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Silver State Scripts Board Meeting

DECEMBER 10, 2020

Table of Contents

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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:	October 27, 2020
Date of Meeting:	Thursday, December 10, 2020 at 1:00 PM
Name of Organization:	The State of Nevada, Department of Health and Human Services, Division of Health Care Financing and Policy (DHCFP), Silver State Script Board.
Place of Meeting:	Please use the teleconference/WebEx options provided below. If accommodations are requested, please advise using the information at the end of this agenda. Out of deference to Declaration of Emergency Directive 006 (https://nvhealthresponse.nv.gov/wp-content/uploads/2020/03/Declaration-of-Emergency-Directive-006-re-OML.3-21-20.pdf) from the State of Nevada Executive Department signed by Governor Sisolak as well as Emergency Directive 003 (https://nvhealthresponse.nv.gov/wp-content/uploads/2020/03/2020-03-20.Declaration-of-Emergency-Directive-003.pdf) signed March 20, 2020, a physical location will not be open to the public for attendance at this time.
Webinar Registration:	https://optum.webex.com/optum/onstage/g.php?MTID=e3ca61eaa974e37de3aaf7ffbdf9da4f0 Or go to www.webex.com and enter the Event Number listed below. Once you have registered for the meeting, you will receive an email message confirming your registration. This message will provide the information that you need to join the meeting.
Event Number:	171 878 1660 Click "Join Now." Follow the instructions that appear on your screen to join the audio portion of the meeting. Audio will be transmitted over the internet. A password should not be necessary, but if asked use: Medicaid1!

For Audio Only:

Phone: 1-763-957-6300
Event: 171 878 1660

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

Closed Executive Session – 1:00 PM

Open Session/Public Meeting – will begin upon completion of the Closed Executive Session

AGENDA

1. Call to Order and Roll Call

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

3. Administrative

a. **For Possible Action:** Review and Approve Meeting Minutes from September 24, 2020.

b. Status Update by the DHCFP.

4. Proposed New Classes

a. **For Possible Action:** Discussion and possible adoption of Hormones and Hormone Modifiers, Pituitary Hormones, Gonadotropin-Releasing Hormone (GNRH) Receptor Antagonists and Combinations.

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

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

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

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

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

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

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

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

6. Established Drug Classes

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

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

b. **For Possible Action:** Discussion and possible adoption of Ophthalmic Agents, Ophthalmics for Dry Eye Disease

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

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

8. Closing Discussion

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

b. Date and location of the next meeting.

i. Discussion of the time of the next meeting.

c. Adjournment.

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

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

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

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

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

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

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

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

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

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Summary of Silver State Scripts Board

Silver State Scripts Board

By statute (NRS 422.4025), the State of Nevada requires the DHCFP to develop and maintain a Preferred Drug List (PDL) to be used for the Medicaid program and CHIP, and each public or nonprofit health benefit plan that elects to use the PDL. The Silver State Scripts Board (formerly known as the Pharmacy & Therapeutics or P&T Committee) was established to identify prescription drugs to be included on the PDL.

A governing body of a county, school district, municipal corporation, political subdivision, public corporation or other local government agency of the State of Nevada that provides coverage of prescription drugs pursuant to NRS 287.010 or any issuer of a policy health insurance purchased pursuant to NRS 287.010 may use the PDL developed by DHHS as its PDL.

The PDL is not a restricted formulary. Drugs not on the PDL are still available to recipients if they meet the Standard Preferred Drug List Exception criteria.

The Silver State Scripts Board consists of members who are Director-appointed physicians and pharmacists. Members must be licensed to practice in the State of Nevada as either an actively practicing physician or an actively practicing pharmacist.

Meetings are held quarterly and are open to the public. Anyone wishing to address the Silver State Scripts Board may do so. Public comment is limited to 5 minutes per speaker/organization (due to time constraints). Anyone presenting documents for consideration must provide sufficient copies for each Board member and an electronic copy to the DHCFP Coordinator for official record.

For pharmacists and physicians wishing to serve on the Silver State Scripts Board, please email your contact information, NPI and current CV/Resume to rxinfo@dhcfp.nv.gov

Current Board Members:

Mark Decerbo, PharmD (Chairman)

Kate Ward, PharmD (Vice Chairman)

Joseph Adashek, MD

Evelyn Chu, Pharm.D.

Mark Crumby, Pharm.D.

Michael Hautekeet, R.Ph

Sapandeep Khurana, MD

Brian Passalacqua, MD

Aditi Singh, MD

Silver State Scripts Board Meeting scheduled for 2020

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

Silver State Scripts Board Meeting scheduled for 2021

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

Web References

Preferred Drug List:

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

Medicaid Services Manual (MSM) Chapter 1200:

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

Silver State Scripts Board Bylaws:

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

The Division of Health Care Financing and Policy Public Notices:

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

Definition of "Therapeutic Alternative"

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

Standard Preferred Drug List Exception Criteria

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

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

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Current Preferred Drug List

	Preferred Products	PA Criteria	Non-Preferred Products
	RHOPRESSA® ROCKLATAN® SIMBRINZA® TIMOLOL DROPS/ GEL SOLN TRAVATAN Z® TRAVATAN®		VYZULTA® XALATAN® XELPROS® ZIOPTAN®
Ophthalmic Antihistamines			
	BEPREVE® KETOTIFEN PAZEO® ZADITOR OTC®		ALAWAY® AZELASTINE ALOMIDE ALOCRIL ELESTAT® EMADINE® EPINASTINE LASTACRAFT® OLOPATADINE (drop/sol) OPTIVAR® PATADAY® PATANOL® ZERVIATE® NEW
Ophthalmic Anti -infectives			
Ophthalmic Macrolides			
	ERYTHROMYCIN OINTMENT		
Ophthalmic Quinolones			
	BESIVANCE® CIPROFLOXACIN LEVOFLOXACIN MOXEZA® VIGAMOX®		CILOXAN® MOXIFLOXACIN OFLOXACIN® ZYMAXID®
Ophthalmic Anti -infective/Anti -inflammatory Combinations			
	NEO/POLY/DEX PRED-G SULF/PRED NA SOL OP TOBRADEX OIN TOBRADEX SUS ZYLET SUS		BLEPHAMIDE MAXITROL NEO/POLY/BAC OIN /HC NEO/POLY/HC SUS OP TOBRA/DEXAME SUS TOBRADEX SUS TOBRADEX ST SUS
Ophthalmic Anti -inflammatory Agents			
Ophthalmic Corticosteroids			
	ALREX® DEXAMETHASONE DUREZOL®		FLAREX® FML® FML FORTE®

	Preferred Products	PA Criteria	Non-Preferred Products
	FLUOROMETHOLONE LOTEMAX® PREDNISOLONE		MAXIDEX® OMNIPRED® PRED FORTE® PRED MILD® VEXOL®
Ophthalmic Nonsteroidal Anti -inflammatory Drugs (NSAIDs)			
	DICLOFENAC FLURBIPROFEN ILEVRO® KETOROLAC NEVANAC®		ACULAR® ACULAR LS® ACUVAIL® BROMDAY® BROMFENAC® PROLENSA®
Ophthalmics for Dry Eye Disease			
	ARTIFICIAL TEARS 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® NEW AMPHETAMINE SALT COMBO IR CONCERTA® DEXMETHYLPHENIDATE DEXTROAMPHETAMINE SA TAB DEXTROAMPHETAMINE TAB DAYTRANA® DYANAVEL® FOCALIN XR® GUANFACINE ER METADATE CD® METHYLIN®	PA required for entire class Children's Form: https://www.medicaid.nv.gov/Downloads/provider/FA-69.pdf	ADDERALL® ADHANSIA® XR NEW ADZENYS® AMPHETAMINE ER SUSP NEW AMPHETAMINE SALT COMBO XR NEW APTENSIO XR® ATOMOXETINE NEW CLONIDINE HCL ER COTEMPLA XR®-ODT DESOXYN® DEXEDRINE®

Preferred Products	PA Criteria	Non-Preferred Products
METHYLPHENIDATE METHYLPHENIDATE ER (All forms generic extended release) METHYLPHENIDATE SOL PROCENTRA® QUILLICHEW® QUILLIVANT® XR SUSP RITALIN LA® STRATTERA® NEW VYVANSE®	Adult Form: https://www.medicaid.nv.gov/Downloads/provider/FA-68.pdf	DEXTROAMPHETAMINE SOLUTION EVEKEO® EVEKEO® ODT FOCALIN® INTUNIV® JORNAY PM® METADATE ER® METHYLPHENIDATE TAB ER (RELEXXII) METHYLPHENIDATE CHEW MYDAYIS® 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 * PA required No PA required if ICD-10 - M79.1; M60.0-M60.9, M61.1.	APLENZIN® BRINTELLIX® (Discontinued) CYMBALTA® * DESVENLAFAXINE FUMARATE EFFEXOR® (ALL FORMS) FETZIMA® FORFIVO XL® KHEDEZLA® TRINTELLIX® VIIBRYD® WELLBUTRIN®
Selective Serotonin Reuptake Inhibitors (SSRIs)		
CITALOPRAM ESCITALOPRAM FLUOXETINE PAROXETINE PEXEVA® SERTRALINE	PA required for members under 18 years old	CELEXA® FLUVOXAMINE QL LEXAPRO® LUVOX® PAROXETINE ER PAXIL® PROZAC®

Preferred Products	PA Criteria	Non-Preferred Products
		SARAFEM® ZOLOFT®
Antipsychotics		
Atypical Antipsychotics - Oral		
ARIPIPRAZOLE CLOZAPINE FANAPT® LATUDA® NUPLAZID®* OLANZAPINE QUETIAPINE QUETIAPINE XR REXULTI® RISPERIDONE SAPHRIS® VRAYLAR® ZIPRASIDONE	PA required for Ages under 18 years old PA Forms: https://www.medicaid.nv.gov/Downloads/provider/FA-70A.pdf (ages 0-5) https://www.medicaid.nv.gov/Downloads/provider/FA-70B.pdf (ages 6-18) *(No PA required Parkinson's related psychosis ICD code on claim)	ABILIFY® ABILIFY MYCITE ® CAPLYTA® NEW CLOZARIL® FAZACLO® GEODON® INVEGA® PALIPERIDONE RISPERDAL® SECUADO® NEW SEROQUEL® SEROQUEL XR® ZYPREXA®
Atypical Antipsychotics – Long Acting Injectable NEW		
ABILIFY® MAINTENA NEW ARISTADA® NEW ARISTADA® INITIO NEW INVEGA® SUSTENNA NEW INVEGA® TRINZA* NEW RISPERDAL® CONSTA NEW PERSERIS® NEW ZYPREXA® RELPREVV NEW	*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)	AMBIEN® AMBIEN CR® BELSOMRA® DORAL® ESZOPICLONE EDLUAR® HETLIOZ® INTERMEZZO®

Preferred Products	PA Criteria	Non-Preferred Products
		LUNESTA® SILENOR® SOMNOTE® SONATA® ZOLPIDEM CR ZOLPIMIST®
	PA required for members under 18 years old	
Psychostimulants		
Narcolepsy Agents		
ARMODAFINIL * NEW NUVIGIL® PROVIGIL® * WAKIX® **NEW	* (No PA required for ICD-10 code G47.4) **PA Required for all ages	MODAFINIL SUNOSI®** XYREM®
Respiratory Agents		
Nasal Antihistamines		
AZELASTINE DYMISTA® OLOPATADINE		ASTEPRO® PATANASE®
Respiratory Anti -inflammatory Agents		
Leukotriene Receptor Antagonists		
MONTELUKAST ZAFIRLUKAST ZYFLO® ZYFLO CR®		ACCOLATE® SINGULAIR® ZILEUTON ER
Nasal Corticosteroids		
FLUTICASONE TRIAMCINOLONE ACETONIDE		BECONASE AQ® FLONASE® FLUNISOLIDE NASACORT AQ® NASONEX® OMNARIS® QNASL® RHINOCORT AQUA® VERAMYST® XHANCE™ ZETONNA®
Phosphodiesterase Type 4 Inhibitors		
DALIRESP® QL	PA required	
Long -acting/Maintenance Therapy		
ADVAIR HFA® ANORO ELLIPTA® ARNUITY ELLIPTA® ASMANEX®		ADVAIR® DISKUS AEROSPAN HFA® AIRDUO® ALVESCO® ARCAPTA NEOHALER® ARMONAIR®

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

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Meeting Minutes

SILVER STATE SCRIPTS BOARD

DRAFT MEETING MINUTES

Date of Meeting: Thursday, September 24, 2020 at 1:00 PM

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

Agenda Item	Record			Notes
Closed Executive Session		Present	Absent	DHCFP Staff Present were as follows: Long, Holly, Social Services Program Specialist III Lither, Gabriel, DAG Flowers, Ellen, Program Officer I Gudino-Vargas, Antonio, Social Services Program Specialist II Moffitt, Tammy, Social Services Chief III
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	
	Adashek, Joseph, MD	☐	☒	
	Chu, Evelyn, Pharm.D.	☒	☐	
	Crumby, Mark, Pharm.D.	☒	☐	
	Hautekeet, Mike, R.Ph	☒	☐	
	Khurana, Sapandeep, MD	☒	☐	
	Passalacqua, Brian, MD	☒	☐	
	Singh, Aditi, MD	☒	☐	
	Ward, Kate, Pharm.D.	☒	☐	

		DXC Staff Present were as follows: Leid, Jovanna, Pharm.D. OptumRx Staff Present were as follows: Jeffery, Carl, Pharm.D. Whittington, Kevin, R.Ph
1. Call to Order and Roll Call	Chairman Decerbo called the meeting to order at 2:00 p.m. on September 24, 2020. Roll was taken by Chairman Decerbo. Decerbo, Mark, Pharm.D. – Chair ☒ Present ☐ Absent Adashek, Joseph, MD ☒ ☐ Chu, Evelyn, Pharm.D. ☒ ☐ Crumby, Mark, Pharm.D. ☒ ☐ Hautekeet, Mike, R.Ph ☒ ☐ Khurana, Sapandeep, MD ☒ ☐ Passalacqua, Brian, MD ☒ ☐ Singh, Aditi, MD ☒ ☐ Ward, Kate, Pharm.D. ☒ ☐ A quorum was present.	DHCFP Staff Present were as follows: Long, Holly, Social Services Program Specialist III Lither, Gabriel, DAG Flowers, Ellen, Program Officer I Gudino-Vargas, Antonio, Social Services Program Specialist II Moffitt, Tammy, Social Services Chief III DXC Staff Present were as follows: Leid, Jovanna, Pharm.D. OptumRx Staff Present were as follows: Jeffery, Carl, Pharm.D. Whittington, Kevin, R.Ph Medina, Daniel Public attendee list included at attachment A. Note:

		participants may not have chosen to reveal their identity and in the absence of a sign in sheet the accuracy of the attendee list is not assured.
2. General Public Comment	Telephonic and web comment was called for and the phone lines were opened. Comment was made by Ewa Olech, a rheumatologist in Nevada. Informed the board of her attendance in the meeting and offers herself as a resource for questions during the biologicals class for rheumatology. Asked for continued access to biologics for rheumatology on the preferred drug list. Informed the board she will have more comment during the class review. No further public comment was offered.	
3. Administrative		
a. For Possible Action: Review and Approve Meeting Minutes from June 25, 2020.	No corrections were offered. Board Member Khurana moved to approve the minutes as presented. Board Member Adashek seconded the motion. A vote was taken and the results were as follows from members in attendance (in favor, against, and abstentions where applicable): Yes / No / Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Adashek, Joseph, MD ☒ ☐ ☐ Chu, Evelyn, Pharm.D. ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐	

