placebo group, 1 patient developed cervical adenocarcinoma in situ and 1 patient developed basal-cell carcinoma.
  - Between the clinical cutoff date (July 24, 2015) and June 30, 2016, 2 additional cases of neoplasm (1 case of basal-cell skin carcinoma and 1 case of squamous-cell carcinoma) were detected during the open-label extension phase in which all patients received ocrelizumab.

Symptomatic MS

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

Clinically Isolated Syndrome (CIS)

- IFNs, Copaxone (glatiramer acetate) and Aubagio (teriflunomide) have evidence supporting a significant delay in the time to development of a second exacerbation, compared to placebo, in patients with an isolated demyelinating event.
  - In the PRECISE trial, glatiramer acetate significantly reduced the risk of converting to a CDMS diagnosis by 45% compared to placebo in patients with CIS ($p = 0.005$). In addition, the time for 25% of patients to convert to CDMS was significantly prolonged with glatiramer acetate compared to placebo (722 vs 336 days; $p = 0.0041$) *(Comi et al 2009)*. In the 2 year, open-label extension phase of PRECISE, early initiation of glatiramer acetate demonstrated a 41% reduced risk of CDMS compared to delayed glatiramer acetate (HR, 0.59; 95% CI, 0.44 to 0.8; $p = 0.0005$). Over the 2-year extension, the baseline-adjusted proportions of patients who developed CDMS were 29.4% and 46.5% for the early and late initiation treatment groups (odds ratio [OR], 0.48; 95% CI, 0.33 to 0.7; $p = 0.0002$) *(Comi et al 2012)*.
  - A meta-analysis of double-blind, placebo-controlled RCTs in patients with CIS found a significantly lower risk of CDMS with IFN therapy compared to placebo ($p < 0.0001$) *(Clerico et al 2008)*. A 10-year, multicenter RCT with IFNβ-1a IM demonstrated that immediate initiation of therapy in patients with CIS reduced the risk for relapses over 10 years, but it was not associated with improved disability outcomes compared to a control group that also initiated therapy relatively early in the disease *(Kinkel et al 2012)*. Over the 10-year study, the drop-out rate was significant. Similar results were observed with IFNβ-1b (BENEFIT study) over an 8-year observation period. Patients who received treatment early had a lower overall ARR compared to those patients who delayed treatment *(Kappos et al*

2007, Edan et al 2014). In the first 3 years of BENEFIT, early treatment with IFNβ-1b reduced the risk for progression of disability by 40% compared to delayed treatment (16% vs 25%, respectively; HR, 0.6; 95% CI, 0.39 to 0.92; p = 0.022).

- A 2018 systematic review and network meta-analysis of RCTs was conducted to assess the potential short- and long-term benefits of treatment with IFN-β or glatiramer acetate in patients with CIS (*Armoiry et al 2018)*. The review identified 5 primary RCTs that assessed the time to CDMS in patients with CIS treated with IFN-β or glatiramer acetate vs placebo. They found that all drugs reduced the time to CDMS when compared with placebo, with a pooled HR of 0.51 (95% CI, 0.44 to 0.61) and low heterogeneity, and there was no evidence that indicated that 1 active treatment was superior to another when compared indirectly. The authors noted that there was insufficient information to rate the risk of selection bias, 4 of the 5 studies were at high risk of performance bias, and 1 study was rated to have a high risk for attrition bias. Four of the trials had open-label extension studies performed over 5 to 10 years, all of which indicated that early DMT therapy (regardless of agent) led to an increase in time to CDMS when compared with placebo (HR, 0.64; 95% CI, 0.55 to 0.74; low heterogeneity). These results should be taken with caution; however, as all of the open-label extension arms were at a high risk for attrition bias and had large losses to follow-up noted.
- The TOPIC study enrolled 618 patients with CIS and found teriflunomide 7 and 14 mg doses reduced the risk of relapse defining CDMS compared to placebo *(Miller et al 2014)*. Teriflunomide 14 mg reduced the risk of conversion to CDMS by 42.6% compared to placebo (HR, 0.574; 95% CI, 0.379 to 0.869; p = 0.0087) whereas teriflunomide 7 mg reduced the conversion to CDMS by 37.2% compared to placebo (HR, 0.628; 95% CI, 0.416 to 0.949; p = 0.0271).

Progressive MS

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

Timing of DMT initiation

- The best initial treatment strategy is uncertain, but 2 main concepts include safety focused (IFNs or glatiramer) and efficacy (ie, natalizumab, ocrelizumab, ofatumumab) approaches (*Olek & Mowry 2021*). Retrospective observational studies have supported the earlier initiation of high efficacy DMT to reduce the risk of disability progression; however, evidence from RCTs is needed to determine the appropriate stage of MS in which to use a high efficacy DMT (*He et al 2020*).
- A 2017 systematic review evaluated the effect of high efficacy immunotherapies (ie, fingolimod, natalizumab, alemtuzumab) at different stages of MS (*Merkel et al 2017*). Twelve publications (9 RCTs + 3 observational studies) were identified as reporting information relevant to the outcomes of early vs delayed initiation of high efficacy DMTs for

RRMS. A number of these studies suggested that earlier commencement of high efficacy DMTs resulted in more effective control of relapse activity than their later initiation. The evidence regarding the effect of the timing of high efficacy therapies on disability outcomes was conflicting; additional data are required to answer this question.

Decisions to discontinue DMTs in MS

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

Meta-Analyses

- A 2017 systematic review conducted by the Institute for Clinical and Economic Review (ICER) included ocrelizumab in a comparative efficacy analysis with other DMTs used in the treatment of MS.
  - Network meta-analyses demonstrated that for the treatment of RRMS, alemtuzumab, natalizumab, and ocrelizumab (in that order) were the most effective DMTs for reducing ARRs (~70% reduction vs placebo).
  - Ocrelizumab and alemtuzumab had the greatest reductions in disability progression (53% to 58% reduction vs placebo, respectively), closely followed by natalizumab (44%).
- A systematic review that identified 28 RCTs found that the magnitude of ARR reduction varied between 15 to 36% for all IFNβ products, glatiramer acetate, and teriflunomide; and from 50 to 69% for alemtuzumab, dimethyl fumarate, fingolimod, and natalizumab. The risk of 3-month CDP was reduced by 19 to 28% with IFNβ products, glatiramer acetate, fingolimod, and teriflunomide; by 38 to 45% for peginterferon IFNβ, dimethyl fumarate, and natalizumab; and by 68% with alemtuzumab *(Fogarty et al 2016)*.
- A total of 39 RCTs evaluating 1 of 15 treatments for MS were analyzed for benefits and acceptability in 25,113 patients with RRMS *(Tramacere et al 2015)*. Drugs included were IFNβ-1b, IFNβ-1a (IM and SC), glatiramer acetate, natalizumab, mitoxantrone, fingolimod, teriflunomide, dimethyl fumarate, alemtuzumab, peginterferon IFNβ-1a, azathioprine, and immunoglobulins. Investigational agents, daclizumab and laquinimod, were also included. The studies had a median duration of 24 months with 60% of studies being placebo-controlled. The network meta-analysis evaluated the recurrence of relapses and disability progression.
  - Relapses: alemtuzumab, mitoxantrone, natalizumab, and fingolimod were reported to have greater treatment benefit compared to placebo. Over 12 months (29 studies; N = 17,897):
    - alemtuzumab: RR, 0.40; 95% CI, 0.31 to 0.51; moderate quality evidence
    - mitoxantrone: RR, 0.40; 95% CI, 0.20 to 0.76; low quality evidence
    - natalizumab: RR, 0.56; 95% CI, 0.43 to 0.73; high quality evidence
    - fingolimod: RR, 0.63; 95% CI, 0.53 to 0.74; low quality evidence
    - dimethyl fumarate: RR, 0.78; 95% CI, 0.65 to 0.93; moderate quality evidence
    - daclizumab (no longer on the market): RR, 0.79; 95% CI, 0.61 to 1.02; moderate quality evidence
    - glatiramer acetate: RR, 0.80; 95% CI, 0.68 to 0.93; moderate quality evidence
  - Relapses over 24 months vs placebo (26 studies; N = 16,800):
    - alemtuzumab: RR, 0.46; 95% CI, 0.38 to 0.55; moderate quality evidence
    - mitoxantrone: RR, 0.47; 95% CI, 0.27 to 0.81; very low quality evidence
    - natalizumab: RR, 0.56; 95% CI, 0.47 to 0.66; high quality evidence
    - fingolimod: RR, 0.72; 95% CI, 0.64 to 0.81; moderate quality evidence
  - Disability worsening over 24 months vs placebo (26 studies; N = 16,800):
    - mitoxantrone: RR, 0.20; 95% CI, 0.05 to 0.84; low quality evidence
    - alemtuzumab: RR, 0.35; 95% CI, 0.26 to 0.48; low quality evidence
    - natalizumab: RR, 0.64; 95% CI, 0.49 to 0.85; moderate quality evidence
  - Relapses and disability worsening over 36 months were only tested in 2 studies (CombiRx and CAMMS223). Both studies had a high risk of bias.