	Passalacqua, Brian, MD ☒ ☐ ☐ Singh, Aditi, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
b. Status Update by DHCFP	Holly Long updated the Board regarding the SUPPORT Act, effective October 1, 2020, which requires State Medicaid Agencies to cover all FDA-approved prescription drugs used for medication assisted treatment through September 2025. As a result, not all drugs will be considered covered outpatient drugs and will no longer be included in the Federal Medicaid Drug Rebate Program. The DHCFP is preparing for the changes and announcements will be posted by October 1, 2020. However, the DHCFP is monitoring Bill HR 8337 that would allow continuation of these drugs as covered outpatient drugs and subject to rebates. Ms. Long continued with an update on the economic strain on the State budget due to COVID-19 resulting in a $1.2 billion shortfall. Governor Sisolak signed Assembly Bill 83 which implemented and required budgetary changes including reductions in rates and the fee schedule for providers by six percent, reduced the reimbursement rate for neonatal intensive care units, eliminated the increase in acute care per diem for hospital reimbursement rates that passed in the 2019 legislative session, revised the rate methodology for habilitation providers, delayed non-capitated payments to managed care organizations until fiscal year 21-22, implemented a specialty pharmacy network. Assembly Bill Three of the 2020 Special Session provided Nevada Medicaid with flexibility to accept additional money not appropriated from the state general fund allowing flexibility critical for the Medicaid program. Three variabilities contribute to the budget, federal funding, caseload changes and utilization patterns. A public hearing was held August 13 regarding the rate reductions. There were no further questions.	
4. Annual Review – Established Drug Classes Being Reviewed		

Due to the Release of New Drugs		
a. For Possible Action: Discussion and possible adoption of Biologic Response Modifiers, Immunomodulators, Targeted Immunomodulators, and Multiple Sclerosis Agents, Oral		
Biologic Response Modifiers, Immunomodulators, Targeted Immunomodulators		
i. Public Comment on proposed drug class.	The following written public comment is attached hereto: 1) Letter dated August 27, 2020 from Yung, Christianne, MD supporting keeping Cimzia Injections preferred. The public comment referenced above was highlighted on the record for members of the Board by Dr. Jeffery. Telephonic and web comment was called for and the phone lines were opened. Comment was made by Ben Droese with Amgen Medical Affairs, indicating support for Otezla remaining preferred. Mr. Droese highlighted Otezla's indications for psoriatic arthritis, moderate to severe plaque psoriasis and a new indication for oral ulcers associated with Behçet's Disease. Mr. Droese detailed the warning and precautions and referred members to the package insert. Mr. Droese continued providing updates to clinical guidelines and studies supporting the safety and efficacy of Otezla. Comment was made by Robert Reemts with UCB, indicating support for Cimzia to remain preferred. Identified Cimzia is the only medication indicated to treat active non-radiographic axial spondyloarthritis and lists	

	the other FDA-approved indications. Mr. Reemts detailed the updated guidelines and updated clinical study information and refers to the package insert with reference to the minimal placenta transfer of Cimzia in pregnant women and in human breast milk. No further public comment was offered.	
ii. Drug class review presentation by OptumRx	Dr. Jeffery highlighted the new biosimilar, Avsola, an FDA approved biosimilar to Remicade. He pointed out the indications for Entyvio, Ilumya, Stelara and Taltz, the medications discussed for changes, have similar indications. Dr. Jeffery displayed the list of medications in the class and recommended the Board consider the class clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Board Member Adashek moved to accept the class as clinically and therapeutically equivalent and Board Member Chu seconded. A vote was held: Yes / No / Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Adashek, Joseph, MD ☒ ☐ ☐ Chu, Evelyn, Pharm.D. ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Passalacqua, Brian, MD ☒ ☐ ☐ Singh, Aditi, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx	Dr. Jeffery outlined the proposed changes to the Immunomodulator class, adding Avsola, Stelara and Taltz as preferred and moving Entyvio, Ilumya, Inflectra and Renflexis to non-preferred.	

v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL	Board Member Ward moved to add Inflectra and Renflexis to preferred and Board Member Adashek seconded. Board Member Ward explained her motion is to keep accessibility to the Medicaid population at all infusion centers. A vote was held: Deputy Attorney General Lither clarified Board Member Adashek's vote was based on clinical information and not based on cost since he was not able to attend the closed-door session where cost was discussed. Board Member Adashek confirmed cost did not impact his decision. Board Member Adashek moved to accept the remaining recommendation as presented and Board Member Ward seconded. A vote was held:	

	Yes	No	Abst.
Decerbo, Mark, Pharm.D. – Chair	☐	☒	☐
Adashek, Joseph, MD	☒	☐	☐
Chu, Evelyn, Pharm.D.	☐	☒	☐
Crumby, Mark, Pharm.D.	☒	☐	☐
Hautekeet, Mike, R.Ph	☐	☒	☐
Khurana, Sapandeep, MD	☒	☐	☐
Passalacqua, Brian, MD	☐	☒	☐
Singh, Aditi, MD	☒	☐	☐
Ward, Kate, Pharm.D.	☒	☐	☐

	Yes	No	Abst.
Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐
Adashek, Joseph, MD	☒	☐	☐
Chu, Evelyn, Pharm.D.	☒	☐	☐
Crumby, Mark, Pharm.D.	☒	☐	☐
Hautekeet, Mike, R.Ph	☒	☐	☐
Khurana, Sapandeep, MD	☒	☐	☐

	Passalacqua, Brian, MD	☒	☐	☐	
	Singh, Aditi, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
Biologic Response Modifiers, Multiple Sclerosis Agents, Oral					
i. Public Comment on proposed drug class.	Telephonic and web comment was called for and the phone lines were opened. Comment was made by Gary Okano with Bristol Myers Squibb offering information on Zeposia. Mr. Okano highlighted the indication, clinical studies demonstrating the efficacy of the medication relative to interferon. Further discussion on trials compared to Gilenya demonstrating efficacy. Mr. Okano described the advantages of Zeposia being once daily and does not have a first-dose observations like others in the class. Requested Zeposia be made preferred for Nevada Medicaid. Comment was made by Melissa Sommers with Novartis offering information on Gilenya. Ms. Sommers pointed out that Gilenya does not require genetic testing and does not require first-dose observation on Mayzent. Comment was by Kaysen Bala with Biogen speaking on behalf of Vumerity. Described the similarities to Tecfidera in efficacy and indication, but with better GI tolerability. Offered some new information on clinical study information, GI tolerability was better in Vumerity compared to Tecfidera resulting in better quality of life score and better long-term adherence. Requested the committee add Vumerity as preferred. No further public comment was offered.				
ii. Drug class review presentation by OptumRx	Dr. Jeffery provided an overview of the new agents in the class, Bafiertam, Dimethyl Fumarate and Zeposia. Dr. Jeffery highlighted that Bafiertam is considered a bioequivalent alternative to dimethyl fumarate, the prodrug of monomethyl fumarate and has fewer GI side effects. Dr. Jeffery also described Dimethyl Fumarate as the approved generic form of Tecfidera. Dr. Jeffery offered information on Zeposia's indication and overview of				

<table>
<tr><td></td><td>clinical studies demonstrating efficacy compared to interferon. Dr. Jeffery recommended the Board consider the class as clinically and therapeutically equivalent.</td><td></td></tr>
<tr><td>iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.</td><td>Board Member Crumby moved to accept the class as clinically and therapeutically equivalent and Board Member Chu seconded. 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>Adashek, Joseph, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Chu, Evelyn, Pharm.D.</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>Passalacqua, Brian, 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. Presentation of recommendations for PDL inclusion by OptumRx</td><td>Dr. Jeffery recommended the Board add the new products Bafiertam, Dimethyl Fumarate and Zeposia as non-preferred and the rest of the class remain the same.</td><td></td></tr>
<tr><td>v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL</td><td>Board Member Adashek moved to approve the preferred drug list as presented and Board Member Passalacqua seconded. 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>Adashek, Joseph, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Chu, Evelyn, Pharm.D.</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>
</table></td><td></td></tr>
</table>

	Passalacqua, Brian, MD	☒	☐	☐	
	Singh, Aditi, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
b. For possible action: Discussion and possible adoption of Cardiovascular Agents, Antihypertensive Agents, Calcium-Channel Blockers					
Cardiovascular Agents, Antihypertensive Agents, Calcium-Channel Blockers					
i. Public Comment on proposed drug class.	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. Jeffery highlighted the new medication in the class, Nymalize as a medication with a unique indication for the improvement of neurological outcomes by reducing the incidence and severity of ischemic deficits in adult patients with subarachnoid hemorrhage from ruptured intracranial berry aneurysms. Dr. Jeffery pointed out this is administered every four hours for 21 consecutive days enterally. Dr. Jeffery recommended the board consider the class clinically and therapeutically equivalent.				
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Board Member Adashek moved to accept the class as clinically and therapeutically equivalent and Board Member Khurana seconded. A vote was held:				
		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
	Adashek, Joseph, MD	☒	☐	☐	
	Chu, Evelyn, Pharm.D.	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	

	Khurana, Sapandeep, MD	☒	☐	☐	
	Passalacqua, Brian, MD	☒	☐	☐	
	Singh, Aditi, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx	Dr. Jeffery recommended moving generic amlodipine/benazepril and amlodipine/valsartan to preferred and amlodipine/valsartan/HCT, Exforge, Exforge HCT, isradipine, Lotrel, nisoldipine ER and Nymalize to non-preferred.				
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL	Chairman Decerbo moved to make amlodipine/benazepril/HCT preferred and Board Member Crumby seconded. Chairman Decerbo explained his reasoning being to help reduce pill burden for Nevada Medicaid recipients. A vote was held:				
		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
	Adashek, Joseph, MD	☒	☐	☐	
	Chu, Evelyn, Pharm.D.	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Passalacqua, Brian, MD	☒	☐	☐	
	Singh, Aditi, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
	Board Member Ward moved to approve the preferred drug list as presented with the one change and Board Member Crumby seconded. A vote was held:				
		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
	Adashek, Joseph, MD	☒	☐	☐	

	Chu, Evelyn, Pharm.D.	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Passalacqua, Brian, MD	☒	☐	☐	
	Singh, Aditi, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
c. For Possible Action: Discussion and possible adoption of Dermatological Agents, Topical Anti-infectives, Acne Agents: Topical, Benzoyl Peroxide, Antibiotics and Combination Products					
Dermatological Agents, Topical Anti-infectives, Acne Agents: Topical, Benzoyl Peroxide, Antibiotics and Combination Products					
i. Public Comment on proposed drug class.	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. Jeffery provided information on Amzeeq Foam, a topical minocycline indicated to treat inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients nine years of age and older. Clinical trials were highlighted demonstrated superiority over vehicle alone. Dr. Jeffery recommended the board consider the class clinically and therapeutically equivalent.				
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Board Member Adashek moved to accept the class as clinically and therapeutically equivalent and Board Member Crumby seconded. A vote was held:				
		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	

	Adashek, Joseph, MD	☒	☐	☐	
	Chu, Evelyn, Pharm.D.	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Passalacqua, Brian, MD	☒	☐	☐	
	Singh, Aditi, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx	Dr. Jeffery recommend the board make Aczone Gel and erythromycin/benzoyl peroxide as preferred and Amzeeq Foam, Benzaclin, Dapsone Gel and Onexton Gel non-preferred.				
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL	Board Member Adashek moved to approve the preferred drug list as presented and Board Member Crumby seconded. A vote was held:				
		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
	Adashek, Joseph, MD	☒	☐	☐	
	Chu, Evelyn, Pharm.D.	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Passalacqua, Brian, MD	☒	☐	☐	
	Singh, Aditi, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
d. For Possible Action: Discussion and possible adoption of Gastrointestinal Agents, Functional Gastrointestinal Disorder Drugs					

Gastrointestinal Agents, Functional Gastrointestinal Disorder Drugs		
i. Public Comment on proposed drug class.	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. Jeffery detailed Motegrity including the indication for the treatment of chronic idiopathic constipation and discussed the six trials demonstrating improvement compared to placebo. Dr. Jeffery also described the information for Zelnorm including the indication for the treatment of adult women less than 65 years of age with irritable bowel syndrome with constipation. Clinical trials where highlighted demonstrating improvement compared to placebo. Dr. Jeffery recommended the board consider the class clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Board Member Adashek moved to accept the class as clinically and therapeutically equivalent and Board Member Crumby seconded. A vote was held: Yes / No / Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Adashek, Joseph, MD ☒ ☐ ☐ Chu, Evelyn, Pharm.D. ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Passalacqua, Brian, MD ☒ ☐ ☐ Singh, Aditi, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx	Dr. Jeffery recommended the board add Motegrity and Zelnorm as non-preferred and the rest of the class remain the same.	

<table>
<tr><td>v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL</td><td>Board Member Adashek moved to approve the preferred drug list as presented and Board Member Chu seconded. 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>Adashek, Joseph, MD</td><td>☒</td><td>☐</td><td>☐</td></tr><tr><td>Chu, Evelyn, Pharm.D.</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>Passalacqua, Brian, 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>e. For Possible Action: Discussion and possible adoption of Hormones and Hormone Modifiers, Antidiabetic Agents, Insulins (Vials, Pens and Inhaled)</td><td></td><td></td></tr>
<tr><td colspan="3">Hormones and Hormone Modifiers, Antidiabetic Agents, Insulins (Vials, Pens and Inhaled)</td></tr>
<tr><td>i. Public Comment on proposed drug class.</td><td>Telephonic and web comment was called for and the phone lines were opened.

No public comment was offered.</td><td></td></tr>
<tr><td>ii. Drug class review presentation by OptumRx</td><td>Dr. Jeffery provided information on the new Insulin Lispro Mix product that is similar to Humalog Mix, but not rated as interchangeable. Dr. Jeffery also discussed Lyumjev, a rapid-acting insulin analog indicated to improve glycemic control in adults with diabetes mellitus. Two clinical trials were described demonstrating Lyumjev is non-inferior to Humalog. Dr. Jeffery recommended the board consider the class clinically and therapeutically equivalent.</td><td></td></tr>
</table>

<table>
<tr>
<td>iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.</td>
<td>Board Member Adashek moved to accept the class as clinically and therapeutically equivalent and Board Member Crumby seconded. 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>Adashek, Joseph, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Chu, Evelyn, Pharm.D.</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>Passalacqua, Brian, 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. Presentation of recommendations for PDL inclusion by OptumRx</td>
<td>Dr. Jeffery recommended the board add insulin lispro mix and Lyumjev as non-preferred and keep the rest of the class the same.</td>
<td></td>
</tr>
<tr>
<td>v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL</td>
<td>Board Member Ward moved to approve the preferred drug list as presented and Board Member Passalacqua seconded. 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>Adashek, Joseph, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Chu, Evelyn, Pharm.D.</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>Passalacqua, Brian, 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>
</table>

f. For Possible Action: Discussion and possible adoption of Neurological Agents, Anticonvulsants, and Benzodiazepines		
Neurological Agents, Anticonvulsants		
i. Public Comment on proposed drug class.	The following written public comment is attached hereto: 1) Letter dated September 1, 2020 from Chez, Michael, MD of Sutter Medical Group Epilepsy Program. 2) An undated letter from Rodriguez-Gomez, Gerardo, MD of UNR School of Medicine, Pediatric Neurology. 3) Letter dated September 2, 2020 from Ait-Ouyahia, Yasin, Pharm.D. of Neurelis Medical Information. 4) Letter dated September 21, 2020 from Marano, Danielle of Epilepsy Foundation Nevada. 5) Letter dated September 20, 2020 from Bangalor, Samir, MD of Epilepsy Center at Sunrise Hospital 6) Letter dated September 22, 2020 from Gardner, Rachael, FNP The public comment referenced above was highlighted on the record for members of the Board by Dr. Jeffery Telephonic and web comment was called for and the phone lines were opened. Comment was made by Derek Ems with UCB Pharmaceuticals providing information for Briviact. They described the current situation with an unmet need for treatment despite having multiple products available describing the indication for Briviact. Mr. Ems described the clinical trials demonstrating efficacy compared to placebo and described the dosing. Mr. Ems asked the board to ensure access to Briviact by keeping it preferred.	

	Comment was made by Stephanie Kennedy with Greenwich Biosciences speaking on behalf of Epidiolex. Ms. Kennedy reviewed the indication and dosage of Epidiolex, and stated Epidiolex is no longer scheduled under the Controlled Substances Act. Trials demonstrating efficacy compared to placebo were presented with adverse effects and asks for the clinical criteria to be updated to reflect new guidelines and indications. Comment was made by Danielle Marano with The Epilepsy Foundation of Nevada. Shared information on epilepsy where some patients do very well with minimal intervention and then others that require ongoing attention. Emphasized the importance for patients and families to have open access and avoid formulary changes and step therapies that could delay treatment. Asked the board to continue to keep open access to all medications. No further public comment was offered.	
ii. Drug class review presentation by OptumRx	Dr. Jeffery provided an overview of Xcopri, indicated for the treatment of partial-onset seizures in adult patients and covers the two studies demonstrating superiority to placebo in both trials. Dr. Jeffery recommended the board consider the class clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Board Member Crumby moved to accept the class as clinically and therapeutically equivalent and Board Member Adashek seconded. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Adashek, Joseph, MD: Yes ☒ No ☐ Abst. ☐ Chu, Evelyn, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Passalacqua, Brian, MD: Yes ☒ No ☐ Abst. ☐	

	Singh, Aditi, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx	Dr. Jeffery recommended adding Qudexy XR as preferred and adding topiramate ER, Vigabatrin and Xcopri as non-preferred.	
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL	Board Member Chu moved to approve the preferred drug list as presented and Board Member Crumby seconded. A vote was held: Yes / No / Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Adashek, Joseph, MD ☒ ☐ ☐ Chu, Evelyn, Pharm.D. ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Passalacqua, Brian, MD ☒ ☐ ☐ Singh, Aditi, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
Neurological Agents, Anticonvulsants, Benzodiazepines		
i. Public Comment on proposed drug class.	Telephonic and web comment was called for and the phone lines were opened. Comment was made by Derek Ems with UCB Pharmaceuticals speaking for Nayzilam. Mr. Ems describes seizure clusters and the unmet need for rescue therapy and demographics of incidence. He described therapy available prior to Nayzilam and the low utilization of rescue treatments resulting in high medical costs and reduced quality of live. He described the indication, the clinical trials demonstrating Nayzilam is superior to placebo. Asked the board to continue access to Nayzilam for patients with epilepsy.	

	Comment was made by Deborah Sheppe with Neurelis in support of Valtoco. Described the indication and efficacy studies demonstrating clinical superiority to placebo, pharmacokinetics, safety and adverse effects. She summarized the use of Valtoco with patients with epilepsy by making it easier to administer and keeps patients out of the hospitals and emergency rooms. Asked the board to keep Valtoco available on the preferred drug list. No further public comment was offered.	
ii. Drug class review presentation by OptumRx	Dr. Jeffery provided details of Valtoco nasal spray including the indication of acute treatment of intermittent, stereotypic episodes of frequent seizure activity (i.e., seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy 6 years of age and older. Dr. Jeffery described the studies demonstrating it is bioavailable to diazepam rectal gel. Dr. Jeffery recommended the board consider the class clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Board Member Crumby moved to accept the class as clinically and therapeutically equivalent and Board Member Adashek seconded. A vote was held: Yes / No / Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Adashek, Joseph, MD ☒ ☐ ☐ Chu, Evelyn, Pharm.D. ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Passalacqua, Brian, MD ☒ ☐ ☐ Singh, Aditi, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
iv. Presentation of recommendations for	Dr. Jeffery recommended the board add Diastat and Valtoco Spray as preferred and diazepam rectal soln as non-preferred.	

PDL inclusion by OptumRx		
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL	Board Member Khurana moved to approve the preferred drug list as presented and Board Member Chu seconded. A vote was held: Yes / No / Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Adashek, Joseph, MD ☒ ☐ ☐ Chu, Evelyn, Pharm.D. ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Passalacqua, Brian, MD ☒ ☐ ☐ Singh, Aditi, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
g. For Possible Action: Discussion and possible adoption of Ophthalmic Agents, Ophthalmic Anti-inflammatory Agents, Ophthalmic Corticosteroids		
Ophthalmic Agents, Ophthalmic Anti-inflammatory Agents, Ophthalmic Corticosteroids		
i. Public Comment on proposed drug class.	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. Jeffery provided details for Inveltys, indicated for the treatment of post-operative inflammation and pain following ocular surgery. Two studies demonstrate Inveltys is superior to placebo. Dr. Jeffery recommended the board consider the class clinically and therapeutically equivalent.	

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<tr>
<td>iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.</td>
<td>Board Member Crumby moved to accept the class as clinically and therapeutically equivalent and Board Member Adashek seconded. 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>Adashek, Joseph, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Chu, Evelyn, Pharm.D.</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>Passalacqua, Brian, 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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</tr>
<tr>
<td>iv. Presentation of recommendations for PDL inclusion by OptumRx</td>
<td>Dr. Jeffery recommended the board add Flarex, FML Forte, FML and Pred Forte as preferred and dexamethasone, fluorometholone, Inveltys, Lotemax, loteprednol and prednisolone as non-preferred.</td>
<td></td>
</tr>
<tr>
<td>v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL</td>
<td>Chairman Decerbo moved to add Maxidex as preferred and Board Member Crumby seconded. Chairman Decerbo offered an explanation that adding a dexamethasone product. Board Member Adashek abstained from the vote due to not attending the closed session. 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>Adashek, Joseph, MD</td><td>☐</td><td>☐</td><td>☒</td></tr>
<tr><td>Chu, Evelyn, Pharm.D.</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>Passalacqua, Brian, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Singh, Aditi, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
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<td></td>
</tr>
</table>

	Ward, Kate, Pharm.D. ☒ ☐ ☐ Board Member Chu moved to approve the preferred drug list as presented with the one change and Board Member Khurana seconded. A vote was held: Yes No Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Adashek, Joseph, MD ☐ ☐ ☒ Chu, Evelyn, Pharm.D. ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Passalacqua, Brian, MD ☒ ☐ ☐ Singh, Aditi, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
h. For Possible Action: Discussion and possible adoption of Respiratory Agents, Long-acting/Maintenance Therapy		
Respiratory Agents, Long-acting/Maintenance Therapy		
i. Public Comment on proposed drug class.	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. Jeffery highlighted the new product in the class, Duaklir Pressair, indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD) and the four trials demonstrating it was safe and effective compared to placebo. Dr. Jeffery also provided	

<table>
<tr><td></td><td>information on Yupelri, an inhaled anticholinergic indicated for the maintenance treatment of patients with COPD and the two trials demonstrating improvement in lung function. Dr. Jeffery recommended the board consider the class clinically and therapeutically equivalent</td><td></td></tr>
<tr><td>iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.</td><td>Board Member Crumby moved to accept the class as clinically and therapeutically equivalent and Board Member Hautekeet seconded. 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>Adashek, Joseph, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Chu, Evelyn, Pharm.D.</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>Passalacqua, Brian, 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. Presentation of recommendations for PDL inclusion by OptumRx</td><td>Dr. Jeffery recommended the board add Advair Diskus, Breo Ellipta, Incruse Ellipta, Qvar Redihaler and Spiriva Respimat as preferred and budesonide/formoterol, Duaklir Pressair, fluticasone propionate/salmeterol powder and Yupelri as non-preferred.</td><td></td></tr>
<tr><td>v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL</td><td>Board Member Adashek moved to approve the preferred drug list as presented and Board Member Crumby seconded. 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>Adashek, Joseph, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Chu, Evelyn, Pharm.D.</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>
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</table>

	Khurana, Sapandeep, MD	☒	☐	☐	
	Passalacqua, Brian, MD	☒	☐	☐	
	Singh, Aditi, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
5. Annual Review - Established Drug Classes Being Reviewed Due to the Release of New Generics					
a. For Possible Action: Discussion and possible adoption of Anti-infective Agents, Cephalosporins, Third-Generation Cephalosporins					
Anti-infective Agents, Cephalosporins, Third-Generation Cephalosporins					
i. Public Comment on proposed drug class.	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. Jeffery pointed out the new product cefixime is generic for Suprax. Dr. Jeffery recommended the board consider the class clinically and therapeutically equivalent.				
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Board Member Crumby moved to accept the class as clinically and therapeutically equivalent and Board Member Adashek seconded. A vote was held: Yes / No / Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Adashek, Joseph, MD ☒ ☐ ☐ Chu, Evelyn, Pharm.D. ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐				

	Khurana, Sapandeep, MD	☒	☐	☐	
	Passalacqua, Brian, MD	☒	☐	☐	
	Singh, Aditi, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx	Dr. Jeffery recommended the board add the new generic cefixime as non-preferred and keep the rest of the class the same.				
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL	Board Member Chu moved to approve the preferred drug list as presented and Board Member Passalacqua seconded. A vote was held:				
		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
	Adashek, Joseph, MD	☒	☐	☐	
	Chu, Evelyn, Pharm.D.	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Passalacqua, Brian, MD	☒	☐	☐	
	Singh, Aditi, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
b. For Possible Action: Discussion and possible adoption of Cardiovascular Agents, Antihypertensive Agents, Vasodilators, Oral					
Cardiovascular Agents, Antihypertensive Agents, Vasodilators, Oral					
i. Public Comment on proposed drug class.	Telephonic and web comment was called for and the phone lines were opened. No public comment was offered.				

<table>
<tr><td>ii. Drug class review presentation by OptumRx</td><td>Dr. Jeffery highlighted the new generic bosentan, which is generic for Tracleer. Dr. Jeffery recommended the board consider the class clinically and therapeutically equivalent.</td><td></td></tr>
<tr><td>iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.</td><td>Board Member Crumby moved to accept the class as clinically and therapeutically equivalent and Board Member Chu seconded. 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>Adashek, Joseph, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Chu, Evelyn, Pharm.D.</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>Passalacqua, Brian, 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. Presentation of recommendations for PDL inclusion by OptumRx</td><td>Dr. Jeffery recommended the board add bosentan, Revatio as preferred and sildenafil and Tracleer as non-preferred and keep the rest of the class the same.</td><td></td></tr>
<tr><td>v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL</td><td>Board Member Adashek moved to approve the preferred drug list as presented and Board Member Chu seconded. 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>Adashek, Joseph, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Chu, Evelyn, Pharm.D.</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>
</table></td><td></td></tr>
</table>

	Passalacqua, Brian, MD	☒	☐	☐	
	Singh, Aditi, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
c. For Possible Action: Discussion and possible adoption of Dermatological Agents, Topical Anti-infectives, Topical Antivirals					
Dermatological Agents, Topical Anti-infectives, Topical Antivirals					
i. Public Comment on proposed drug class.	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. Jeffery provided information on the generic acyclovir cream available for Zovirax cream. Recommended the board consider the class clinically and therapeutically equivalent.				
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Board Member Adashek moved to accept the class as clinically and therapeutically equivalent and Board Member Crumby seconded. A vote was held:				
		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
	Adashek, Joseph, MD	☒	☐	☐	
	Chu, Evelyn, Pharm.D.	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Passalacqua, Brian, MD	☒	☐	☐	
	Singh, Aditi, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
iv. Presentation of recommendations for	Dr. Jeffery recommended Zovirax Cream added as preferred and acyclovir cream added as non-preferred and the rest of the class remain the same.				