- Acceptability: Higher rates of withdrawal due to adverse events compared to placebo over 12 months were reported for teriflunomide (RR, 2.24; 95% CI, 1.5 to 3.34); peginterferon β-1a (RR, 2.8; 95% CI, 1.39 to 5.64); Avonex (RR, 4.36; 95% CI, 1.98 to 9.6); Rebif (RR, 4.83; 95% CI, 2.59 to 9); and fingolimod (RR, 8.26; 95% CI, 3.25 to 20.97).
- Over 24 months, only fingolimod had a significantly higher proportion of participants who withdrew due to any adverse event (RR vs placebo, 1.69; 95% CI, 1.32 to 2.17).
  - mitoxantrone: RR, 9.82; 95% CI, 0.54 to 168.84
  - natalizumab: RR, 1.53; 95% CI, 0.93 to 2.53
  - alemtuzumab: RR, 0.72; 95% CI, 0.32 to 1.61

- Filippini et al (2013) conducted a Cochrane review of 44 RCTs on the relative effectiveness and acceptability of DMTs and immunosuppressants in patients with either RRMS or progressive MS (N = 17,401).
  - On the basis of high quality evidence, natalizumab and Rebif were superior to all other treatments for preventing clinical relapses in the short-term (24 months) in RRMS compared to placebo (OR = 0.32; 95% CI, 0.24 to 0.43; OR = 0.45; 95% CI, 0.28 to 0.71, respectively); they were also more effective than Avonex (OR = 0.28; 95% CI, 0.22 to 0.36; OR = 0.19; 95% CI, 0.06 to 0.6, respectively).
  - Based on moderate quality evidence, natalizumab and Rebif decreased the odds of patients with RRMS having disability progression in the short-term, with an absolute reduction of 14% and 10%, respectively, vs placebo.
  - Natalizumab and Betaseron were significantly more effective (OR = 0.62; 95% CI, 0.49 to 0.78; OR = 0.35; 95% CI, 0.17 to 0.7, respectively) than Avonex in reducing the number of patients with RRMS who had progression at 2 years of follow-up, and confidence in this result was graded as moderate.
  - The lack of convincing efficacy data showed that Avonex, IV immunoglobulins (IVIG), cyclophosphamide, and long-term corticosteroids have an unfavorable benefit-risk balance in RRMS.
- Hamidi et al (2018) conducted a systematic review and network meta-analysis of 37 studies including 26 RCTs from a health technology assessment (HTA) report and 11 supplemental RCTs published after the HTA. Eleven agents, including dimethyl fumarate, teriflunomide, IFNs, peginterferon, glatiramer acetate, natalizumab, fingolimod, and alemtuzumab were included and were compared to either placebo or any drug treatment in patients of varying treatment experience levels. Key findings from the network meta-analysis include:
  - Alemtuzumab 12 mg had the highest probability of preventing annual relapses (RR, 0.29; 95% CI, 0.23 to 0.35; high quality evidence).
  - Alemtuzumab 12 mg (RR, 0.40; 95% CI, 0.27 to 0.60; very low quality evidence) was the most effective against progression of disability.
  - Dimethyl fumarate 240 mg and fingolimod 0.5 mg and 1.25 mg were more effective treatments when considering annual relapse and disability progression:
    - Annual relapse:
      - Dimethyl fumarate 240 mg twice daily: RR, 0.5; 95% CI, 0.42 to 0.6; high quality evidence
      - Fingolimod 0.5 mg: RR, 0.46; 95% CI, 0.39 to 0.54; high quality evidence
      - Fingolimod 1.25 mg: RR, 0.45; 95% CI, 0.39 to 0.53; high quality evidence
    - Disability progression:
      - Dimethyl fumarate 240 mg twice daily: RR, 0.65; 95% CI, 0.49 to 0.85; high quality evidence
      - Fingolimod 0.5 mg: RR, 0.71; 95% CI, 0.55 to 0.90; high quality evidence
      - Fingolimod 1.25 mg: RR, 0.71; 95% CI, 0.56 to 0.90; high quality evidence
  - Withdrawal due to adverse events was difficult to assess due to the low quality of available evidence, however, the authors determined that:
    - Fingolimod 1.25 mg (RR, 2.21; 95% CI, 1.42 to 2.5; moderate quality evidence), and Rebif 44 mcg (RR, 2.21; 95% CI, 1.29 to 3.97; low quality evidence) were associated with higher withdrawals due to adverse events when compared with other treatment options.
  - Alemtuzumab 12 mg (mean difference, -0.6; 95% CI, -1.02 to -0.24) was more effective than other therapies in lowering the EDSS.
  - No treatments were found to significantly increase serious adverse events; peginterferon β-1a was associated with more adverse events overall when compared with other medications (RR, 1.66; 95% CI, 1.21 to 2.28).
  - None of the 11 agents studied were associated with a statistically significantly higher risk of mortality when compared to placebo.
- A Bayesian network meta-analysis evaluating DMTs for RRMS ranked the most effective therapies based on SUCRA analysis (*Lucchetta et al 2018*). A total of 33 studies were included in the analysis. For the ARR, alemtuzumab (96%

probability), natalizumab (96%), and ocrelizumab (85%) were determined to be the most effective therapies (high-quality evidence).

- A meta-analysis of RCTs was conducted to evaluate the efficacy and safety of teriflunomide in reducing the frequency of relapses and progression of physical disability in patients with relapsing multiple sclerosis (*Xu et al 2016*). The results showed that teriflunomide (7 and 14 mg) reduced the ARR and teriflunomide 14 mg decreased the disability progression in comparison to placebo (RR, 0.69; 95% CI, 0.55 to 0.87).
- A 2020 network meta-analysis of 34 RCTs compared ofatumumab with other DMTs for RRMS *(Samjoo et al 2020)*. For the outcome of ARR, rate ratios were significantly improved with ofatumumab compared with teriflunomide, IFN β-1a SC and IM, IFN β-1b, glatiramer acetate, dimethyl fumarate, and fingolimod; no differences were detected in comparisons with cladribine, ocrelizumab, natalizumab, or alemtuzumab. Values for SUCRA indicated alemtuzumab was most likely to be most effective (96%), followed by ofatumumab (91%), natalizumab (88%), and ocrelizumab (85%).
- A 2021 network meta-analysis of 21 RCTs in patients with RRMS found that, except for Betaseron, all DMTs showed significant reductions in relapse rate over 24 months *(Liu et al 2021)*. When plotting efficacy using SUCRA, ofatumumab was considered the best treatment in respect to ARR, but it was not considered superior to natalizumab or alemtuzumab.
- A systematic review and comparative efficacy summary of 4 RCTs using matching-adjusted comparison in patients with RRMS found that, after adjustment for baseline characteristics, ozanimod was associated with a decreased risk of relapse compared to dimethyl fumarate (RR, 0.88; 95% CI, 0.67 to 0.97) *(Cohan et al 2021)*. Ozanimod also decreased the rate of CDP at 3 months compared to dimethyl fumarate (HR, 0.67; 95% CI, 0.53 to 0.86); however, disability progression was similar between groups at 6 months.

Ulcerative Colitis

Zeposia (ozanimod)

- The efficacy and safety of ozanimod were evaluated across 2 cohorts in a multicenter, double-blind, placebo controlled RCT in adult patients with moderately to severely active ulcerative colitis (*Sandborn et al 2021)*. Patients were randomized to oral ozanimod 0.92 mg daily or placebo. All patients received an initial dose escalation of ozanimod or placebo prior to receiving their assigned dose on day 8. Patients with moderately or severely active ulcerative colitis were included if they had an inadequate response or were intolerant to previous therapies, including oral aminosalicylates, corticosteroids, immunomodulators, or biologic agents. In cohort 1, patients (n = 645) received induction treatment for 10 weeks. In cohort 2, patients who achieved a clinical response in cohort 1 or an open-label arm at week 10 (n = 457) were re-randomized to maintenance treatment with ozanimod or placebo for 42 additional weeks (52 weeks total). Use of corticosteroids or aminosalicylates was allowed in cohort 1, while patients had to be tapered from corticosteroids for entry into cohort 2. The primary endpoint was clinical remission at week 10 in cohort 1 and at 52 weeks in cohort 2. Clinical remission was defined as a 3-component Mayo score (without the physician global assessment) which included the rectal bleeding subscore, stool frequency subscore, and endoscopy subscore.
  - In cohort 1, the induction phase, clinical remission was achieved by 18% with ozanimod and 6% of patients with placebo at 10 weeks (treatment difference, 12%; 95% CI, 8 to 17; $p < 0.0001$). In addition, the following secondary endpoints were improved with ozanimod vs placebo, respectively: clinical response (48% vs 26%; $p < 0.0001$), endoscopic improvement (27% vs 12%; $p < 0.0001$), and endoscopic-histologic mucosal improvement (13% vs 4%; $p < 0.001$).
  - In cohort 2, the maintenance phase, clinical remission was achieved by 37% of patients with ozanimod and 19% of patients with placebo at 52 weeks (treatment difference, 19%; 95% CI, 11 to 26). In addition, the following secondary endpoints were improved with ozanimod vs placebo, respectively: clinical response (60% vs 41%; $p < 0.0001$), endoscopic improvement (46% vs 26%; $p < 0.0001$), corticosteroid-free clinical remission (32% vs 17%; $p < 0.001$), and endoscopic-histologic mucosal improvement (30% vs 14%; $p < 0.001$).
- In both induction and maintenance cohorts, patients without prior exposure to TNF blockers saw the greatest improvements across all endpoints.

Crohn's Disease

Tysabri (natalizumab)

- The efficacy and safety of natalizumab were evaluated in 3 RCTs in adults with moderate to severely active Crohn's disease (Crohn's Disease Activity Index [CDAI] score between 220 and 450) (*Sandborn et al 2005, Tysabri prescribing information 2020*). Patients were randomized to either natalizumab 300 mg or placebo IV every 4 weeks. Concomitant

TNF blockers were prohibited in the studies, while stable doses of 5-ASA, corticosteroids, and/or immunosuppressants (eg, 6-MP, azathioprine, methotrexate) were allowed. While allowed in the clinical trials, natalizumab is not indicated to be used in combination with immunosuppressant therapy. In Study 1 and Study 2, the induction of clinical response, defined as a ≥ 70-point decrease from baseline CDAI was evaluated. In Study 2, both clinical response, and remission, defined as a CDAI score of < 150, were required to be met at weeks 8 and 12. In Study 3, patients who achieved clinical response at both weeks 10 and 12 in Study 1 and 2 were re-randomized to natalizumab or placebo for an additional 6 and 12 months of treatment. Patients who did not lose clinical response at any study visit were considered responders.

- In Study 1, clinical response was not significantly different between placebo and natalizumab groups at 10 weeks. In a post-hoc analysis of the 653 patients with high C-reactive protein (CRP) however, response was achieved in 57% of natalizumab patients compared to 45% of placebo patients (treatment difference, 12%; 95% CI, 3 to 22). Due to these findings, the second induction study, Study 2, assessed only patients with an elevated CRP. The cumulative clinical response for weeks 8 and 12 was improved with natalizumab vs placebo (48% vs 32%; p < 0.005). Cumulative clinical remission was also improved for weeks 8 and 12 with natalizumab vs placebo (26% vs 16%; p < 0.005).
- In Study 3, the maintenance of clinical response assessed at month 9 was improved with natalizumab vs placebo treatment (61% vs 29%; p < 0.005). The maintenance of clinical remission at month 9 was also found to improve with natalizumab vs placebo (45% vs 26%; p < 0.005). Both response and remission at month 15 were improved with natalizumab vs placebo, however, were not considered significantly different. For patients in Study 3, the treatment effect was considered similar across groups based on inadequate response to prior therapies (eg, corticosteroids, immunosuppressants, TNF blockers).

CLINICAL GUIDELINES

Multiple Sclerosis

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

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

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

- In September 2019, the MS Coalition published an update to its consensus paper on the principles and current evidence concerning the use of DMTs in MS *(MS Coalition 2019)*. Major recommendations included the following:
  - Initiation of treatment with an FDA-approved DMT is recommended as soon as possible following a diagnosis of relapsing MS, regardless of the person's age. Relapsing MS includes CIS, RRMS, and active SPMS with clinical relapses or inflammatory activity on MRI.
  - Clinicians should consider prescribing a high efficacy medication such as alemtuzumab, cladribine, fingolimod, ocrelizumab or natalizumab for newly diagnosed individuals with highly active MS.

- Clinicians should also consider prescribing a high efficacy medication for patients who have breakthrough activity on another DMT, regardless of the number of previously used agents.
- Treatment with a given DMT should be continued indefinitely unless any of the following occur (in which case an alternative DMT should be considered):
  - Suboptimal treatment response as determined by the individual and his or her treating clinician
  - Intolerable side effects
  - Inadequate adherence to the treatment regimen
  - Availability of a more appropriate treatment option
  - The healthcare provider and patient determine that the benefits no longer outweigh the risks.
- Movement from one DMT to another should occur only for medically appropriate reasons as determined by the treating clinician and patient.
- When evidence of additional clinical or MRI activity while on treatment suggests a sub-optimal response, an alternative regimen (eg, different mechanism of action) should be considered to optimize therapeutic benefit.
- The factors affecting choice of therapy at any point in the disease course are complex and most appropriately analyzed and addressed through a shared decision-making process between the patient and his/her treating clinician. Neither an arbitrary restriction of choice nor a mandatory escalation therapy approach is supported by data.
- Due to significant variability in the MS population, people with MS and their treating clinicians require access to the full range of treatment options for several reasons:
  - MS clinical phenotypes may respond differently to different DMTs.
  - Different mechanisms of action allow for treatment change in the event of a sub-optimal response.
  - Potential contraindications limit options for some individuals.
  - Risk tolerance varies among people with MS and their treating clinicians.
  - Route of delivery, frequency of dosing, and side effects may affect adherence and quality of life.
  - Individual differences related to tolerability and adherence may necessitate access to different medications within the same class.
  - Pregnancy and breastfeeding limit the available options.
- Individuals' access to treatment should not be limited by their frequency of relapses, level of disability, or personal characteristics such as age, sex, or ethnicity.
- Absence of relapses while on treatment is a characteristic of treatment effectiveness and should not be considered a justification for discontinuation of treatment.
- Treatment should not be withheld during determination of coverage by payors as this puts the patient at risk for recurrent disease activity.

- The European Committee for Research and Treatment of Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) published updated guidelines in 2018 (*Montalban et al 2018*). The main recommendations were the following:
  - The entire spectrum of DMTs should be prescribed only in centers with adequate infrastructure to provide proper monitoring of patients, comprehensive patient assessment, detection of adverse effects, and the capacity to address adverse effects properly if they occur. (Consensus statement)
  - Offer IFN or glatiramer acetate to patients with CIS and abnormal MRI findings with lesions suggesting MS who do not fulfill full criteria for MS. (Strong)
  - Offer early treatment with DMTs in patients with active RRMS, as defined by clinical relapses and/or MRI activity (active lesions: contrast-enhancing lesions; new or unequivocally enlarging T2 lesions assessed at least annually). (Strong)
  - For active RRMS, choosing among the wide range of available drugs from the modestly to highly effective will depend on patient characteristics and comorbidity, disease severity/activity, drug safety profile, and accessibility of the drug. (Consensus statement)
  - Consider treatment with IFN in patients with active SPMS, taking into account, in discussion with the patient, the dubious efficacy, as well as the safety and tolerability profile. (Weak)
  - Consider treatment with mitoxantrone in patients with active SPMS, taking into account the efficacy and specifically the safety and tolerability profile of this agent. (Weak)
  - Consider ocrelizumab for patients with active SPMS. (Weak)
  - Consider ocrelizumab for patients with PPMS. (Weak)

- Always consult the summary of product characteristics for dosage, special warnings, precautions, contraindications, and monitoring of side effects and potential harms. (Consensus statement)
- Consider combining MRI with clinical measures when evaluating disease evolution in treated patients. (Weak)
- When monitoring treatment response in patients treated with DMTs, perform standardized reference brain MRI within 6 months of treatment onset and compare the results with those of further brain MRI, typically performed 12 months after starting treatment. Adjust the timing of both MRIs, taking into account the drug's mechanism and speed of action and disease activity, including clinical and MRI measures. (Consensus statement)
- When monitoring treatment response in patients treated with DMTs, the measurement of new or unequivocally enlarging T2 lesions is the preferred MRI method, supplemented by Gd-enhancing lesions for monitoring treatment response. Evaluation of these parameters requires high-quality standardized MRI scans and interpretation by highly qualified readers with experience in MS. (Consensus statement)
- When monitoring treatment safety in patients treated with DMTs, perform a standard reference MRI every year in patients at low risk for PML, and more frequently (3 to 6 months) in patients at high risk for PML (JC virus positivity, natalizumab treatment duration over 18 months) and in patients at high risk for PML who switch drugs at the time the current treatment is discontinued and the new treatment is started. (Consensus statement)
- Offer a more efficacious drug to patients treated with IFN or glatiramer acetate who show evidence of disease activity, assessed as recommended above. (Strong)
- When deciding on which drug to switch to, in consultation with the patient, consider patient characteristics and comorbidities, drug safety profile, and disease severity/activity. (Consensus statement)
- When treatment with a highly efficacious drug is stopped, whether due to inefficacy or safety, consider starting another highly efficacious drug. When starting the new drug, take into account disease activity (clinical and MRI; the greater the disease activity, the greater the urgency to start new treatment), the half-life and biological activity of the previous drug, and the potential for resumed disease activity or even rebound (particularly with natalizumab). (Consensus statement)
- Consider continuing a DMT if the patient is stable (clinically and on MRI) and shows no safety or tolerability issues. (Weak)
- Advise all women of childbearing potential that DMTs are not licensed during pregnancy, except glatiramer acetate 20 mg/mL. (Consensus statement)
- For women planning a pregnancy, if there is a high risk for disease reactivation, consider using IFN or glatiramer acetate until pregnancy is confirmed. In some very specific (active) cases, continuing this treatment during pregnancy could also be considered. (Weak)
- For women with persistent high disease activity, it would generally be advised to delay pregnancy. For those who still decide to become pregnant or have an unplanned pregnancy, treatment with natalizumab throughout pregnancy may be considered after full discussion of potential implications; treatment with alemtuzumab could be an alternative for planned pregnancy in very active cases provided that a 4-month interval is strictly observed from the latest infusion until conception. (Weak)

- The 2015 Association of British Neurologists state that all available DMTs are effective in reducing relapse rate and MRI lesion accumulation *(Scolding et al 2015)*. Evidence is less clear on the impact of DMT on long-term disability. Drugs are separated into 2 categories based on relative efficacy. Category 1 – moderate efficacy includes IFNs (including peginterferon), glatiramer acetate, teriflunomide, dimethyl fumarate, and fingolimod. Category 2 – high efficacy includes alemtuzumab and natalizumab – these drugs should be reserved for patients with very active MS.