PDL inclusion by OptumRx		
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL	Board Member Crumby moved to approve the preferred drug list as presented and Board Member Passalacqua seconded. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Adashek, Joseph, MD: Yes ☒ No ☐ Abst. ☐ Chu, Evelyn, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Passalacqua, Brian, 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 Electrolytic and Renal Agents, Phosphate Binding Agents		
Electrolytic and Renal Agents, Phosphate Binding Agents		
i. Public Comment on proposed drug class.	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. Jeffery discussed the generic availability for Fosrenol, and recommended the board consider the class clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to approve clinical/therapeutic	Board Member Crumby moved to accept the class as clinically and therapeutically equivalent and Board Member Adashek seconded. A vote was held:	

equivalency of agents in class.		Yes No Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Adashek, Joseph, MD ☒ ☐ ☐ Chu, Evelyn, Pharm.D. ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Passalacqua, Brian, MD ☒ ☐ ☐ Singh, Aditi, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx	Dr. Jeffery recommended the board add calcium acetate tab and Phoslyra as preferred and lanthanum carbonate and sevelamer HCl as non-preferred and keep the rest of the class the same.	
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL	Board Member Adashek moved to approve the preferred drug list as presented and Board Member Chu seconded. A vote was held: Yes No Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Adashek, Joseph, MD ☒ ☐ ☐ Chu, Evelyn, Pharm.D. ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Passalacqua, Brian, MD ☒ ☐ ☐ Singh, Aditi, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
e. For Possible Action: Discussion and possible adoption of Genitourinary Agents, Benign Prostatic		

Hyperplasia (BPH) Agents, Alpha-Blockers and Bladder Antispasmodics		
Genitourinary Agents, Benign Prostatic Hyperplasia (BPH) Agents, Alpha-Blockers		
i. Public Comment on proposed drug class.	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. Jeffery highlighted the two new generics, silodosin for Rapaflo and alfuzosin for Uroxatral and recommended the board consider the class clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Board Member Adashek moved to accept the class as clinically and therapeutically equivalent and Board Member Crumby seconded. A vote was held: Decerbo, Mark, Pharm.D. – Chair: ☒ Yes ☐ No ☐ Abst. Adashek, Joseph, MD: ☒ Yes ☐ No ☐ Abst. Chu, Evelyn, Pharm.D.: ☒ Yes ☐ No ☐ Abst. Crumby, Mark, Pharm.D.: ☒ Yes ☐ No ☐ Abst. Hautekeet, Mike, R.Ph: ☒ Yes ☐ No ☐ Abst. Khurana, Sapandeep, MD: ☒ Yes ☐ No ☐ Abst. Passalacqua, Brian, 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. Jeffery recommended the board add alfuzosin as preferred and silodosin as non-preferred and keep the rest of the class the same.	Dr. Adashek left the meeting.
v. Discussion by Board and action by Board for	Board Member Crumby moved to approve the preferred drug list as presented and Board Member Hautekeet seconded. A vote was held:	

	approval of drugs for inclusion on the PDL		Yes	No	Abst.
		Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐
		Chu, Evelyn, Pharm.D.	☒	☐	☐
		Crumby, Mark, Pharm.D.	☒	☐	☐
		Hautekeet, Mike, R.Ph	☒	☐	☐
		Khurana, Sapandeep, MD	☒	☐	☐
		Passalacqua, Brian, MD	☒	☐	☐
		Singh, Aditi, MD	☒	☐	☐
		Ward, Kate, Pharm.D.	☒	☐	☐
Genitourinary Agents, Bladder Antispasmodics					
i.	Public Comment on proposed drug class.	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. Jeffery highlighted the new generics darifenacin for Enablex and solifenacin for Vesicare and recommended the board consider the class clinically and therapeutically equivalent.			
iii.	Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Board Member Crumby moved to accept the class as clinically and therapeutically equivalent and Chairman Decerbo seconded. A vote was held:			
			Yes	No	Abst.
		Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐
		Chu, Evelyn, Pharm.D.	☒	☐	☐
		Crumby, Mark, Pharm.D.	☒	☐	☐
		Hautekeet, Mike, R.Ph	☒	☐	☐
		Khurana, Sapandeep, MD	☒	☐	☐
		Passalacqua, Brian, MD	☒	☐	☐
		Singh, Aditi, MD	☒	☐	☐
		Ward, Kate, Pharm.D.	☒	☐	☐

iv. Presentation of recommendations for PDL inclusion by OptumRx	Dr. Jeffery recommended the board add solifenacin as preferred and darifenacin and Vesicare as non-preferred and keep the rest of the class the same.	
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL	Board Member Crumby moved to approve the preferred drug list as presented and Board Member Hautekeet seconded. A vote was held: Yes / No / Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Chu, Evelyn, Pharm.D. ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Passalacqua, Brian, MD ☒ ☐ ☐ Singh, Aditi, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
f. For Possible Action: Discussion and possible adoption of Musculoskeletal Agents, Antigout Agents		
Musculoskeletal Agents, Antigout Agents		
i. Public Comment on proposed drug class.	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. Jeffery pointed out a new generic is available for Uloric and recommended the board consider the class clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to approve	Board Member Crumby moved to accept the class as clinically and therapeutically equivalent and Board Member Passalacqua seconded. A vote was held:	

clinical/therapeutic equivalency of agents in class.		
iv. Presentation of recommendations for PDL inclusion by OptumRx	Dr. Jeffery recommended the board add Colcrys tabs as preferred and colchicine tab and cap and febuxostat as non-preferred.	
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL	Chairman Decerbo moved to approve the preferred drug list as presented and Board Member Hautekeet seconded. A vote was held:	
g. For Possible Action: Discussion and possible adoption of Ophthalmic Agents, Ophthalmic Anti-		

	Yes	No	Abst.
Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐
Chu, Evelyn, Pharm.D.	☒	☐	☐
Crumby, Mark, Pharm.D.	☒	☐	☐
Hautekeet, Mike, R.Ph	☒	☐	☐
Khurana, Sapandeep, MD	☒	☐	☐
Passalacqua, Brian, MD	☒	☐	☐
Singh, Aditi, MD	☒	☐	☐
Ward, Kate, Pharm.D.	☒	☐	☐

	Yes	No	Abst.
Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐
Chu, Evelyn, Pharm.D.	☒	☐	☐
Crumby, Mark, Pharm.D.	☒	☐	☐
Hautekeet, Mike, R.Ph	☒	☐	☐
Khurana, Sapandeep, MD	☒	☐	☐
Passalacqua, Brian, MD	☒	☐	☐
Singh, Aditi, MD	☒	☐	☐
Ward, Kate, Pharm.D.	☒	☐	☐

infectives, Ophthalmic Quinolones		
Ophthalmic Agents, Ophthalmic Anti-infectives, Ophthalmic Quinolones		
i. Public Comment on proposed drug class.	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. Jeffery pointed out a new generic gatifloxacin is available for Zymaxid and recommended the board consider the class clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Board Member Khurana moved to accept the class as clinically and therapeutically equivalent and Board Member Hautekeet seconded. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Chu, Evelyn, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Passalacqua, Brian, 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. Jeffery recommended the board add Zymaxid as preferred and gatifloxacin, levofloxacin, Moxeza and Vigamox as non-preferred and the rest of the class remain the same.	
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL	Chairman Decerbo moved to make Vigamox preferred and Board Member Hautekeet seconded. Chairman Decerbo described his reasoning being convenience of dosing and to keep a form of moxifloxacin as preferred. A vote was held:	

		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
	Chu, Evelyn, Pharm.D.	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Passalacqua, Brian, MD	☒	☐	☐	
	Singh, Aditi, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
	Board Member Hautekeet moved to approve the preferred drug list as presented with the change and Board Member Chu seconded. A vote was held:				
		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
	Chu, Evelyn, Pharm.D.	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Passalacqua, Brian, MD	☒	☐	☐	
	Singh, Aditi, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
6. Annual Review – Established Drug Classes					
a. For Possible Action: Discussion and possible adoption of Antihistamines, H1 blockers, Non-Sedating H1 Blockers					
Antihistamines, H1 blockers, Non-Sedating H1 Blockers					

<table>
<tr><td>i. Public Comment on proposed drug class.</td><td>Telephonic and web comment was called for and the phone lines were opened.

No public comment was offered.</td><td></td></tr>
<tr><td>ii. Drug class review presentation by OptumRx</td><td>Dr. Jeffery discussed the new generic levocetirizine for Xyzal and recommended the board consider the class clinically and therapeutically equivalent.</td><td></td></tr>
<tr><td>iii. 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 and Board Member Hautekeet seconded. 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>Chu, Evelyn, Pharm.D.</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>Passalacqua, Brian, 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. Presentation of recommendations for PDL inclusion by OptumRx</td><td>Dr. Jeffery recommended the board add Levocetirizine as preferred and add cetirizine D OTC as non-preferred and keep the rest of the class the same.</td><td></td></tr>
<tr><td>v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL</td><td>Board Member Khurana moved to approve the preferred drug list as presented and Board Member Crumby seconded. 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>Chu, Evelyn, Pharm.D.</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>
</table></td><td></td></tr>
</table>

	Khurana, Sapandeep, MD	☒	☐	☐	
	Passalacqua, Brian, MD	☒	☐	☐	
	Singh, Aditi, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
b. For Possible Action: Discussion and possible adoption of Cardiovascular Agents, Antilipemics, Cholesterol Absorption Inhibitors, and HMG-CoA Reductase Inhibitors (Statins)					
Cardiovascular Agents, Antilipemics, Cholesterol Absorption Inhibitors					
i. Public Comment on proposed drug class.	Telephonic and web comment was called for and the phone lines were opened. Comment was made by Ben Droese with Amgen providing information on Repatha. Mr. Droese highlighted indications, warning and precautions and discussed the updated guidelines based on new clinical trial information which demonstrated event and LDL reduction with Repatha compared to other products. No further public comment was offered.				
ii. Drug class review presentation by OptumRx	Dr. Jeffery highlighted the one product in the class Zetia and its generic ezetimibe and recommended the board consider the class clinically and therapeutically equivalent.				
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Board Member Crumby moved to accept the class as clinically and therapeutically equivalent and Board Member Chu seconded. A vote was held:				
		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
	Chu, Evelyn, Pharm.D.	☒	☐	☐	

	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Passalacqua, Brian, MD	☒	☐	☐	
	Singh, Aditi, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx	Dr. Jeffery recommended the board move the generic ezetimibe to preferred and the brand Zetia to non-preferred.				
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL	Chairman Decerbo moved to approve the preferred drug list as presented and Board Member Chu seconded. A vote was held:				
		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
	Chu, Evelyn, Pharm.D.	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Passalacqua, Brian, MD	☒	☐	☐	
	Singh, Aditi, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
Cardiovascular Agents, Antilipemics, HMG-CoA Reductase Inhibitors (Statins)					
i. Public Comment on proposed drug class.	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. Jeffery mentioned the list of products and their respective generics with nothing new added to the class recently and recommended the board consider the class clinically and therapeutically equivalent.				

<table>
<tr>
<td>iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.</td>
<td>Board Member Crumby moved to accept the class as clinically and therapeutically equivalent and Board Member Chu seconded. 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>Chu, Evelyn, Pharm.D.</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>Passalacqua, Brian, 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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<td></td>
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<tr>
<td>iv. Presentation of recommendations for PDL inclusion by OptumRx</td>
<td>Dr. Jeffery recommended the board add rosuvastatin and Vytorin to preferred and Crestor to non-preferred.</td>
<td></td>
</tr>
<tr>
<td>v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL</td>
<td>Board Member Hautekeet moved to approve the preferred drug list as presented and Board Member Crumby seconded. 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>Chu, Evelyn, Pharm.D.</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>Passalacqua, Brian, 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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<td></td>
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<tr>
<td>c. For Possible Action: Discussion and possible</td>
<td></td>
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adoption of Dermatological Agents, Topical Antineoplastics, Topical Retinoids		
Dermatological Agents, Topical Antineoplastics, Topical Retinoids		
i. Public Comment on proposed drug class.	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. Jeffery referenced the breakdown of the different products within the class, pointing out the single entity topical retinoids and the combination topical retinoids. Recommended the board consider the class clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Board Member Crumby moved to accept the class as clinically and therapeutically equivalent and Board Member Hautekeet seconded. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Chu, Evelyn, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Passalacqua, Brian, 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. Jeffery recommended the board make Differin and Retin-A as preferred and adapalene/benzoyl peroxide, Retin-A micro and tazarotene as non-preferred and the rest of the class remain the same.	
v. Discussion by Board and action by Board for	Board Member Hautekeet moved to approve the preferred drug list as presented and Board Member Crumby seconded. A vote was held:	

approval of drugs for inclusion on the PDL	<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>Chu, Evelyn, Pharm.D.</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>Passalacqua, Brian, 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>	
d. For Possible Action: Discussion and possible adoption of Gastrointestinal Agents, Antiemetics, Pregnancy-induced Nausea and Vomiting Treatment, and Gastrointestinal Anti-inflammatory Agents		
Gastrointestinal Agents, Antiemetics, Pregnancy-induced Nausea and Vomiting Treatment		
i. Public Comment on proposed drug class.	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. Jeffery reminded the board that OTC doxylamine and pyridoxine is listed on the preferred drug list to encourage that option for providers, but it is not included in the normal class list. Dr. Jeffery recommended the board consider the class clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to approve clinical/therapeutic	Board Member Crumby moved to accept the class as clinically and therapeutically equivalent and Board Member Hautekeet seconded. A vote was held:	

	equivalency of agents in class.	Yes No Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Chu, Evelyn, Pharm.D. ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Passalacqua, Brian, MD ☒ ☐ ☐ Singh, Aditi, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
iv.	Presentation of recommendations for PDL inclusion by OptumRx	Dr. Jeffery recommended making Bonjesta preferred and Diclegis non-preferred.	
v.	Discussion by Board and action by Board for approval of drugs for inclusion on the PDL	Board Member Khurana asked if it would be possible to defer the vote to the next meeting so Board Member Adashek would be able to participate. Chairman Decerbo suggested taking the class out of order and readdress at the end of the meeting. The class review was moved to the end of the meeting. Board Member Ward asked if the difference between Diclegis and Bonjesta was discussed, because the difference is minimal. Dr. Jeffery explained the medications are the same ingredients, Bonjesta is dosed once per day and Diclegis is dosed twice per day Board Member Ward moved to approve the preferred drug list as presented and Board Member Passalacqua seconded. A vote was held: Yes No Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Chu, Evelyn, Pharm.D. ☒ ☐ ☐	Taken out of order, discussed at the end of the meeting.

	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☐	☒	☐	
	Passalacqua, Brian, MD	☒	☐	☐	
	Singh, Aditi, MD	☐	☐	☒	
	Ward, Kate, Pharm.D.	☒	☐	☐	
Gastrointestinal Agents, Gastrointestinal Anti-inflammatory Agents					
i. Public Comment on proposed drug class.	Telephonic and comment was called for and the phone lines were opened. No public comment was offered.				
ii. Drug class review presentation by OptumRx	Dr. Jeffery discussed the products available in the class and their respective generics adding that nothing new has been added to the class since the last review and recommended the board consider this 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 and Board Member Khurana seconded. A vote was held:				
		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
	Chu, Evelyn, Pharm.D.	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Passalacqua, Brian, MD	☒	☐	☐	
	Singh, Aditi, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx	Dr. Jeffery recommended the board add Colazal and Delzicol as preferred and Asacol HD, mesalamine (generic Apriso), mesalamine (generic Delzicol) and mesalamine suppository be added as non-preferred.				

v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL	Board Member Khurana moved to approve the preferred drug list as presented and Board Member Hautekeet seconded. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Chu, Evelyn, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Crumby, Mark, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Hautekeet, Mike, R.Ph: Yes ☒ No ☐ Abst. ☐ Khurana, Sapandeep, MD: Yes ☒ No ☐ Abst. ☐ Passalacqua, Brian, MD: Yes ☒ No ☐ Abst. ☐ Singh, Aditi, MD: Yes ☒ No ☐ Abst. ☐ Ward, Kate, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
e. For Possible Action: Discussion and possible adoption of Hematological Agents, Platelet Inhibitors		
Hematological Agents, Platelet Inhibitors		
i. Public Comment on proposed drug class.	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. Jeffery informed the board that no new medications have been added and the brand and generics available remain the same since the last review. Dr. Jeffery recommended the board consider the class clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Board Member Khurana moved to accept the class as clinically and therapeutically equivalent and Board Member Hautekeet seconded. A vote was held: Decerbo, Mark, Pharm.D. – Chair: Yes ☒ No ☐ Abst. ☐ Chu, Evelyn, Pharm.D.: Yes ☒ No ☐ Abst. ☐	

	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Passalacqua, Brian, MD	☒	☐	☐	
	Singh, Aditi, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx	Dr. Jeffery recommended the board add prasugrel as preferred and anagrelide as non-preferred and the rest of the class the same.				
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL	Chairman Decerbo moved to approve the preferred drug list as presented and Board Member Chu seconded. A vote was held:				
		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
	Chu, Evelyn, Pharm.D.	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Passalacqua, Brian, MD	☒	☐	☐	
	Singh, Aditi, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
f. For Possible Action: Discussion and possible adoption of Hormones and Hormone Modifiers, Antidiabetic Agents, Incretin Mimetics; Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors					Board Member Singh left the meeting. A quorum is still present.
Hormones and Hormone Modifiers, Antidiabetic Agents, Incretin Mimetics					

<table>
<tr><td>i. Public Comment on proposed drug class.</td><td>Telephonic and web comment was called for and the phone lines were opened.