Ulcerative Colitis

- For the treatment of UC, 2019 guidelines from the American College of Gastroenterology (ACG) recommend 5-ASA therapy for induction of remission in mildly active UC, and budesonide, systemic corticosteroids, TNF inhibitor therapy (adalimumab, golimumab, or infliximab), vedolizumab, and tofacitinib for induction of remission in moderately to severely active disease. Vedolizumab and tofacitinib are recommended for induction of remission in patients who have failed previous TNF inhibitor therapy. For maintenance of remission in patients with previously mildly active disease, 5-ASA therapy is recommended, and in patients with previously moderately to severely active disease, continuation of anti-TNF therapy, vedolizumab, or tofacitinib is recommended after induction of remission with these agents. The use of S1P receptor modulators is not addressed in the ACG guidelines (*Rubin et al 2019*).
- The American Gastroenterological Association (AGA) recommends standard-dose mesalamine or diazo-bonded 5-ASA (balsalazide, olsalazine) as first-line options for most patients with mild to moderate disease (*Ko et al 2019*). For adult

outpatients with moderate to severe UC, the AGA strongly recommends using infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or ustekinumab over no treatment. The use of S1P receptor modulators is not addressed in the AGA guidelines for the treatment of adult outpatients with moderate to severe UC (*Feuerstein et al 2020*).

Crohn's Disease

- A 2018 ACG guideline on the management of CD in adults states that TNF inhibitors adalimumab, certolizumab, and infliximab are effective in the treatment of moderate to severely active CD in patients who are resistant to corticosteroids or are refractory to thiopurines or methotrexate. These agents can be considered for treating perianal fistulas, and infliximab can also treat enterocutaneous and rectovaginal fistulas in CD. Adalimumab, certolizumab, and infliximab are effective for the maintenance of TNF inhibitor induced remission; due to the potential for immunogenicity and loss of response, combination with azathioprine/6-MP or methotrexate should be considered. The combination of infliximab with an immunomodulator (thiopurine) is more effective than monotherapy with individual agents in patients with moderate to severe CD and who are naïve to both agents. Infliximab can also treat fuliminant CD. Vedolizumab with or without an immunomodulator can be used for induction and maintenance of remission in patients with moderate to severe CD. Patients are candidates for ustekinumab therapy, including for the maintenance of remission, if they have moderate to severe CD and have failed corticosteroids, thiopurines, methotrexate, or TNF inhibitors. The guideline acknowledges the effectiveness of biosimilar infliximab and biosimilar adalimumab for the management of moderate to severe CD (*Lichtenstein et al 2018*).
- The 2020 European Crohn's and Colitis Organisation (ECCO) guideline on medical treatment in CD recommends the use of TNF inhibitors (infliximab, adalimumab, and certolizumab pegol) to induce remission in patients with moderate-to-severe CD who have not responded to conventional therapy (*Torres et al 2020*). Other immunomodulator-related recommendations within the guideline include:
  - Suggesting against the combination of adalimumab and thiopurines over adalimumab alone to achieve clinical remission and response.
  - Recommending combination therapy with a thiopurine when starting infliximab to induce remission in patients with moderate-to-severe CD, who have had an inadequate response to conventional therapy.
  - Recommending ustekinumab for induction of remission in patients with moderate-to-severe CD with inadequate response to conventional therapy and/or to TNF inhibitors.
  - Recommending vedolizumab for induction of response and remission in patients with moderate-to-severe CD with inadequate response to conventional therapy and/or to TNF inhibitors.
  - Equally suggesting the use of either ustekinumab or vedolizumab for the treatment of moderate-to-severe active luminal CD in patients who have previously failed TNF inhibitors.
- A 2021 AGA guideline on the medical management of moderate to severe CD (CDAI of > 220) strongly recommends the use of biologic monotherapy over thiopurine monotherapy for the induction of remission in adult outpatients and recommends TNF inhibitors or ustekinumab over no treatment for induction and maintenance of remission. In patients who are naïve to biologic drugs, infliximab, adalimumab, or ustekinumab are recommended over certolizumab pegol for the induction of remission and vedolizumab is suggested over certolizumab pegol. In patients who never responded to TNF inhibitors, the use of ustekinumab is recommended and the use of vedolizumab is suggested over no treatment for the induction of remission. In patients who previously responded to infliximab, the use of adalimumab or ustekinumab is recommended and the use of vedolizumab is suggested over no treatment for the induction of remission. The AGA recommends against the use of 5-ASA or sulfasalazine over no treatment for the induction or maintenance of remission. In patients with CD and active perianal fistula, infliximab is recommended over no treatment for the induction and maintenance of fistula remission. In patients with CD and active perianal fistula without perianal abscess, the use of biologic agents in combination with an antibiotic over a biologic drug alone is recommended for the induction of fistula remission.
  - In adult outpatients, the AGA recommends against the use of natalizumab over no treatment for the induction and maintenance of clinical remission. This recommendation, the AGA states, is due to the availability of other agents and the evidence of harm due to progressive multifocal leukoencephalopathy (PML) in post-marketing data. Patients who will adhere to ongoing monitoring for the John Cunningham Virus (JCV) and put a high value on the potential benefits of therapy versus the risks of PML, can consider using natalizumab (*Feuerstein et al 2021*).

SAFETY SUMMARY

Interferons and glatiramer acetate

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

Oral agents

- Fingolimod is contraindicated in patients with a variety of cardiac issues and those with a hypersensitivity to the product. Because of a risk for bradyarrhythmia and atrioventricular (AV) blocks, patients should be monitored during fingolimod treatment initiation. In controlled clinical trials, first-degree AV block after the first dose occurred in 4.7% of patients receiving fingolimod and 1.6% of patients on placebo.
  - Posterior Reversible Encephalopathy Syndrome (PRES) has been reported with fingolimod. Patients with pre-existing cardiac disease may poorly tolerate fingolimod and may require additional monitoring. In clinical trials, the most common adverse reactions (incidence ≥ 10% and > placebo) were headache, liver transaminase elevation, diarrhea, cough, influenza, sinusitis, back pain, abdominal pain, and pain in extremity. If a serious infection develops, consider suspending fingolimod and reassess risks and benefits prior to re-initiation. Elimination of the drug may take up to 2 months; thus, monitoring for infections should continue during this time. Do not start fingolimod in patients with an active acute or chronic infection until the infection is resolved. Life-threatening and fatal infections have been reported in patients taking fingolimod. Establish immunity to varicella zoster virus prior to therapy initiation. Vaccination against human papilloma virus (HPV) should be considered before initiating treatment with fingolimod; HPV infections including papilloma, dysplasia, warts, and HPV-related cancer have been reported in post marketing reports. Safety labeling changes warn of an increased risk of cutaneous malignancies, including melanoma and lymphoma, in patients treated with fingolimod. Clinically significant hepatic injury has occurred in patients treated with fingolimod in the postmarketing setting; hepatic function should be monitored prior to, during, and until 2 months after medication discontinuation. Cases of PML have occurred in the postmarketing setting, primarily in patients who were treated with fingolimod for at least 2 years. At the first sign or symptom suggestive of PML, fingolimod should be withheld and an appropriate diagnostic evaluation performed. Monitoring for signs consistent with PML on MRI may be useful to allow for an early diagnosis. Additionally, severe increases in disability after discontinuation of fingolimod have been described in post marketing reports. Relapses of MS with tumefactive demyelinating lesions on imaging have been observed both during therapy with fingolimod and after discontinuation in post marketing reports. If a severe MS relapse occurs during or after discontinuation of treatment with fingolimod, tumefactive MS should be considered, and imaging evaluation and initiation of appropriate treatment may be necessary.
- Siponimod is contraindicated in patients with a cytochrome P4502C9*3/*3 genotype, presence of Mobitz type II second-degree, third degree AV block or sick sinus syndrome. It is also contraindicated in patients that have experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, Class III/IV heart failure, or decompensated heart failure requiring hospitalization in the past 6 months. Warnings and precautions of siponimod include an increased infection risk, macular edema, increased blood pressure, bradyarrhythmia and AV conduction delays, decline in pulmonary function, cutaneous malignancies, and liver injury. Siponimod may result in a transient decrease in heart rate; titration is required for treatment initiation. Consider resting heart rate with concomitant beta-blocker use; obtain cardiologist consultation before concomitant use with other drugs that decrease heart rate. Women of childbearing

potential should use effective contraception during and for 10 days after stopping siponimod due to fetal risk. The most common adverse events (incidence > 10%) are headache, hypertension, and transaminase increases.