No public comment was offered.</td><td></td></tr>
<tr><td>ii. Drug class review presentation by OptumRx</td><td>Dr. Jeffery discussed this established class with new literature demonstrating cardiovascular benefits for Ozempic and Trulicity. Dr. Jeffery mentioned the Byetta Pen is being discontinued by the manufacturer and recommended the board consider the class clinically and therapeutically equivalent.</td><td></td></tr>
<tr><td>iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.</td><td>Board Member Khurana moved to accept the class as clinically and therapeutically equivalent and Board Member Hautekeet seconded. 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>Chu, Evelyn, Pharm.D.</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>Passalacqua, Brian, 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. Presentation of recommendations for PDL inclusion by OptumRx</td><td>Dr. Jeffery recommended the board move Trulicity to non-preferred and keep the rest of the class the same.</td><td></td></tr>
<tr><td>v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL</td><td>Chairman Decerbo offered his insight into the different medications and the level of literature available for each and Trulicity being the market leader by volume.

Board Member Ward stated route of administration should also be considered with the oral Rybelsus.</td><td></td></tr>
</table>

	Chairman Decerbo further explained the proposed list would essentially lead patients to Victoza, but Ozempic has superior head-to-head clinical data vs. Trulicity. Board Member Chu asked if Trulicity is the only medication with cardio-protective properties? Dr. Jeffery replied that Ozempic and Victoza also have that indication for cardio-protective properties. Board Member Hautekeet offered personal experience with Trulicity and Victoza and Trulicity worked better for him and would not like to see Trulicity removed from the preferred list. Chairman Decerbo summarized the discussion that the board is suggesting at least two weekly-dosed products, and discussed tabling the vote until the next meeting to give board members more time to research. Dr. Jeffery explained the option to grandfather members who are currently on a preferred product if it moves to non-preferred. Ms. Long encouraged the board to discuss and vote on the class during the meeting rather than tabling to the next meeting. Board Member Passalacqua moved to keep Trulicity as preferred and Board Member Hautekeet seconded. Board Member Ward offered her thoughts that Trulicity use is high because it is preferred and moving it to non-preferred may jeopardize the care for diabetics. Chairman Decerbo described the difference between Ozempic and Trulicity with Ozempic having better A1c control and more weight loss.	

A vote was held to add Trulicity as preferred:

	Yes	No	Abst.
Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐
Chu, Evelyn, Pharm.D.	☒	☐	☐
Crumby, Mark, Pharm.D.	☒	☐	☐
Hautekeet, Mike, R.Ph	☒	☐	☐
Khurana, Sapandeep, MD	☒	☐	☐
Passalacqua, Brian, MD	☒	☐	☐
Ward, Kate, Pharm.D.	☒	☐	☐

Chairman Decerbo moved to add Ozempic as preferred and Board Member Crumby seconded. A vote was held:

	Yes	No	Abst.
Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐
Chu, Evelyn, Pharm.D.	☒	☐	☐
Crumby, Mark, Pharm.D.	☒	☐	☐
Hautekeet, Mike, R.Ph	☒	☐	☐
Khurana, Sapandeep, MD	☒	☐	☐
Passalacqua, Brian, MD	☒	☐	☐
Ward, Kate, Pharm.D.	☒	☐	☐

Board Member Hautekeet moved to accept the rest of the list as presented with the two changes as voted to add Ozempic and Trulicity as preferred and Board Member Crumby seconded. A vote was held:

	Yes	No	Abst.
Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐
Chu, Evelyn, Pharm.D.	☒	☐	☐
Crumby, Mark, Pharm.D.	☒	☐	☐
Hautekeet, Mike, R.Ph	☒	☐	☐

	Khurana, Sapandeep, MD	☒	☐	☐	
	Passalacqua, Brian, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
Hormones and Hormone Modifiers, Antidiabetic Agents, Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors					
i. Public Comment on proposed drug class.	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. Jeffery highlighted the newest indication for Farxiga added to improve cardiovascular risk factors but reminded the board Invokana and Jardiance have similar indications. Dr. Jeffery recommended the board consider this 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 and Board Member Crumby seconded. A vote was held:				Board Member Passalacqua was temporarily unavailable for this vote.
		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
	Chu, Evelyn, Pharm.D.	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx	Dr. Jeffery recommended the board add Glyxambi, Synjardy and Synjardy XR as preferred and the rest of the class remain the same.				
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL	Board Member Hautekeet moved to approve the preferred drug list as presented and Chairman Decerbo seconded. A vote was held:				
		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	

	Chu, Evelyn, Pharm.D.	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Passalacqua, Brian, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
g. For Possible Action: Discussion and possible adoption of Monoclonal Antibodies for the treatment of Respiratory Conditions					
Monoclonal Antibodies for the treatment of Respiratory Conditions					
i. Public Comment on proposed drug class.	The following written public comment is attached hereto: 1) An undated document titled "Public Testimony for Nevada Medicaid CINQAIR". The public comment referenced above was highlighted on the record for members of the Board by Dr. Jeffery Telephonic and web comment was called for and the phone lines were opened. Comment was made by Maria Agapova with Teva Pharmaceuticals to provided information on Cinqair. Ms. Agapova highlighted one post hoc analysis evaluating doses based on body weight demonstrating improvement in asthma exacerbations compared to the overall population. Asked the board to consider adding Cinqair as preferred. No further public comment was offered.				

<table>
<tr><td>ii. Drug class review presentation by OptumRx</td><td>Dr. Jeffery listed the medications in the class and recommended the board consider the class clinically and therapeutically equivalent.</td><td></td></tr>
<tr><td>iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.</td><td>Board Member Khurana moved to accept the class as clinically and therapeutically equivalent and Chairman Decerbo seconded. 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>Chu, Evelyn, Pharm.D.</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>Passalacqua, Brian, 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. Presentation of recommendations for PDL inclusion by OptumRx</td><td>Dr. Jeffery recommended the board add Fasenra as preferred and keep the rest of the class the same. Dr. Jeffery pointed out that because Cinqair is administered intravenously, it is billed on a physician office claim and is not subject to the preferred drug list.</td><td></td></tr>
<tr><td>v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL</td><td>Board Member Hautekeet moved to approve the preferred drug list as presented and Board Member Crumby seconded. 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>Chu, Evelyn, Pharm.D.</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>Passalacqua, Brian, 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>
</table>

h. For Possible Action: Discussion and possible adoption of Musculoskeletal Agents, Restless Leg Syndrome Agents		
Musculoskeletal Agents, Restless Leg Syndrome Agents		
i. Public Comment on proposed drug class.	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. Jeffery listed the products in the class and recommended the board consider the class as clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Board Member Khurana moved to accept the class as clinically and therapeutically equivalent and Chairman Decerbo seconded. A vote was held: Decerbo, Mark, Pharm.D. – Chair ☒ Yes ☐ No ☐ Abst. Chu, Evelyn, Pharm.D. ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Passalacqua, Brian, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx	Dr. Jeffery recommended the board move Requip XL to non-preferred and the rest of the class remain the same.	
v. Discussion by Board and action by Board for	Board Member Crumby moved to approve the preferred drug list as presented and Board Member Hautekeet seconded. A vote was held:	

approval of drugs for inclusion on the PDL		Yes	No	Abst.	
	Decerbo, Mark, Pharm.D. – Chair	☒	☐	☐	
	Chu, Evelyn, Pharm.D.	☒	☐	☐	
	Crumby, Mark, Pharm.D.	☒	☐	☐	
	Hautekeet, Mike, R.Ph	☒	☐	☐	
	Khurana, Sapandeep, MD	☒	☐	☐	
	Passalacqua, Brian, MD	☒	☐	☐	
	Ward, Kate, Pharm.D.	☒	☐	☐	
i. For Possible Action: Discussion and possible adoption of Psychotropic Agents, ADHD Agents					
Psychotropic Agents, ADHD Agents					
i. Public Comment on proposed drug class.	The following written public comment is attached hereto: 1) An undated document titled, "Ironshore JORNAY PM Medical Testimonial". The public comment referenced above was highlighted on the record for members of the Board by Dr Jeffery. Telephonic and web comment was called for and the phone lines were opened. Comment was made by Dr. Justin Barnes with Ironshore Pharmaceuticals speaking for Jornay PM. Dr. Barnes provided information on the unique properties and dosing of Jornay PM and the clinical trials demonstrating efficacy with ADHD symptom control throughout the day and early morning and evening behavior compared to placebo. Dr. Barnes asked the board to consider adding Jornay PM as preferred. No further public comment was offered.				

<table>
<tr><td>ii. Drug class review presentation by OptumRx</td><td>Dr. Jeffery listed the medications in the class and reported there are no new products and recommended the board consider the class clinically and therapeutically equivalent.</td><td></td></tr>
<tr><td>iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.</td><td>Board Member Khurana moved to accept the class as clinically and therapeutically equivalent and Board Member Crumby seconded. 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>Chu, Evelyn, Pharm.D.</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>Passalacqua, Brian, 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. Presentation of recommendations for PDL inclusion by OptumRx</td><td>Dr. Jeffery recommended the board add Desoxyn as preferred and Dyanavel, Procentra, Quillichew and Quillivant XR Suspension as non-preferred and the rest of the class remain the same.</td><td></td></tr>
<tr><td>v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL</td><td>Board Member Crumby moved to approve the preferred drug list as presented and Board Member Hautekeet seconded.

Board Member Khurana asked if the kids who are stabilized on these medications would be grandfathered on their medications or would they have to switch?

Dr. Jeffery answered that normally we would ask the member to switch to a preferred product. Adding if the board wished to add grandfathering, it should be added as a motion.

Board Member Khurana advocated to add Jornay PM as preferred because of it being one of its kind with administration timing.</td><td></td></tr>
</table>

	Board Member Ward asked a question directed at Board Member Khurana if Jornay PM is something used first-line or something used after trying something else? Board Member Khurana responded that normally Jornay PM is not first-line, usually generics are tried first. Board Member Crumby withdrew the motion to accept the preferred drug list as presented. Board Member Khurana moved to add Jornay PM as preferred and accept the rest of the preferred drug list as presented. Board Member Crumby seconded the motion. A vote was held: Yes / No / Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Chu, Evelyn, Pharm.D. ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Passalacqua, Brian, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐ Board Member Khurana moved to grandfather the current recipients on medications being moved to non-preferred and Chairman Decerbo seconded. Ms. Long asked for clarification for how long the grandfathering should be added. Board Member Khurana added they should be grandfathered for however long they continue to do well on the products.	

	Dr. Jeffery offered input that since these products already have a prior authorization requirement, grandfathering to bypass the non-preferred status would be indefinite and they would still need to meet the clinical criteria. Chairman Decerbo clarified the motion is to grandfather the recipients indefinitely. A vote was held: Decerbo, Mark, Pharm.D. – Chair ☒ Yes ☐ No ☐ Abst. Chu, Evelyn, Pharm.D. ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Passalacqua, Brian, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
j. For Possible Action: Discussion and possible adoption of Respiratory Agents, Short-Acting/Rescue Therapy		
Respiratory Agents, Short-Acting/Rescue Therapy		
i. Public Comment on proposed drug class.	Telephonic and web comment was called for and the phone lines were opened. Comment was made by Maria Agapova from Teva Pharmaceuticals announced the availability of Proair Digihaler that is able to capture both quality and quantity of inhalations for asthma and COPD patients and allows for remote monitoring from the provider. No further public comment was offered.	

<table>
<tr><td>ii. Drug class review presentation by OptumRx</td><td>Dr. Jeffery listed the available medications in the class, identified nothing new is available since the last review and recommend the board consider the class clinically and therapeutically equivalent.</td><td></td></tr>
<tr><td>iii. 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 and Board Member Hautekeet seconded. 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>Chu, Evelyn, Pharm.D.</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>Passalacqua, Brian, 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. Presentation of recommendations for PDL inclusion by OptumRx</td><td>Dr. Jeffery recommended the board add Proair HFA, Ventolin HFA and Xopenex solution to preferred and Levalbuterol nebulizer solution and Proventil HFA to non-preferred.</td><td></td></tr>
<tr><td>v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL</td><td>Chairman Decerbo moved to approve the preferred drug list as presented and Board Member Hautekeet seconded. 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>Chu, Evelyn, Pharm.D.</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>Passalacqua, Brian, 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>
</table>

k. For Possible Action: Discussion and possible adoption of Toxicology Agents, Substance Abuse Agents		
Toxicology Agents, Substance Abuse Agents		
i. Public Comment on proposed drug class.	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. Jeffery provided details of the medications in the class, identifying the single-entity and combo agents within the class and recommended the board accept the class as clinically and therapeutically equivalent.	
iii. Discussion by Board and action by Board to approve clinical/therapeutic equivalency of agents in class.	Board Member Khurana moved to accept the class as clinically and therapeutically equivalent and Board Member Hautekeet seconded. A vote was held: Yes / No / Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Chu, Evelyn, Pharm.D. ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Passalacqua, Brian, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
iv. Presentation of recommendations for PDL inclusion by OptumRx	Dr. Jeffery recommended the board add the generic buprenorphine/naloxone tablet as preferred and Suboxone as non-preferred and keep the rest of the class the same.	
v. Discussion by Board and action by Board for approval of drugs for inclusion on the PDL	Board Member Hautekeet moved to approve the preferred drug list as presented and Board Member Chu seconded.	

	Chairman Decerbo identified the significant change with moving from a film to a tablet. Board Member Khurana agreed and asked the board to consider keeping Suboxone Film as preferred as there are studies showing tabs have a higher risk of diversion and exposure to kids and there is data lacking for bioavailability between the higher doses of the tablets versus the film. Board Member Ward confirmed the tablets and films are not bioequivalent and a conversion would need to be done to transition from one to another and there would be risk to the member. Chairman Decerbo agreed there would be some negative outcomes with the change. Board Member Hautekeet withdrew the motion. Board Member Ward moved to accept the preferred drug list as presented except for keeping Suboxone as preferred. Board Member Hautekeet seconded. A vote was held: Yes / No / Abst. Decerbo, Mark, Pharm.D. – Chair ☒ ☐ ☐ Chu, Evelyn, Pharm.D. ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Hautekeet, Mike, R.Ph ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Passalacqua, Brian, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
7. Annual Review – Drug Classes Without Proposed Changes		
a. Public Comment	The following written public comment is attached hereto:	

	1) Letter dated August 21, 2020 from Mara Costa at Neurology Center of Nevada advocating for access to Nurtec ODT. 2) An undated letter from Michael Sullivan, MD, Neurologist at Carson Valley Medical Group advocating for the access to Nurtec ODT. 3) An undated letter from Lisa Hammargren-Kuykendall, APRN, Neurology, advocating for access to Nurtec ODT. 4) Letter dated August 24, 2020 from Mehdi Ansarinia, MD, Headache Specialist, advocating for access to Nurtec ODT. 5) An undated letter from Adam Antflick, DO, Nevada Pain Care, advocating for access to Nurtec ODT. 6) An undated letter from Quang Nguyen, DO, Endocrinologist, advocating for access to Nurtec ODT. 7) Letter dated August 26, 2020 from Rachael Gardner, MSN, FNP, Renown Institute of Neuroscience, advocating for access to Nurtec ODT. 8) Letter dated August 19, 2020 from Danny Thai from 986 Specialty Pharmacy advocating for access to Nurtec ODT. 9) Letter dated August 26, 2020 from Jocelyn Segovia, PA-C, advocating for open access to Nurtec ODT. 10) Letter dated September 8, 2020 from Lydia Borja Estanislao, MD, Board Certified Neurology, advocating for access to Nurtec ODT. 11) An undated information sheet from Hiten Patadia from Otsuka Pharmaceuticals advocating for Abilify Maintena. 12) An undated letter from David Ramsey, MN, APRN, FNP-BC, Community Counseling Center, advocating for maintaining access to Rexulti. 13) An undated information sheet from Hiten Patadia from Otsuka Pharmaceuticals advocating for Rexulti. 14) Letter dated September 11, 2020 from Philip Rich, MD, advocating for access to Rexulti. The public comment referenced above was highlighted on the record for members of the Board by Dr Jeffery.	

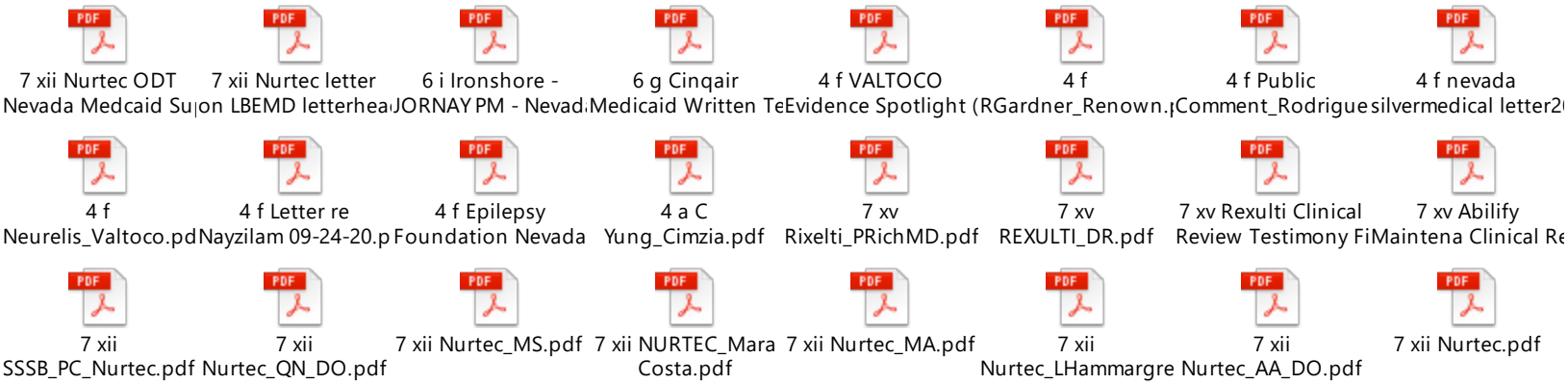
	Telephonic and web comment was called for and the phone lines were opened. Comment was made by Melissa Sommers with Novartis providing information on Xiidra for dry eye disease. Ms. Sommers outlined the indication and asked the board to add Xiidra as preferred because Xiidra treats signs and symptoms of dry eye disease. Ms. Sommers continued explaining the mechanism of action, pathophysiology of dry eye disease and clinical trial information demonstrating efficacy. Ms. Sommers asked again for the board to add Xiidra as preferred. Comment was made by Rachel Gardner, a Nurse Practitioner in Reno, Nevada. Advocated for access to Nurtec ODT so Nevada Medicaid patients have more options available for the treatment of migraines. Ms. Gardner highlighted some issues with using the standard triptan therapy such as ineffective treatment or adverse effects. She stated that her patients quickly experience migraine pain freedom with the acute CGRP use and experience little to no side effects leading to improved quality of life. Ms. Gardner pointed out that CGRP's have fewer drug interactions and fewer restrictions due to comorbid conditions. Asked the board to add Nurtec ODT as preferred. No further public comment was offered.	
b. For Possible Action: Discussion and possible adoption of the Preferred Drug List (PDL) as presented by OptumRx and the Division of Health Care Financing and Policy without changes.	Dr. Jeffery referenced the list of classes from the agenda without proposed changes. Chairman Decerbo asked the DHCFP the best way to handle the requests from the public comment. Ms. Long stated since cost is a factor in the board's consideration, it would be best to bring back the topics for the next meeting.	Board Member Hautekeet was temporarily unavailable for this vote.

	Deputy Attorney Lither agreed the best method to address these comments would be to bring back to the next meeting where a cost analysis could be prepared and discussed. Chairman Decerbo moved to accept the remaining of the preferred drugs with no changes as presented and Board Member Khurana seconded. A vote was held: Decerbo, Mark, Pharm.D. – Chair ☒ Yes ☐ No ☐ Abst. Chu, Evelyn, Pharm.D. ☒ ☐ ☐ Crumby, Mark, Pharm.D. ☒ ☐ ☐ Khurana, Sapandeep, MD ☒ ☐ ☐ Passalacqua, Brian, MD ☒ ☐ ☐ Ward, Kate, Pharm.D. ☒ ☐ ☐	
8. OptumRx Reports: New Drugs to Market and New Line Extensions	Dr. Jeffery bypassed the pipeline report due to the meeting time going over.	
9. Closing Discussion		
a. Public comment	Board Member Khurana asked if the public making testimony at future meetings could disclose any conflicts of interest. Deputy Attorney Lither stated he will work with Ms. Long to best address those concerns. Telephonic and web comment was called for and the phone lines were opened. No public comment was offered.	
b. For Possible Action: Date and location of the next meeting.	Chairman Decerbo identified the next meeting is scheduled for December 10, 2020.	
c. Adjournment	The meeting was adjourned at 5:34 p.m.	

Attachment A – Members of the Public in Attendance

Maria Agapova, Teva Pharmaceuticals
Kevin Aholt, Neurelis
Alan Bailey, UCB
Kaysen Bala, Biogen
Justin Barnes, Ironshore Pharmaceuticals
Kay Onda Bayo
Heather Behnken
J Belz, J. K Belz and Associates
Kenneth Berry, Alkermes
Kevin Black
Sarah Blankenship, Artia Solutions
Nick Boyer, Braeburn
Douglas Britt, SK Life Science
Jacob Brown
Scott Budsberg, Amgen
Kinsey Caldwell
Natalie Cardenas, UCB
Betty Chan, Gilead Sciences
Linda Chen
Michael Chien
Jeana Colabianchi, Sunovion
David Cram, Takeda
Elaine DEFELICE, UCB
Ben Droese, Amgen Medical Affairs
Michelle Duke
Dawn Dynak
Georgette Dzwilewski
Karen Einbinder, Greenwich Biosciences
Derek Ems, UCB, Inc.
Joe Ferroli, Takeda
Mike Finklein
Rachael Gardner, Renown Institute of Neuroscience
Joe Germain, Biogen
Jon Glover
Andrew Gorzynski
Jim Graves
Deron Grothe, Teva Pharmaceuticals
Penny Higashi, Boehringer Ingelheim
Susan Honda-Takeda, Greenwich Biosciences
Sara Hovland
Steve Isaki, Lundbeck
Bashir Kalayeh, Amgen
Alan Kaska, Abbott
Stephanie Kennedy, Greenwich Biosciences
Camille Kerr, Regeneron
Chi Kohlhoff, Viela Bio
Adam Kopp, Zogenix
David Large, Biohaven Pharmaceuticals
Jimmy Lau
Chelsea Leroue
Lauren Malko, Greenwich Biosciences
Danielle Marano, Epilepsy Foundation of Nevada
Lori McDermott, Supernus
Melisa McEwen, OAPI
Margot Miglins, Amgen
Hector Mobine, Amgen
Jeff Mussack
Joanne Nguyen
Gary Okano, Bristol Myers Squibb
Ewa Olech
Carmen Oliver, Biohaven Pharmaceuticals
Hiten Patadia, Otsuka Pharmaceuticals
Warner Quon, Ascendis
Lisa Rand
Robert Reemts, UCB
Jean Ritter
Nicole Robling
Amy Rodenburg
Gibby Rodriguez, Indivior
Raj Sandhar, UCB
Christopher Santarone
Deborah Sheppe, Neurelis
William Simons, Artia Solutions
Mark Snyder
Melissa Sommers, Novartis
Sibin Stephen, Zogenix
Jeannie Timberman
Jennifer Todd, UCB, Inc.
Mike Willett
Jonathan Wolin
Pin Xiang
Barbara Yaeger, UCB
Kelvin Yamashita
Sara Young
Jeanne Zanden, Biocodex
Michael Zarob, Alkermes

Attachment B – Submitted Written Comment



OPTUMRx®

Proposed New Classes

Therapeutic Class Overview
GnRH modulators

INTRODUCTION

Central Precocious Puberty (CPP)

- Puberty is a period of physical, hormonal, and psychological transition from childhood to adulthood, with accelerated linear growth and achievement of reproductive function *(Britto et al 2016)*. Pubertal timing is influenced by complex interactions of genetic, nutritional, environmental, and socioeconomic factors *(Macedo et al 2014).*
  - While there has been extensive discussion with regard to the definition of puberty, most pediatricians give an age limit of 8 years in girls and 9 to 9.5 years in boys for the lower limit of normal pubertal development *(Carel et al 2004)*.
- CPP is characterized by the early onset of pubertal manifestations in girls and boys *(Carel et al 2004)*.
  - CPP is caused by the disruption of the hypothalamic-pituitary-gonadal axis, which results in the early activation of pulsatile gonadotropin-releasing hormone (GnRH) secretion *(Carel and Léger 2008).*
  - These manifestations consist primarily of breast development in girls and testicular enlargement in boys *(Carel and Léger 2008)*.
- GnRH agonists are the treatment of choice for CPP. Chronic administration of potent GnRH agonists causes down-regulation of pituitary GnRH receptors, suppression of gonadotropin (luteinizing hormone [LH] and follicle-stimulating hormone [FSH]) secretion and finally suppression of the release of gonadal sex hormones *(Fuqua 2013, Klein et al 2016).*
  - There are several GnRH agonists available in varying doses and formulations. Depot formulations are generally preferred due to improved compliance *(Guaraldi et al 2016).* GnRH agonists that are Food and Drug Administration (FDA)-approved for the treatment of CPP include:
    - Lupron Depot-Ped (leuprolide), available as monthly or every 3 month intramuscular (IM) injections.
    - Synarel (nafarelin) intranasal spray, a short-acting spray that requires multiple inhalations daily.
    - Supprelin LA (histrelin), available as a 1-year subcutaneous (SC) implant device.
    - Triptodur (triptorelin), administered as a single IM injection every 24 weeks. Of note, Trelstar (triptorelin pamoate) IM injection was the first FDA-approved triptorelin formulation; it was used off-label to treat CPP until Triptodur was made available in 2017 *(Klein et al 2016)*.
  - The optimal time to discontinue a GnRH agonist has not been established, but retrospective analyses suggest that discontinuation around the age of 11 years is associated with optimal height outcomes *(Carel and Léger 2008).*

Endometriosis

- Endometriosis is a chronic, estrogen-dependent disorder characterized by deposits of endometrial tissue outside the endometrial cavity, such as the liver, diaphragm, umbilicus, and pleural cavity *(Brown and Farquhar 2015, Giudice 2010, Schenken 2018).*
  - Endometriosis affects 6% to 10% of women of reproductive age; it is present in approximately 38% of women with infertility and in up to 87% of women with chronic pelvic pain (*Armstrong 2010).*
  - The clinical presentation of endometriosis is highly variable and ranges from debilitating non-menstrual pelvic pain (NMPP) to infertility to no symptoms. Patients can present with dysmenorrhea, abdominal or pelvic pain, dyspareunia, and infertility *(Schrager et al 2013).*
- Although several pharmacological options are available for the treatment of endometriosis, none provide a cure, long-term relief of symptoms, or resolution of infertility.
  - GnRH agonists, such as Zoladex 3.6 mg (goserelin), Lupaneta Pack (leuprolide acetate/norethindrone), Lupron Depot 3.75 mg or Lupron Depot 11.25 mg 3-month injection (leuprolide), and Synarel (nafarelin) are recommended as second-line pharmacologic therapy after non-steroidal anti-inflammatory drugs (NSAIDS) and oral contraceptives *(American College of Obstetricians and Gynecologists [ACOG] 2010, Armstrong 2010, American Society for Reproductive Medicine [ASRM] 2014).*
    - GnRH agonists are generally not recommended as a long-term therapy, due to the potential for dose and duration-dependent bone loss *(ACOG 2010).*
  - Orilissa (elagolix), the first and only available oral GnRH antagonist, was FDA-approved in July 2018 for the management of moderate to severe pain associated with endometriosis.

- Elagolix exerts its effect by rapidly suppressing the pituitary ovarian hormones and produces a dose-dependent suppression of ovarian estrogen production that varies from partial to full suppression.
- Similar to GnRH agonists, elagolix is indicated for short-term use, ie, 6 months for patients taking 200 mg orally twice daily (for coexisting dyspareunia) and 24 months for patients taking 150 mg orally daily.
- Other GnRH antagonists, such as Cetrotide (cetrorelix), Firmagon (degarelix), and ganirelix are only available as an injectable formulation; however, these agents are not FDA-approved for the treatment of endometriosis.

Uterine fibroids

- Uterine fibroids, also known as uterine leiomyomas or myomas, are monoclonal tumors that arise from the uterine smooth-muscle tissue *(Sohn et al 2018).*
  - It is estimated that 60% of women of reproductive age are affected, and 80% of women develop the disease during their lifetime.
  - Heavy or prolonged menstrual bleeding, abnormal uterine bleeding, resultant anemia, pelvic pain, infertility, and/or recurrent pregnancy loss are generally associated with uterine fibroids.
  - The majority of women with uterine fibroids either remain asymptomatic or develop symptoms gradually over time. When patients are symptomatic, the number, size, and/or location of fibroids are critical determinants of its clinical manifestations.
- Although curative treatment of uterine fibroids relies on surgical therapies, medical treatments are considered first-line to preserve fertility and avoid or delay surgery. Lupron Depot 3.75 mg is the only GnRH agonist that has been FDA-approved for the preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata *(Sohn et al 2018).*
  - Lupron Depot 3.75 mg is administered concomitantly with iron therapy. The clinician may wish to consider a 1-month trial period on iron alone inasmuch as some of the patients will respond to iron alone. Lupron may be added if the response to iron alone is considered inadequate.