- Ozanimod and ponesimod are contraindicated in patients that have experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, Class III/IV heart failure, or decompensated heart failure requiring hospitalization in the past 6 months. They are also contraindicated in patients with Mobitz type II second- or third-degree AV block, sick sinus syndrome, or sinoatrial attack unless the patient has a functioning pacemaker. Ozanimod is also contraindicated in patients with severe, untreated sleep apnea and those taking a monoamine oxidase inhibitor. Warnings and precautions for ozanimod and ponesimod include an increased infection risk, macular edema, increased blood pressure, bradyarrhythmia and AV conduction delays, decline in pulmonary function, liver injury, and cutaneous malignancies (ponesimod only). Women of childbearing potential should use effective contraception during and for 3 months after stopping ozanimod and 1 week after stopping ponesimod due to fetal risk. The most common adverse events (incidence > 10%) with ozanimod and ponesimod are upper respiratory tract infections, hepatic transaminase elevations, and hypertension (ponesimod only). Zeposia (ozanimod) does not have a recommendation for first-dose cardiac observation like fingolimod, ponesimod, and siponimod; however, patients taking ozanimod should have their blood pressure monitored for changes.
- Dimethyl fumarate, diroximel fumarate, and monomethyl fumarate are contraindicated in patients with hypersensitivity to the products or any of their excipients. Warnings include anaphylaxis and angioedema, PML, lymphopenia, and clinically significant cases of liver injury. Serious cases of herpes zoster and other opportunistic viral (eg, herpes simplex virus, West Nile virus, cytomegalovirus), fungal (eg, *Candida* and *Aspergillus*), and bacterial (eg, *Nocardia*, *Listeria monocytogenes, Mycobacterium tuberculosis*) infections have been reported in patients treated with dimethyl fumarate, and may occur at any time during treatment with the fumarates. Patients with signs/symptoms of any of these infections should undergo diagnostic evaluation and receive appropriate treatment; treatment with dimethyl fumarate, diroximel fumarate, or monomethyl fumarate may need to be withheld until the infection has resolved. Consider therapy interruption if severe lymphopenia for more than 6 months occurs. Cases of PML have been reported following therapy. Monitoring for signs consistent with PML on MRI may be useful to allow for an early diagnosis. Common adverse events (incidence ≥ 10% and ≥ 2% more than placebo) were flushing, abdominal pain, diarrhea, and nausea. Administration of non-enteric aspirin up to 325 mg given 30 minutes prior to each dose or a temporary dose reduction may reduce flushing. Diroximel fumarate should not be coadministered with dimethyl fumarate.
- Teriflunomide is contraindicated in patients with severe hepatic impairment; pregnancy; those with a history of hypersensitivity to the medication; women of childbearing potential who are not using reliable contraception; and with concurrent use of leflunomide. Labeling includes boxed warnings regarding hepatotoxicity and teratogenicity/embryolethality that occurred in animal reproduction studies at plasma teriflunomide exposures similar to or lower than in humans. Other warnings include bone marrow effects, immunosuppression leading to potential infections, malignancy risk, interstitial lung disease, peripheral neuropathy, severe skin reactions, drug reaction with eosinophilia and systemic symptoms, and elevated blood pressure. Although not approved in pediatric patients, use of teriflunomide was associated with pancreatitis in a pediatric clinical trial. Teriflunomide has a half-life of 4 to 5 months; therefore, use of activated charcoal or cholestyramine in an 11-day regimen upon discontinuation of teriflunomide is recommended to reduce serum levels more rapidly. The most common adverse reactions (≥ 10% and ≥ 2% greater than placebo) are headache, diarrhea, nausea, alopecia, and an increase in alanine aminotransferase (ALT).
- Cladribine is contraindicated in patients with current malignancy, HIV infection, active chronic infection such as hepatitis or tuberculosis, hypersensitivity to cladribine, and in pregnant women. There is a boxed warning for potential malignancy and risk of teratogenicity. The warnings and precautions are lymphopenia, active infection, hematologic toxicity, liver injury, and graft vs host disease with blood transfusion. The most common adverse events (incidence > 20%) are upper respiratory tract infection, headache, and lymphopenia.

High Efficacy Infusibles and Injectables

- Natalizumab has a boxed warning regarding the risk of PML, which is an opportunistic viral infection of the brain that usually leads to death or severe disability. Due to the risk of PML, natalizumab is only available through the TOUCH® Prescribing Program, which is a restricted distribution program. Natalizumab is contraindicated in patients who have or have had PML and in patients who have had a hypersensitivity reaction. The most common adverse reactions (incidence ≥ 10% in MS) were headache, fatigue, arthralgia, urinary tract infection (UTI), lower respiratory tract infection, gastroenteritis, vaginitis, depression, pain in extremity, abdominal discomfort, diarrhea, and rash. Monitoring for signs consistent with PML on MRI may be useful to allow for an early diagnosis. Other warnings with natalizumab include hypersensitivity reactions, increased risk of herpes encephalitis and meningitis, increased risk of infections (including

opportunistic infections), thrombocytopenia, and hepatotoxicity. The AAN recommends only initiating treatment with natalizumab if the JCV antibody index is 0.9 or less; high index values preclude initiating therapy unless there is a reasonable chance of benefit compared to risk (*Rae-Grant et al 2018*).

- Alemtuzumab is contraindicated in patients with HIV or active infection. The boxed warning for alemtuzumab includes autoimmunity conditions (immune thrombocytopenia, autoimmune hepatitis, and anti-glomerular basement membrane disease), serious and life-threatening infusion reactions, serious and life-threatening stroke within 3 days of administration, and the possibility of an increased risk of malignancies (ie, thyroid cancer, melanoma, and lymphoproliferative disorders/lymphoma).
  - Alemtuzumab is only available through a restricted distribution and REMS program, which requires the member, provider, pharmacy, and infusion facility to be certified.
  - Approximately one-third of patients who received alemtuzumab in clinical trials developed thyroid disorders. The most commonly reported adverse events reported in at least 10% of alemtuzumab-treated patients and more frequently than with IFNβ-1a were rash, headache, pyrexia, nasopharyngitis, nausea, UTI, fatigue, insomnia, upper respiratory tract infection, herpes viral infection, urticaria, pruritus, thyroid disorders, fungal infection, arthralgia, pain in extremity, back pain, diarrhea, sinusitis, oropharyngeal pain, paresthesia, dizziness, abdominal pain, flushing, and vomiting. Nearly all patients (99.9%) in clinical trials had lymphopenia following a treatment course of alemtuzumab. Alemtuzumab may also increase the risk of acute acalculous cholecystitis; in controlled clinical studies, 0.2% of alemtuzumab-treated MS patients developed acute acalculous cholecystitis, compared to 0% of patients treated with IFNβ-1a. During postmarketing use, additional cases of acute acalculous cholecystitis have been reported in alemtuzumab-treated patients.
  - Other safety concerns within the product labeling include a warning that patients administered alemtuzumab are at risk for serious infections, including those caused by *Listeria monocytogenes,* the potential development of pneumonitis, and PML. Patients that are prescribed alemtuzumab should be counseled to avoid or appropriately heat any foods that may be a source of *Listeria*, such as deli meats and unpasteurized cheeses. Patients should also undergo tuberculosis screening according to local guidelines. With regard to PML, alemtuzumab should be withheld, and appropriate diagnostic evaluations performed, at the initial occurrence of suggestive signs or symptoms.
- The labeling of ocrelizumab does not contain any boxed warnings; however, ocrelizumab is contraindicated in patients with active hepatitis B virus (HBV) infection and in those with a history of life-threatening infusion reactions to ocrelizumab. Additional warnings for ocrelizumab concern infusion reactions, infections, decreased immunoglobulin levels, and an increased risk of malignancies.
  - As of June 30, 2016, the overall incidence rate of first neoplasm among ocrelizumab-treated patients across all 3 pivotal studies and a Phase 2, dose-finding study *(Kappos et al 2011)* was 0.40 per 100 patient-years of exposure to ocrelizumab (6467 patient-years of exposure) vs 0.20 per 100 patient-years of exposure in the pooled comparator groups (2053 patient-years of exposure in groups receiving Rebif or placebo) *(Hauser et al 2017, Ocrevus Formulary Submission Dossier 2017)*.
    - Since breast cancer occurred in 6 out of 781 females treated with ocrelizumab (vs in none of 668 females treated with Rebif or placebo), the labeling of ocrelizumab additionally recommends that patients follow standard breast cancer screening guidelines.
    - No cases of PML were reported in the controlled Phase 2 or 3 studies or in the OLE of these studies. Outside of clinical trials, as of January 31, 2020, there have been 9 confirmed cases of PML in patients treated with ocrelizumab for MS. Of the 9 cases, 8 patients had been switched from natalizumab (n = 7) or fingolimod (n = 1). In 1 additional case, the patient had no prior exposure to DMTs but had contributing factors for PML including advanced age (78 years) and preexisting grade 1 lymphopenia which progressed to grade 2 during treatment (*Genentech 2020[c], Hauser et al 2020[b], Ng et al 2020*).
  - In patients with relapsing MS, the most common adverse reactions with ocrelizumab (incidence ≥ 10% and greater than Rebif) were upper respiratory tract infections and infusion reactions. In patients with PPMS, the most common adverse reactions (incidence ≥ 10% and greater than placebo) were upper respiratory tract infections, infusion reactions, skin infections, and lower respiratory tract infections.
  - Live or live-attenuated vaccines should not be administered until B-cell count recovery is confirmed (as measured by CD19+ B-cells) in infants born from mothers who were exposed to ocrelizumab during pregnancy.
- Ofatumumab is contraindicated in patients with active HBV infection. The prescribing information contains warnings and precautions regarding the risk of infection, injection-related reactions, reduction in immunoglobulins, and fetal risk. The

most common adverse events (incidence > 10%) include upper respiratory tract infection, headache, injection-related reactions, and local injection site reactions.

- Mitoxantrone has boxed warnings for the risk of cardiotoxicity, risk of bone marrow suppression, and secondary leukemia. Congestive heart failure, potentially fatal, may occur either during therapy with mitoxantrone or months to years after termination of therapy. The maximum cumulative lifetime dose of mitoxantrone for MS patients should not exceed 140 mg/kg/m^2. Monitoring of cardiac function is required prior to all mitoxantrone doses.
- A meta-analysis of PML rates with DMT use found natalizumab to have the greatest association, followed by fingolimod, dimethyl fumarate, ocrelizumab, and alemtuzumab. In patients with disability progression after PML treatment (measured by an EDSS increase of ≥ 1), natalizumab had been used in 85.5% of patients. Disability progression after PML treatment occurred at a lower rate in patients treated with fingolimod (55%, respectively) (*Sriwastava et al 2021*).