Infertility

- Infertility is typically defined as the inability to achieve pregnancy after 1 year of unprotected sexual intercourse *(Anwar and Anwar 2016).*
  - Infertility is common with a prevalence estimated at 9 to 18% *(Hanson et al 2017).*
  - Patients who are struggling to conceive report feelings of depression, anxiety, isolation, and loss of control *(Rooney and Domar 2018).*
  - An estimated 50% of infertility cases among heterosexual couples are attributable to female factors, 20% to male factors, and 30% to combined female and male factors or unknown factors (*Centers for Disease Control [CDC] 2018*, *Fauser 2018, Shreffler et al 2017*).
    - The most common causes of female infertility include ovulatory disorders (most commonly due to polycystic ovary syndrome [PCOS]), endometriosis, pelvic adhesions, tubal blockage, other tubal abnormalities, and hyperprolactinemia.
    - The most common causes of male infertility are low concentrations, poor motility, and abnormal morphology of sperm.
- Pharmacologic agents used in anovulatory women to induce or control ovulation include clomiphene (the most widely used fertility treatment), letrozole (off-label indication), gonadotropins (FSH products and human chorionic gonadotropin [hCG] products), and GnRH antagonists (cetrorelix and ganirelix). Other pharmacological agents used include metformin (in PCOS patients) and dopamine agonists (for hyperprolactinemic anovulation) *(Seli and Arici 2018).*
  - GnRH antagonists, such as cetrorelix and ganirelix, are used in conjunction with assisted reproductive technology (ART), which is defined as any fertility treatment in which either eggs or embryos are handled. The 2 most common ART procedures utilized in the U.S. are in-vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) *(CDC 2018).*
- Of note, all cancer indications for GnRH agonists are outside of the scope of this review.
- Medispan Class: Gonadotropin Releasing Hormone Agonists; Gonadotropin Releasing Hormone Antagonist

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Cetrotide (cetrorelix) 0.25 mg injection	-
ganirelix 250 mcg injection	✔

Drug	Generic Availability
Lupaneta Pack (leuprolide acetate 3.75 mg depot suspension; norethindrone acetate 5 mg tablets and leuprolide acetate 11.25 mg depot suspension; norethindrone acetate 5 mg tablets)	-
Lupron Depot-Ped (leuprolide acetate for depot suspension) 7.5 mg, 11.25 mg, 15 mg (monthly) & 11.25 mg, 30 mg (3-month)	-
Lupron Depot (leuprolide acetate for depot suspension) 3.75 mg (monthly), 11.25 mg (3-month)	-
Orilissa (elagolix) 150 mg, 200 mg tablets	-
Supprelin LA (histrelin) 50 mg implant	-
Synarel (nafarelin) nasal spray	-
Triptodur (triptorelin) 22.5 mg extended-release suspension	-
Zoladex (goserelin) 3.6 mg implant	-

(*Drugs@FDA 2019, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2019*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Cetrotide (cetrorelix)	ganirelix	Lupaneta Pack (leuprolide/ norethindrone)	Lupron (leuprolide) Depot	Lupron Depot-Ped (leuprolide)	Orilissa (elagolix)	Supprelin LA (histrelin)	Synarel (nafarelin) intranasal spray	Triptodur (triptorelin)	Zoladex (goserelin) implant
Treatment of children with CPP					✔		✔	✔	✔	
Management of endometriosis, including pain relief and reduction of endometriotic lesions				✔				✔		✔
Use as an endometrial-thinning agent prior to endometrial ablation for dysfunctional uterine bleeding										✔
Initial management of the painful symptoms of endometriosis			✔	✔ †						
Management of recurrence of endometriosis symptoms			✔	✔ †						
Preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata				✔ ‡						
Management of moderate to severe pain associated with endometriosis						✔				
Inhibition of premature LH surges in women undergoing controlled ovarian stimulation*	✔	✔								

Abbreviations: CPP = central precocious puberty; LH = luteinizing hormone

*The word “stimulation” is used in the cetrorelix indication, while the word “hyperstimulation” is used in the ganirelix indication.

† In combination with norethindrone acetate 5 mg tablet taken once daily

‡ Concomitantly with iron therapy

(*Prescribing information: Cetrotide 2018, ganirelix 2018, Lupaneta Pack 2015, Lupron Depot-Ped 2017, Lupron Depot 2018, Orilissa 2018, Supprelin LA 2017, Synarel 2017, Triptodur 2018, Zoladex 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

CPP

- The choice of GnRH agonist formulation depends on patient and clinician preference. These preparations have not been directly compared in randomized trials, but appear to be similarly effective in suppressing the pituitary-gonadal axis (*Harrington and Palmert 2017)*.
  - In a multicenter trial with histrelin implant for the treatment of CPP, peak LH and estradiol or testosterone were effectively suppressed, and no significant adverse events (AEs) were noted. Positive long-term safety and efficacy data were reported in 2 studies (a 2- and a 6-year study) that evaluated long-term hormonal suppression in CPP patients post histrelin implant insertion. More specifically, peak LH and FSH levels remained suppressed in both the 2- and the 6-year trial *(Harrington and Palmert 2017, Rahhal et al 2009, Silverman et al 2015*).
  - A randomized controlled trial (RCT) with 54 patients compared the 1-month (7.5 mg) and 3-month (11.25 mg and 22.5 mg) leuprolide formulations for the treatment of CPP. There were more patients with inadequate pubertal suppression in the 11.25 mg 3-month leuprolide depot group (as measured by mean stimulated LH levels > 4 IU/L) compared to the 7.5 mg monthly and 22.5 mg 3-month groups. Mean LH and FSH levels in the 22.5 mg 3-month dose group were not different from the monthly depot injections. No differences in estradiol levels, growth velocity, or bone age progression were observed between the dosing groups *(Fuld et al 2011).*
  - In a phase 3, randomized, open-label (OL) study (N = 84), leuprolide 11.25 mg 3-month depot was compared to leuprolide 30 mg 3-month depot in children with CPP. There were 9 treatment failures (peak stimulated LH > 4 IU/L) in the 11.25 mg group and 2 in the 30 mg group. Basal sex steroid suppression, growth rates, pubertal progression, bone age advancement, and AEs were similar between both doses *(Lee et al 2012).*
  - Clinical trials with nafarelin demonstrated a reduction in the peak response of LH to GnRH stimulation from a pubertal response to a pre-pubertal response within 1 month of treatment. Additionally, breast development was arrested or regressed in 82% of girls, while genital development was arrested or regressed in 100% of boys *(Synarel Product Information 2017)*.
  - The efficacy of triptorelin 6-month injection was evaluated in an OL, single-arm clinical trial in females and males with CPP, ages 2 to 9 (N = 44). At 12 months, 97.7% of patients achieved pre-pubertal LH levels. Mean stimulated FSH and mean basal FSH levels were also lower at 12 months, compared to baseline. Additionally, the Tanner stage (a scale of physical development) was stable or reduced (manifested by a reduction in physical development) in 88.6% of patients *(Klein et al 2016)*.

Endometriosis

- A Cochrane Review meta-analysis of 41 trials (N = 4935) in patients with endometriosis compared the safety and effectiveness of GnRH agonists to no treatment, placebo, danazol, intrauterine progestins, or other GnRH agonists (*Brown et al 2010*).
  - GnRH agonists were more effective than no treatment or placebo.
  - There was no statistically significant difference between GnRH agonists and danazol for dysmenorrhea associated with endometriosis.
  - There was a benefit in overall resolution for GnRH agonists compared with danazol.
  - There was no statistically significant difference in overall pain between GnRH agonists and levonorgestrel.
  - More AEs were reported in the GnRH agonist group.
  - No route of administration for GnRH agonists appeared to be superior to another.
- A RCT (N = 315) compared the efficacy of goserelin (3.6 mg every 28 days) to danazol 400 mg orally twice daily in females with endometriosis. Goserelin was found to be similar in efficacy and safety as compared to danazol. Both treatments significantly reduced mean subjective signs and symptoms scores during and after treatment *(Rock et al 1993).*
- A meta-analysis of 13 RCTs (N = 945) evaluated the effectiveness of GnRH agonists for endometriosis, with and without add-back therapy. Add-back therapy refers to the addition of hormone replacement therapy to GnRH agonists, in order to avoid AEs that are caused by GnRH agonist-induced hormone suppression. The evidence suggested that add-back therapy was more effective for symptomatic relief than GnRH agonists alone, both immediately after

treatment and at 6 months. Add-back therapy increased estrogen levels, but did not reduce the efficacy of GnRH agonists for treating dysmenorrhea and dyspareunia *(Wu et al 2014)*.

- The FDA approval of elagolix was based on the results of the Elaris Endometriosis trials, EM-I and EM-II, which were 2 phase 3, 6-month, double-blind (DB), placebo-controlled (PC), RCTs in women 18 to 49 years of age with moderate to severe endometriosis. Three treatment groups, elagolix 150 mg orally daily (n = 475), elagolix 200 mg orally twice daily (n = 477), and placebo (n = 734) were evaluated for efficacy and safety. (*Orilissa Dossier 2018, Taylor et al 2017*).
  - Patients were considered responders if they experienced a reduction of ≥ -0.81 from baseline score in dysmenorrhea pain and a reduction of ≥ -0.36 from baseline score in NMPP, and no increase in rescue analgesic use. At months 3 and 6, a significantly greater proportion of women in both elagolix dose groups met the clinical response criteria for the co-primary endpoints of dysmenorrhea and NMPP ($p < 0.001$).
  - The most common AEs were hot flushes, headache, and nausea. Bone mineral density (BMD) loss was significantly greater than placebo in the 150 mg daily and 200 mg twice daily groups at 6 months. Liver and kidney function parameters/analytes exhibited sporadic statistically significant changes throughout treatment but none of the differences between the elagolix doses and placebo were considered clinically significant. Additionally, there was 1 suicide reported in the EM-II trial, which was related to overdose with multiple non-trial medications.
  - Patients who completed EM-I or EM-II continued on to 1 of the 2 phase 3 extension trials, EM-III or EM-IV. The duration of treatment was 6 months (with continuation of the same elagolix dose from the 6-month EM-I/EM-II trials, for a total of 12 months of treatment), followed by a 12 month observation period *(Surrey et al 2018)*.
    - The data from EM-III and EM-IV demonstrated that the response rates for dysmenorrhea and NMPP were maintained in women who continued treatment with elagolix. A decrease of 5 to 8% in lumbar spine BMD after 12 months of continuous treatment occurred in 2 to 3% of the 150 mg daily group and in 26 to 30% of the 200 mg twice daily group. The percentage of women with > 8% decrease in BMD in the lumbar spine, total hip, or femoral neck was 2 to 8% in the 150 mg daily group and 21% in the 200 mg twice daily group.

Uterine fibroids

- PEARL II was a DB, non-inferiority trial that included 307 patients randomly assigned to 5 or 10 mg of ulipristal vs leuprolide acetate depot, for 3 months of treatment. Uterine bleeding was controlled in 90% of patients receiving 5 mg of ulipristal acetate, in 98% of those receiving 10 mg of ulipristal acetate, and in 89% of those receiving leuprolide acetate, for differences (as compared with leuprolide acetate) of 1.2% (95% confidence interval [CI], -9.3 to 11.8) for 5 mg of ulipristal acetate and 8.8% (95% CI, 0.4 to 18.3) for 10 mg of ulipristal acetate. Median times to amenorrhea were 7 days for patients receiving 5 mg of ulipristal acetate, 5 days for those receiving 10 mg of ulipristal acetate, and 21 days for those receiving leuprolide acetate. Moderate-to-severe hot flashes were reported for 11% of patients receiving 5 mg of ulipristal acetate, for 10% of those receiving 10 mg of ulipristal acetate, and for 40% of those receiving leuprolide acetate ($p < 0.001$ for each dose of ulipristal acetate vs leuprolide acetate) *(Donnez et al 2012)*.

Infertility

- A meta-analysis of 73 RCTs (N = 12,212) compared the efficacy and safety of GnRH antagonists (cetrorelix or ganirelix) to long-course GnRH agonist regimens in patients using these agents for controlled ovarian hyperstimulation in ART (*Al Inany et al 2016*).
  - There was no evidence of a difference in live birth rate between GnRH antagonist and long-course GnRH agonist regimens in 2303 patients (odds ratio [OR] = 1.02; 95% CI, 0.85 to 1.23; 12 RCTs; $I^2 = 27\%$).
  - GnRH antagonists were associated with a lower incidence of any grade of ovarian hyperstimulation syndrome (OHSS) compared to GnRH agonists in 7944 patients (OR = 0.61; 95% CI, 0.51 to 0.72; 36 RCTs; $I^2 = 31\%$).
  - There was no difference in miscarriage rate per woman between the GnRH antagonist group and GnRH agonist group as evaluated in 7082 patients (OR = 1.03; 95% CI, 0.82 to 1.29; 34 RCTs; $I^2 = 0\%$).

CLINICAL GUIDELINES

CPP

- American Academy of Pediatrics (AAP): Evaluation and referral of children with signs of early puberty *(Kaplowitz and Bloch 2016)*
  - Treatment with GnRH agonists such as leuprolide can be administered via injection at monthly or 3-month intervals or with annual insertion of SC histrelin implant.
  - If suppression of menses is the primary concern (rather than preservation of linear growth potential), then medroxyprogesterone depot IM injection every 3 months can be considered.

- Therapy should be continued until the physician determines that continued pubertal suppression is no longer beneficial to the child.

Endometriosis

- ACOG: Updates Guideline on Diagnosis and Treatment of Endometriosis (*ACOG 2010, Armstrong 2010)*
  - Progestins, danazol, extended-cycle combined oral contraceptives, NSAIDs, and GnRH agonists can be used for the initial treatment of pain in women with suspected endometriosis.
    - However, recurrence rates are high after the medication is discontinued. Empiric therapy with another suppressive medication is an option. For example, empiric therapy with a 3-month course of a GnRH agonist is appropriate if the initial treatment with an oral contraceptive or NSAID is unsuccessful.
  - In women with a history of endometriosis who wish to preserve their fertility, NSAIDs or combined oral contraceptives can be used to treat recurrent pain.
    - Oral or depot medroxyprogesterone acetate is also an effective treatment option.
    - If none of the above therapies is successful, then progestins, GnRH agonists, and androgens may be used.
    - The use of Mirena (levonorgestrel-releasing intrauterine system) reduces pelvic pain associated with endometriosis, but AEs are common.
  - If treatment with a GnRH agonist is successful, the use of an add-back regimen can reduce or eliminate bone mineral loss and provide symptomatic relief without reduction in pain relief.
    - Add-back regimens have been used in women undergoing long-term therapy; they may include progestins alone, low dose progestins, progestins plus bisphosphonates, or estrogens.
- ASRM: Treatment of pelvic pain associated with endometriosis: A committee opinion *(ASRM 2014)*
  - Endometriosis should be viewed as a chronic disease that requires a lifelong management plan with the goal of maximizing the use of medical treatment and avoiding repeated surgical procedures.
  - Definitive diagnosis via laparoscopic surgery is recommended, with the option of treating visible endometriosis at that time.
  - Pharmacologic therapies such as NSAIDs, combined hormonal contraceptives, progestins, danazol, and GnRH agonists are recommended for the treatment of endometriosis.
    - Surgical treatment with removal of the uterus and ovaries (total hysterectomy and bilateral salpingo-oophorectomy) is recommended in women with disabling symptoms who have completed childbearing and have failed to respond to multiple alternative regimens.