Symptomatic therapy

- Dalfampridine is contraindicated in patients with a history of seizure, moderate or severe renal impairment (creatinine clearance [CrCl] ≤ 50 mL/min), and a history of hypersensitivity to dalfampridine or 4-aminopyridine. Dalfampridine may cause seizures; permanently discontinue this medication in patients who have a seizure while on treatment. Dalfampridine can also cause anaphylaxis; signs and symptoms of anaphylaxis have included respiratory compromise, urticaria, and angioedema of the throat and/or tongue. Urinary tract infections were reported more frequently as an adverse reaction in controlled studies in patients receiving dalfampridine 10 mg twice daily (12%) as compared to placebo (8%). The most common adverse events (incidence ≥ 2% and at a rate greater than the placebo rate) for dalfampridine were UTI, insomnia, dizziness, headache, nausea, asthenia, back pain, balance disorder, MS relapse, paresthesia, nasopharyngitis, constipation, dyspepsia, and pharyngolaryngeal pain.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration*

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Ampyra (dalfampridine)	Tablet	Oral	Twice daily	• May be taken with or without food. • Tablets should only be taken whole; do not divide, crush, chew, or dissolve. • Must be taken exactly as prescribed. No more than 2 tablets should be taken in a 24-hour period. There must be an approximate 12-hour interval between doses. • In patients with mild renal impairment (CrCl 51 to 80 mL/min), dalfampridine may reach plasma levels associated with a greater risk of seizures, and the potential benefits of dalfampridine should be carefully considered against the risk of seizures in these patients. Dalfampridine is contraindicated in patients with moderate or severe renal impairment (CrCl ≤ 50 mL/min). • There are no adequate and well-controlled studies of dalfampridine in pregnant women; use during pregnancy only if the benefit justifies the potential fetal risk.
Aubagio (teriflunomide)	Tablet	Oral	Once daily	• May be taken with or without food. • No dosage adjustment is necessary for patients with mild and moderate hepatic

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				impairment; contraindicated in patients with severe hepatic impairment. • Teriflunomide is contraindicated for use in pregnant women and in women of reproductive potential who are not using effective contraception because of the potential for fetal harm. Exclude pregnancy before the start of treatment with teriflunomide in females of reproductive potential and advise females of reproductive potential to use effective contraception during teriflunomide treatment and during an accelerated drug elimination procedure after teriflunomide treatment. Teriflunomide should be stopped and an accelerated drug elimination procedure used if the patient becomes pregnant. • Teriflunomide is detected in human semen; to minimize any possible risk, men not wishing to father a child and their female partners should use effective contraception. Men wishing to father a child should discontinue use of teriflunomide and either undergo an accelerated elimination procedure or wait until verification that the plasma teriflunomide concentration is < 0.02 mg/L. • Transaminase and bilirubin levels should be obtained within 6 months before initiation; transaminase levels should be monitored for at least 6 months after initiation.
Avonex (interferon β-1a)	Injection; pen, prefilled syringe	IM	Once weekly Titration: To reduce the incidence and severity of flu-like symptoms that may occur during initiation, Avonex may be started at a dose of 7.5 mcg and the dose may be increased by 7.5 mcg each week for the next 3 weeks until the recommended dose of 30 mcg is achieved.	• Following initial administration by a trained healthcare provider, Avonex may be self-administered. • Rotate injection sites to minimize the likelihood of injection site reactions. • Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with Avonex use. • Use caution in patients with hepatic dysfunction.
Bafiertam (monomethyl fumarate)	Capsule (delayed-release)	Oral	Twice daily Titration:	• May be taken with or without food; must be swallowed whole. Do not crush, chew, or sprinkle capsule contents on food.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			95 mg twice daily for 7 days (initiation), then 190 mg twice daily (maintenance) Temporary dose reductions to 95 mg twice a day may be considered for individuals who do not tolerate the maintenance dose.	• The incidence or severity of flushing may be reduced by administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to monomethyl fumarate; studies did not show that the presence of food had an impact on the incidence of flushing with monomethyl fumarate. • Obtain a complete blood cell count including lymphocyte count, serum aminotransferase, alkaline phosphatase, and total bilirubin levels before initiation of therapy.
Betaseron (interferon β-1b)	Injection	SC	Every other day Titration: Generally, start at 0.0625 mg (0.25 mL) every other day, and increase over a 6-week period to 0.25 mg (1 mL) every other day.	• Following initial administration by a trained healthcare provider, IFNβ-1b may be self-administered. • Rotate injection sites to minimize the likelihood of injection site reactions. • Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with IFNβ-1b use.
Copaxone (glatiramer acetate) [and Glatopa]	Injection	SC	20 mg once daily **OR** 40 mg 3 times per week at least 48 hours apart Note: The 2 strengths are not interchangeable.	• Following initial administration by a trained healthcare provider, glatiramer acetate may be self-administered. • Areas for SC self-injection include arms, abdomen, hips, and thighs.
Extavia (interferon β-1b)	Injection	SC	Every other day Titration: Generally, start at 0.0625 mg (0.25 mL) every other day, and increase over a 6-week period to 0.25 mg (1 mL) every other day.	• Following initial administration by a trained healthcare provider, IFNβ-1b may be self-administered. • Rotate injection sites to minimize the likelihood of injection site reactions. • Concurrent use of analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms associated with IFNβ-1b use.
Gilenya (fingolimod)	Capsule	Oral	Once daily Approved for adults and pediatric patients 10 years of age or older. For pediatric patients ≤ 40 kg, a lower dose is recommended. Note: Patients who initiate fingolimod and those who re-initiate treatment after	• May be taken with or without food. First dose monitoring: • Observe all patients for bradycardia for at least 6 hours; monitor pulse and blood pressure hourly. Electrocardiograms (ECGs) prior to dosing and at end of the observation period are required. • Monitor until resolution if heart rate [HR] < 45 bpm in adults, < 55 bpm in pediatric patients ≥ 12 years of age, or < 60 bpm in pediatric patients 10 or 11 years of age, new onset second degree or higher

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			discontinuation for longer than 14 days require first dose monitoring (see right).	AV block, or if the lowest post-dose heart rate is at the end of the observation period. Monitor symptomatic bradycardia with continuous ECG until resolved. Continue overnight if intervention is required; repeat first dose monitoring for second dose. • Observe patients overnight if at higher risk of symptomatic bradycardia, heart block, prolonged QTc interval, or if taking drugs with a known risk of torsades de pointes or drugs that slow heart rate or AV conduction. • Fingolimod exposure is doubled in patients with severe hepatic impairment so patients should be closely monitored. No dose adjustment is necessary in mild-to-moderate hepatic impairment. • The blood level of some fingolimod metabolites is increased (up to 13-fold) in patients with severe renal impairment; blood levels were not assessed in patients with mild or moderate renal impairment. • Fingolimod may cause fetal harm when administered to a pregnant woman. Before initiation of treatment with fingolimod, females of reproductive potential should be counseled on the potential for serious risk to the fetus and the need for effective contraception during treatment and for 2 months after treatment to allow the compound to be eliminated from the body. In females planning to become pregnant, fingolimod should be stopped 2 months before planned conception.
Kesimpta (ofatumumab)	Injection	SC	20 mg at weeks 0, 1, and 2 followed by subsequent dosing of 20 mg once monthly starting at week 4	• Prior to initiation, perform hepatitis B virus screening and tests for quantitative serum immunoglobulins. For patients with low serum immunoglobulins, immunology experts should be consulted.
Lemtrada (alemtuzumab)†	Injection	IV	**2 treatment courses** First course: 12 mg/day on 5 consecutive days Second course: 12 mg/day on 3 consecutive days 12 months after the first treatment course	• Pre-medicate with high-dose corticosteroids prior to Lemtrada infusion for the first 3 days of each treatment course. • Infused over 4 hours for both treatment courses; patients should be observed for infusion reactions during and for at least 2 hours after each Lemtrada infusion.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Subsequent course: 12 mg/day for 3 consecutive days may be administered, as needed, at least 12 months after the last dose of any prior treatment courses.	Vital signs should be monitored before the infusion and periodically during the infusion. • Administer antiviral agents for herpetic prophylaxis starting on the first day of alemtuzumab dosing and continuing for a minimum of 2 months after completion of Lemtrada dosing or until CD4+ lymphocyte count is > 200 cells/microliter, whichever occurs later. • Patients should complete any necessary immunizations at least 6 weeks prior to treatment with alemtuzumab. Important monitoring: • Complete blood count with differential, serum creatinine, and urinalysis (prior to treatment initiation and at monthly intervals thereafter); a test of thyroid function, such as thyroid stimulating hormone level (prior to treatment initiation and every 3 months thereafter); serum transaminases and total bilirubin (prior to treatment initiation and periodically thereafter) • Measure the urine protein to creatinine ratio prior to treatment initiation • Conduct baseline and yearly skin exams to monitor for melanoma.
Mavenclad (cladribine)	Tablet	Oral	Cumulative dosage of 3.5 mg/kg divided into 2 yearly treatment courses of 1.75 mg/kg per treatment course. Each treatment course is divided into 2 treatment cycles: • First course/first cycle: start anytime • First course/second cycle: administer 23 to 27 days after the last dose of first course/first cycle. • Second course/first cycle: administer at least 43 weeks after the last dose of first course/second cycle. • Second course/second cycle: administer 23 to 27 days after the last	• The use of Mavenclad in patients weighing less than 40 kg has not been investigated. • Mavenclad is contraindicated in pregnant women and in female/males of reproductive potential that do not plan to use effective contraception. • Follow standard cancer screening guidelines because of the risk of malignancies. • Administer all immunizations according to guidelines prior to treatment initiation. • Obtain a complete blood count with differential including lymphocyte count. Lymphocytes must be within normal limits before treatment initiation and at least 800 cells/microliter before starting the second treatment course.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			dose of second course/first cycle.	
Mayzent (siponimod)	Tablet	Oral	Once daily Initiate treatment with a 5-day titration; a starter pack should be used for patients who will be titrated to the maintenance dosage starting on Day 6 (refer to prescribing information for titration regimen).	• Mayzent can cause fetal harm when administered to pregnant women. • Dosage should be titrated based on patient's CYP2C9 genotype. • Patients with sinus bradycardia (HR < 55 bpm), first- or second-degree AV block, or a history of myocardial infarction or heart failure should undergo first dose monitoring for bradycardia.
mitoxantrone	Injection	IV	Every 3 months For MS-related indications: 12 mg/m^2 given as a short IV infusion over 5 to 15 minutes Note: Left ventricular ejection fraction (LVEF) should be evaluated prior to administration of the initial dose of mitoxantrone injection (concentrate) and all subsequent doses. In addition, LVEF evaluations are recommended if signs or symptoms of CHF develop at any time during treatment with mitoxantrone.	• Mitoxantrone injection (concentrate) should not be administered to MS patients with an LVEF < 50%, with a clinically significant reduction in LVEF, or to those who have received a cumulative lifetime dose of ≥ 140 mg/m^2. • Mitoxantrone generally should not be administered to MS patients with neutrophil counts < 1500 cells/mm^3. • Mitoxantrone therapy in MS patients with abnormal liver function tests is not recommended because mitoxantrone clearance is reduced by hepatic impairment and no laboratory measurement can predict drug clearance and dose adjustments. • Mitoxantrone may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant. • Complete blood counts, including platelets, should be monitored prior to each course of mitoxantrone and in the event that signs or symptoms of infection develop. • Liver function tests should be monitored prior to each course of therapy.
Ocrevus (ocrelizumab)	Injection	IV	Every 6 months (24 weeks) Titration: Initial dose: 300 mg IV, followed 2 weeks later by a second 300 mg IV infusion. Subsequent doses: 600 mg IV infusion every 6 months	• Pre-medicate with methylprednisolone (or an equivalent corticosteroid) and an antihistamine (eg, diphenhydramine) prior to each infusion. An antipyretic (eg, acetaminophen) may also be considered. • Observe patients for at least 1 hour after the completion of the infusion. Dose modifications in response to infusion reactions depend on the severity. See package insert for more details.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				• Administer all necessary immunizations according to immunization guidelines at least 2 (non-live vaccines) to 4 (live or live-attenuated vaccines) weeks prior to initiation of ocrelizumab. • Women of childbearing potential should use contraception while receiving ocrelizumab and for 6 months after the last infusion of ocrelizumab. • Hepatitis B virus screening is required before the first dose. • Prior to initiation, quantitative serum immunoglobulin levels should be performed. For patients with low serum immunoglobulins, immunology experts should be consulted.
Plegridy (peginterferon β-1a)	Injection; pen, prefilled syringe for SC use; prefilled syringe for IM use	SC, IM	Every 14 days Titration: Start with 63 mcg on day 1, 94 mcg on day 15, and 125 mcg (full dose) on day 29	• Following initial administration by a trained healthcare provider, Plegridy may be self-administered. • Patients should be advised to rotate injection sites. The usual sites for SC administration are the abdomen, back of the upper arm, and thigh; IM injections should be administered in the thigh. • Analgesics and/or antipyretics on treatment days may help ameliorate flu-like symptoms. • Monitor for adverse reactions due to increased drug exposure in patients with severe renal impairment.
Ponvory (ponesimod)	Tablet	Oral	Once daily Titration: Initiate 14-day titration, starting with 2 mg once daily and increase to 20 mg by day 15 (refer to prescribing information for titration regimen).	• May be taken with or without food; must be swallowed whole. • Ponvory can cause fetal harm when administered to pregnant women. • Before treatment initiation, obtain complete blood count, ECG, liver function tests, ophthalmic evaluation, and test for varicella zoster virus. • Patients with sinus bradycardia (HR < 55 bpm), first- or second-degree AV block, or a history of myocardial infarction or heart failure should undergo first dose monitoring for bradycardia.
Rebif (interferon β-1a); Rebif Rebidose	Injection	SC	Three times per week at least 48 hours apart Titration: Generally, the starting dose should be 20% of the prescribed dose 3 times	• Following initial administration by a trained healthcare provider, Rebif may be self-administered. • Patients should be advised to rotate the site of injection with each dose to minimize the likelihood of severe injection site reactions or necrosis.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			per week, and increased over a 4-week period to the targeted recommended dose of either 22 mcg or 44 mcg injected SC 3 times per week	• Decreased peripheral blood counts or elevated liver function tests may necessitate dose reduction or discontinuation of Rebif administration until toxicity is resolved. • Concurrent use of analgesics and/or antipyretics may help ameliorate flu-like symptoms associated with Rebif use on treatment days.
Tecfidera (dimethyl fumarate)	Capsule (delayed-release)	Oral	Twice daily Titration: 120 mg twice daily for 7 days (initiation), then 240 mg twice daily (maintenance) Temporary dose reductions to 120 mg twice a day may be considered for individuals who do not tolerate the maintenance dose.	• May be taken with or without food; must be swallowed whole. Do not crush, chew, or sprinkle capsule contents on food. • The incidence of flushing may be reduced by administration of dimethyl fumarate with food. Alternatively, administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to dimethyl fumarate dosing may reduce the incidence or severity of flushing. • Obtain a complete blood cell count including lymphocyte count, serum aminotransferase, alkaline phosphatase, and total bilirubin levels before initiation of therapy.
Tysabri (natalizumab)†	Injection	IV	Once a month (every 4 weeks) Both MS and Crohn's disease indications are dosed the same: 300 mg infused over 1 hour and given every 4 weeks. Tysabri should not be administered as an IV push or bolus injection.	• Patients should be observed during the infusion and for 1 hour after the infusion is complete.
Vumerity (diroximel fumarate)	Capsule (delayed-release)	Oral	Twice daily Titration: 231 mg twice daily for 7 days (initiation), then 462 mg twice daily (maintenance) Temporary dose reductions to 231 mg twice a day may be considered for individuals who do not tolerate the maintenance dose.	• Must be swallowed whole. Do not crush, chew, or sprinkle capsule contents on food. • Avoid administration with a high-fat, high-calorie meal/snack. Avoid co-administration with alcohol. • The incidence or severity of flushing may be reduced by administration of non-enteric coated aspirin (up to a dose of 325 mg) 30 minutes prior to diroximel fumarate. • Obtain a complete blood cell count including lymphocyte count, serum aminotransferase, alkaline phosphatase,

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				and total bilirubin levels before initiation of therapy.
Zeposia (ozanimod)	Capsule	Oral	Once daily Titration: 0.23 mg once daily on days 1 to 4, then 0.46 mg once daily on days 5 to 7, then 0.92 mg once daily on day 8 and thereafter.	• Dosing recommendations for MS and ulcerative colitis are the same. • May be taken with or without food. Capsules should be swallowed whole. • Obtain a complete blood count (including lymphocyte count), transaminase and bilirubin levels, electrocardiogram, and ophthalmic assessment before initiation of therapy. • If a dose is missed during the first 2 weeks of treatment, treatment should be restarted using the titration regimen; if a dose is missed after 2 weeks of treatment, continue treatment as planned. • Use in patients with hepatic impairment is not recommended.

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

CONCLUSION

- DMTs for MS have shown benefits in patients with relapsing MS such as a decreased relapse rate and a slower accumulation of brain lesions on MRI. Therefore, it is recommended that all patients with a diagnosis of definite relapsing MS begin DMTs *(MS Coalition 2019)*.
- IFNβ products have been shown to decrease MRI lesion activity, prevent relapses, and delay disability progression. In general, patients treated with IFNβ or glatiramer acetate can expect a 30% reduction in ARR during a 2-year period *(MS Coalition 2019)*. Head-to-head clinical trials have found IFNβ and glatiramer acetate to be comparable in terms of efficacy on relapse rate. Several studies have demonstrated an improved tolerability at the cost of a decreased therapeutic response with low dose IM IFNβ-1a compared to higher dose SC IFNβ-1a *(Panitch et al 2002, Panitch et al 2005, Schwid et al 2005, Schwid et al 2007, Traboulsee et al 2008)*.
  - Influenza-type symptoms, injection site reactions, headache, nausea, and musculoskeletal pain are the most frequently reported adverse events with IFNβ products. With IFNβ, use caution in patients with depression or other mood disorders.
  - The most frequently reported adverse events with glatiramer acetate include a transient, self-limiting, post-injection systemic reaction immediately following drug administration consisting of flushing, chest pain, palpitations, anxiety, dyspnea, throat constriction, and urticaria. Glatiramer acetate does not have any known drug interactions and is not associated with an increased risk of hepatotoxicity or depression.
- Despite advancements in treatment, many patients fail initial DMTs with glatiramer acetate or IFNβ, primarily due to intolerable adverse effects or inadequate efficacy *(Coyle 2008, Portaccio et al 2008)*. Clinical trials have shown that patients switching from IFNβ to glatiramer acetate therapy and vice versa, due to poor response, may achieve a significant reduction in relapse rates and a delay in disease and disability progression *(Coyle 2008, Caon et al 2006, Zwibel 2006)*. The guidelines suggest that all first-line MS DMTs should be made accessible, and the choice of initial treatment should be based on patient-specific factors *(MS Coalition 2019, Scolding et al 2015, Montalban et al 2018, Rae-Grant et al 2018)*. The premature discontinuation rate is high among patients with MS; therefore, factors that will maximize adherence should be considered when initiating therapy. Failure with 1 agent does not necessarily predict failure with another. Therefore, patients experiencing an inadequate response or drug-induced adverse event should be switched to a different DMT *(Coyle 2008, Portaccio et al 2008, Rae-Grant et al 2018)*.

- There are now 9 available oral agents. It is expected that the availability of oral agents may increase convenience and improve patient adherence *(Sanvito et al 2011)*. The available oral drugs each have different mechanisms of action and/or tolerability profiles. Cases of PML have been reported in patients taking fingolimod and dimethyl fumarate.
  - Gilenya (fingolimod) is a S1P receptor modulator. In a trial comparing fingolimod to placebo, fingolimod-treated patients had a decreased ARR, improved MRI outcomes, and a lower likelihood of disability progression *(Kappos et al 2010)*. In a trial comparing fingolimod to IFNβ-1a IM (Avonex), fingolimod-treated patients had a decreased ARR and improved MRI outcomes, but disability progression was similar in the 2 groups *(Cohen et al 2010)*. The adverse event profile for fingolimod includes cardiovascular risks including bradycardia. First dose administration of fingolimod requires at least 6 hours of observation with hourly monitoring of heart rate and blood pressure, and patients should have an ECG before dosing and at the end of the observation period.
    - Fingolimod is also FDA-approved for MS in the pediatric population. In a trial evaluating patients between 10 and 17 years of age, fingolimod significantly reduced ARR and the rate of new or newly enlarged lesions compared to IFNβ-1a (*Chitnis et al 2018*).
  - Mayzent (siponimod) is a S1P receptor modulator, similar to fingolimod. In a trial comparing Mayzent to placebo, Mayzent significantly reduced the risk of 3-month CDP, delayed the risk of 6-month CDP, and reduced the ARR (*Kappos et al 2018*). First dose cardiac monitoring is recommended for patients with a heart rate < 55 bpm or a history of cardiac disease. Siponimod shares many of the same warnings as fingolimod.
  - Zeposia (ozanimod), the third S1P receptor modulator, has to significantly decrease ARR compared to IFNβ-1a; however, unlike other drugs in this class, it does not require first dose cardiac monitoring (*Comi et al 2019, Cohen et al 2019*).
  - Ponvory (ponesimod), a fourth S1P receptor modulator, reduced ARR compared to teriflunomide *(Kappos et al 2021).*
  - Tecfidera (dimethyl fumarate) has efficacy similar to that of fingolimod; its benefit-risk profile makes it a reasonable initial or later stage DMT option for most patients with RRMS *(Wingerchuk et al 2014)*. Gastrointestinal intolerance and flushing are common side effects that may wane with time; slow titration to maintenance doses, taking the medication with food, and premedication with aspirin may reduce their severity.
  - Vumerity (diroximel fumarate) is an oral fumarate that is rapidly converted to monomethyl fumarate, which is also the active metabolite of Tecfidera (dimethyl fumarate). Diroximel fumarate may offer improved GI tolerability as compared to dimethyl fumarate (*Naismith et al 2019, Selmaj et al 2019).*
  - Bafiertam (monomethyl fumarate) was approved by the FDA in April 2020 and is considered to be a “bioequivalent alternative” to dimethyl fumarate (*Bafiertam prescribing information 2021*).
  - Aubagio (teriflunomide) inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme involved in de novo pyrimidine synthesis. Although its exact mechanism of action is unknown, it may involve a reduction in the number of activated lymphocytes in the CNS. Patients treated with teriflunomide in a clinical trial experienced a reduction in the ARR and improved MRI outcomes compared to placebo. Patients in the higher dose group (14 mg) also had a lower likelihood of disability progression, but this difference was not statistically significant in the lower dose group (7 mg) as compared to placebo *(O’Connor et al 2011)*. Teriflunomide has boxed warnings for the possibility of severe liver injury and teratogenicity. The most common adverse reactions include increases in liver enzymes, alopecia, diarrhea, influenza, nausea, and paresthesia.
  - Mavenclad (cladribine) is a purine antimetabolite indicated for the treatment of relapsing forms of MS, to include relapsing-remitting disease and active secondary progressive disease. In a trial comparing Mavenclad to placebo, Mavenclad had reduced ARRs and disability progression vs placebo (*Giovannoni et al 2010*). Mavenclad carries a boxed warning for risk of malignancies and teratogenicity. Lymphopenia is the most common adverse effect.
- Tysabri (natalizumab) is a recombinant monoclonal antibody indicated for the treatment of relapsing forms of MS and is also approved for use in the treatment of moderately to severely active CD in patients with an inadequate response to or who are unable to tolerate conventional CD therapies and TNF inhibitors.
  - In a 2011 systematic review of trials evaluating natalizumab for RRMS, pooled efficacy data from 2 RCTs (AFFIRM and SENTINEL) showed that natalizumab significantly reduced the risk for having a relapse during 2 years of treatment. In addition, natalizumab significantly reduced the risk for experiencing 12-week CDP at 2 years *(Pucci et al 2011)*. Natalizumab has been associated with an increased risk of PML; however, the overall incidence of PML has remained low (0.4%). Natalizumab can only be obtained through a restricted distribution program.
- Kesimpta (ofatumumab) is the first self-administered CD20-directed cytolytic antibody indicated for relapsing forms of MS. Ofatumumab has demonstrated superiority to teriflunomide in patients with relapsing forms of MS for the outcome

of ARR *(Hauser et al 2020[a])*. Ofatumumab is self-administered monthly by SC injection after an initial loading regimen. Key warnings include the risk for infections, including PML and HBV reactivation. Injection-related reactions, possible reduction in immunoglobulins, and fetal risk (B cell depletion in infants born to mothers treated with ofatumumab during pregnancy) are other warnings. The most common AEs (incidence > 10%) were upper respiratory tract infection, headache, injection-related reactions, and local injection site reactions.

- Ocrevus (ocrelizumab) is a recombinant monoclonal antibody designed to selectively target CD20-positive B cells. As a humanized form of Rituxan (rituximab), ocrelizumab is expected to be less immunogenic with repeated infusions and may have a more favorable benefit-to-risk profile than Rituxan *(Sorensen et al 2016)*.
  - Ocrevus provides another DMT option to the growing armamentarium of highly effective agents indicated for the treatment of relapsing MS. Ocrelizumab is also indicated for the treatment of PPMS, making it the first DMT with substantial evidence supporting its use in this form of MS. Although the pivotal studies of ocrelizumab were of sufficient length to assess efficacy, more long-term safety data are needed to evaluate the effects of ocrelizumab on emergent neoplasms and the risk of PML.
- Lemtrada (alemtuzumab) is a highly efficacious DMT that has demonstrated superiority in reducing relapses when compared to Rebif in both treatment-naïve and treatment-experienced patients. The dosing schedule of 2 annual treatment courses is counterbalanced by the need for regular monitoring of the increased risk for autoimmunity. Lemtrada is best reserved for patients who have failed at least 2 other DMTs and are not candidates for natalizumab (*Garnock-Jones 2014*).
- Mitoxantrone is a synthetic intercalating chemotherapeutic agent. While it is approved for the treatment of RRMS, SPMS, and PRMS, cumulative dose-related cardiac toxicity and the risk for secondary leukemia markedly limit its use. Mitoxantrone is reserved for use in patients with aggressive disease.
- While DMTs do not sufficiently address quality of life in MS patients, dalfampridine can be used to complement treatment with DMTs. Although a 25% improvement in T25FW may appear marginal, it has been established that improvements in T25FW speed of ≥ 20% are meaningful to people with MS. Improved walking could potentially contain some of the direct and indirect costs (eg, reduced productivity, disability, unemployment, costs of assistive devices and caregivers) associated with MS.
- With an increasing number of DMTs currently on the market and no specific MS algorithm in place to guide treatment decisions, the selection of an agent is generally based on considerations of the risks and benefits of each therapy, physician experience, patient comorbidities, and patient preferences.
  - Clinicians should consider prescribing a high efficacy medication such as alemtuzumab, cladribine, fingolimod, ocrelizumab or natalizumab for newly-diagnosed individuals with highly active MS (*MS Coalition 2019*).
  - Clinicians should also consider prescribing a high efficacy medication for patients who have breakthrough activity on another DMT, regardless of the number of previously used agents (*MS Coalition 2019*).
- Zeposia (ozanimod) is the first S1P receptor modulator that is approved for moderate to severe ulcerative colitis in adults, in addition to its approval for MS *(Zeposia prescribing information 2021).* The role in therapy for S1P receptor modulators in ulcerative colitis is not well-defined.
- Tysabri (natalizumab) is approved for the induction and maintenance of clinical response and remission in moderate to severe Crohn's disease in adults, in addition to its approval for MS (*Tysabri prescribing information 2020*). The AGA currently recommends against the use of natalizumab over no treatment for the induction and maintenance of clinical remission due to the risk of PML (*Feuerstein et al 2021*).

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