Uterine fibroids

- Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program: Management of Uterine Fibroids *(AHRQ 2017)*
  - GnRH agonists, mifepristone, ulipristal, and uterine artery embolism reduce fibroid size, and improve symptoms and quality of life. Myomectomy and hysterectomy also improve quality of life.
    - Moderate-strength evidence suggests that GnRH agonists (with and without add-back therapy) reduce the size of fibroids, the overall size of the uterus, and bleeding symptoms.
    - Low-strength evidence suggests that fibroid-related quality of life improves with GnRH agonists (with and without add-back therapy).
  - For women in their 30s, the chance of needing retreatment for fibroids within the next 2 years was 6 to 7% after medical treatment or myomectomy and 44% after urinary artery embolization (UAE). For older women, the chance was 9 to 19% after medical treatment or UAE and 0% after myomectomy.
- ACOG: Alternatives to hysterectomy in the management of leiomyomas *(ACOG 2008)*
  - GnRH agonists have been shown to improve hematologic parameters, shorten hospital stay, and decrease blood loss, operating time, and postoperative pain when given for 2 to 3 months preoperatively. Benefits of preoperative GnRH agonist administration should be weighed against their cost and side effects for individual patients.
  - Abdominal myomectomy is a safe and effective alternative to hysterectomy for the treatment of women with symptomatic leiomyomas.
  - Hormone therapy may cause some modest increase in uterine leiomyoma size but does not appear to have an impact on clinical symptoms. Therefore, this treatment option should not be withheld from women who desire or need such therapy.

Infertility

- The 2018 ASRM guidelines for PCOS and a 2016 World Health Organization (WHO)-funded PCOS guidelines make the following recommendations *(Balen et al 2016, Teede et al 2018):*
  - Although off-label, letrozole is recommended as first-line therapy for ovulation induction in women with PCOS and anovulatory infertility.
  - Clomiphene is also considered a first-line treatment option in women with PCOS and anovulatory infertility. Per the ASRM guidelines, clomiphene could be used in preference to metformin, when treating an obese patient (BMI ≥ 30 kg/m^2). Both guidelines recommend the use of clomiphene in combination with metformin for PCOS patients with clomiphene resistance.
  - Gonadotropins can be used as second-line pharmacological agents in women with PCOS and anovulatory infertility who have failed oral ovulation induction therapy (clomiphene and/or metformin). No significant differences in efficacy between preparations of gonadotropin agents have been noted.
  - A GnRH antagonist protocol is preferred in women with PCOS undergoing an IVF ± ICSI cycle over a GnRH agonist long protocol. The preferred protocol is known to reduce the duration of stimulation, total gonadotropin dose, and incidence of OHSS.

SAFETY SUMMARY

Contraindications

- Pregnancy
- Cetrotide carries the additional contraindication of severe renal impairment.
- Elagolix carries additional contraindications for known osteoporosis, severe hepatic impairment (Child-Pugh C), and concomitant use with strong OATP1B1 inhibitors (eg, cyclosporine and gemfibrozil).
- Lupaneta Pack carries additional contraindications, including undiagnosed uterine bleeding, breast-feeding, known/suspected/history of breast or other hormone-sensitive cancers, thrombotic/thromboembolic disorders, and liver tumors/liver disease.
- Lupron Depot carries additional contraindications, including undiagnosed abnormal uterine bleeding and breast-feeding.
- Nafarelin carries an additional contraindication for undiagnosed vaginal bleeding.

Warnings and Precautions

- An initial rise in gonadotropin and sex steroid levels may be seen during the first 2 to 4 weeks of therapy, due to the initial stimulatory effect of the drug (leuprolide, histrelin, triptorelin).
- Psychiatric events have been reported in patients taking GnRH agonists. Symptoms include crying, irritability, anger, and aggression (elagolix, histrelin, leuprolide, nafarelin, triptorelin). Suicidal ideation is an additional warning with elagolix.
- Convulsions have been observed in patients with a history of seizures, epilepsy, cerebrovascular disorders, central nervous system anomalies or tumors, or concomitant medications that may be associated with convulsions. Convulsions have also been reported in patients without the conditions mentioned above (leuprolide, histrelin, nafarelin, triptorelin).
- A reduction in BMD may be observed with most of the GnRH agonists/antagonists.
- Ovarian cysts have been reported during the first 2 months of therapy with Synarel and in post-marketing experience with Zoladex. Many, but not all, occurred in women with polycystic ovarian disease. These cystic enlargements may resolve after 4 to 6 weeks of therapy, but in some cases may require discontinuation of drug and/or surgical intervention.

Key Adverse Effects

- The common AEs within this medication class (excluding histrelin) include hot flushes/sweats, headache, depression/emotional lability, acne, decreased libido, insomnia, and weight gain.
- Injection site pain was one of the most commonly reported AEs for leuprolide. Implant site reaction, including discomfort, bruising, soreness, pain, tingling, itching, implant area protrusion or swelling, was reported in 51% of patients in clinical trials with histrelin.
- Infections such as bronchitis, gastroenteritis, influenza, nasopharyngitis, otitis externa, pharyngitis, sinusitis, and upper respiratory tract infection were observed with triptorelin.

- In clinical trials, OHSS has been reported in 2.4% of patients treated with ganirelix and in 3.5% of patients treated with cetrorelix.

Drug Interactions

- Concomitant use of elagolix with a strong OATP1B1 inhibitor (eg. cyclosporine and gemfibrozil) is contraindicated.
- Concomitant use of elagolix with strong cytochrome P450 (CYP) 3A inhibitors should be limited to ≤ 1 month for the 200 mg twice daily dose and ≤ 6 months for the 150 mg daily dose. The co-administration of elagolix with inducers of CYP3A may decrease elagolix plasma concentrations.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Cetrotide (cetrorelix)	0.25 mg injection	SC	3 mg one time dose or 0.25 mg once daily	Dose should be adjusted based on individual response.
ganirelix	250 mcg injection	SC	Once daily	Dose should be adjusted based on individual response.
Lupaneta Pack (leuprolide/ norethindrone)	3.75 mg leuprolide syringe/5 mg norethindrone tablets 11.25 mg leuprolide syringe/5 mg norethindrone tablets	IM	Endometriosis: Leuprolide 3.75 mg monthly or 11.25 mg once every 3 months for up to 6 months and norethindrone once daily for up to 6 months. Retreatment should be considered for up to another 6 months if endometriosis symptoms recur	Initial treatment course is limited to 6 months and use is not recommended longer than a total of 12 months due to concerns about adverse impact on BMD.
Lupron Depot (leuprolide acetate depot) 3.75 & 11.25 mg	Injection	IM	Endometriosis: 3.75 mg once monthly or 11.25 mg once every 3 months, alone or in combination with norethindrone acetate Uterine leiomyomata: 3.75 mg once monthly or one 11.25 mg injection with concomitant iron therapy; 11.25 mg is indicated only for women for whom 3 months of hormonal suppression is deemed necessary	Duration of therapy for endometriosis is 6 months; duration of therapy for uterine leiomyomata is up to 3 months.
Lupron Depot-Ped (leuprolide acetate depot) 7.5 mg, 11.25 mg, 15 mg (monthly) & 11.25, 30 mg (3-month)	Powder for injection	IM	CPP: Once monthly (7.5 mg, 11.25 mg, or 15 mg), or leuprolide 11.25 mg or 30 mg once every 3 months	The dose of Lupron Depot-Ped should be individualized for each patient. The dose should be increased to the next available dose if adequate hormonal and clinical suppression is not achieved

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				with the fixed dosing starting dose.
Orilissa (elagolix)	Tablets	Oral	Once daily for the 150 mg dose (duration = 24 months); twice daily for the 200 mg dose in patients with co-existing dyspareunia (duration = 6 months)	A lower dose and duration of therapy is required for patients with moderate hepatic impairment (Child-Pugh Class B); elagolix is contraindicated in patients with severe hepatic impairment (Child-Pugh C).
Supprelin LA (histrelin)	Implant	SC	CPP: Once every 12 months	Implant injected in the inner aspect of the upper arm.
Synarel (nafarelin)	Nasal spray	Intranasal	CPP: Twice daily (up to 3 times daily when a dose increase is required) Endometriosis: Twice daily	Sneezing during or immediately after treatment should be avoided, as this may impair drug absorption. For the endometriosis indication, treatment should be started between days 2 and 4 of the menstrual cycle.
Triptodur (triptorelin)	Injection	IM	CPP: Once every 24 weeks	Response (LH levels or serum concentration of sex steroid levels) should be monitored beginning 1 to 2 months post therapy initiation and during therapy as necessary to confirm maintenance of efficacy.
Zoladex (goserelin)	3.6 mg implant	SC	Endometriosis: Once every 28 days for a total of 6 months Endometrial thinning: Once every 28 days for a total of 1 to 2 months	No adjustment necessary in renal or hepatic impairment. For the endometriosis indication, data are limited to patients ≥ 18 years of age treated for 6 months. Retreatment is not recommended.

Abbreviations: BMD = bone mineral density; CPP = central precocious puberty; IM = intramuscular; LH = luteinizing hormone; SC = subcutaneous

See the current prescribing information for full details

CONCLUSION

- CPP is characterized by the early onset of pubertal manifestations in girls and boys.
  - GnRH agonists are the treatment of choice for CPP. Chronic administration of potent GnRH agonists causes down-regulation of pituitary GnRH receptors, suppression of gonadotropin (LH and FSH) secretion and finally suppression of the release of gonadal sex hormones.
  - There are several FDA-approved GnRH agonists available in the form of implants, depot injections, and nasal spray. Depot formulations are generally preferred due to improved compliance. These GnRH agonists have not been directly compared in randomized trials, but appear to be similarly effective in suppressing the pituitary-gonadal axis.

- According to the AAP 2016 guidelines on the evaluation and referral of children with signs of early puberty, treatment with GnRH agonists such as leuprolide can be administered via injection at monthly or 3-month intervals or with annual insertion of SC histrelin implant. Therapy should be continued until the physician determines that continued pubertal suppression is no longer beneficial to the child.

- Endometriosis is a common gynecological condition characterized by deposits of endometrial tissue outside the endometrial cavity, such as the liver, diaphragm, umbilicus, and pleural cavity.
  - A Cochrane Review meta-analysis of 41 trials (N = 4935) in patients with endometriosis found no statistically significant difference between GnRH agonists and danazol for dysmenorrhea associated with endometriosis. However, a benefit in overall resolution for GnRH agonists compared with danazol was observed. Additionally, there was no statistically significant difference in overall pain between GnRH agonists and levonorgestrel. No route of administration for GnRH appeared to be superior to another.
  - The safety and efficacy of Orilissa (elagolix), a recently approved oral GnRH antagonist, were demonstrated in 2 placebo-controlled studies in 1686 premenopausal women with moderate to severe endometriosis pain. In both studies, a higher proportion of women treated with elagolix were responders vs placebo for dysmenorrhea and NMPP in a dose-dependent manner at month 3 ($p \leq 0.001$ for all comparisons except non-menstrual pelvic pain with elagolix 150 mg once daily in study 2, $p \leq 0.01$).
  - ACOG's 2010 endometriosis guidelines recommend progestins, danazol, extended-cycle combined oral contraceptives, NSAIDs, and GnRH agonists for the initial treatment of pain in women with suspected endometriosis. GnRH agonists can be used empirically in case of recurrence of endometriosis.
  - The 2014 ASRM guidelines recommend a definitive diagnosis via laparoscopic surgery, with the option of treating visible endometriosis at that time. Pharmacologic therapies such as NSAIDs, combined hormonal contraceptives, progestins, danazol, and GnRH agonists are recommended for the treatment of endometriosis.
- Although curative treatment of uterine fibroids relies on surgical therapies, medical treatments are considered first-line to preserve fertility and avoid or delay surgery. Lupron Depot 3.75 mg is the only GnRH agonist that has been FDA-approved for the preoperative hematologic improvement of patients with anemia caused by uterine leiomyomata.
  - AHRQ's 2017 guidelines for the management of uterine fibroids recommend GnRH agonists to reduce fibroid size and improve symptoms (moderate-strength evidence). Fibroid-related quality of life may also improve with GnRH agonists (low-strength evidence).
- Infertility is a common condition that can have a substantially negative emotional, physical, and financial impact on a couple. GnRH antagonists, such as cetrorelix and ganirelix, may be reserved for second-line treatment to prevent premature LH surges, allowing for controlled ovarian stimulation during ART procedures.
  - The 2018 ASRM guidelines for PCOS and 2016 WHO-funded PCOS guidelines recommend letrozole (off-label) or clomiphene for first-line therapy in women with PCOS who have anovulatory infertility. Gonadotropins are recommended as an option in anovulatory women with PCOS who have failed clomiphene (± metformin).

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OPTUMRx®

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

Therapeutic Class Overview
Multiple Sclerosis Agents

INTRODUCTION

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

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

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

Table 1. Medications Included Within Class Review[§]

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

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

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

INDICATIONS

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

Table 2. Food and Drug Administration Approved Indications

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

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

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

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

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

CLINICAL EFFICACY SUMMARY

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

Interferons and glatiramer acetate

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

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

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

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

Gilenya (fingolimod)

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

Aubagio (teriflunomide)

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

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

Tecfidera (dimethyl fumarate)

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

Bafiertam (monomethyl fumarate)

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

Tysabri (natalizumab)

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

Lemtrada (alemtuzumab)

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

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

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

Ocrevus (ocrelizumab)

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Mayzent (siponimod)

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

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

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

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

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

Mavenclad (cladribine)

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

Vumerity (diroximel fumarate)

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

Zeposia (ozanimod)

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

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

Symptomatic MS

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

Clinically Isolated Syndrome (CIS)

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

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

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

Progressive MS

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

Timing of DMT initiation

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

Decisions to discontinue DMTs in MS

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

Meta-Analyses

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

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

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

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

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

CLINICAL GUIDELINES

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

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

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

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

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

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

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

SAFETY SUMMARY

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

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

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

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

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

Table 3. Dosing and Administration*

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

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

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

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

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

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

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

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

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

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

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

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

CONCLUSION

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

progression *(Kappos et al 2010)*. In a trial comparing fingolimod to IFNβ-1a IM (Avonex), fingolimod-treated patients had a decreased ARR and improved MRI outcomes, but disability progression was similar in the 2 groups *(Cohen et al, 2010)*. The adverse event profile for fingolimod includes cardiovascular risks including bradycardia. First dose administration of fingolimod requires at least 6 hours of observation with hourly monitoring of heart rate and blood pressure, and patients should have an ECG before dosing and at the end of the observation period.
    - Fingolimod is also FDA-approved for MS in the pediatric population. In a trial evaluating patients between 10 and 17 years of age, fingolimod significantly reduced ARR and the rate of new or newly enlarged lesions compared to IFNβ-1a (*Chitnis et al 2018*).
- Mayzent (siponimod) is a sphingosine 1-phosphate receptor modulator, similar to fingolimod. In a trial comparing Mayzent to placebo, Mayzent significantly reduced the risk of 3-month CDP, delayed the risk of 6-month CDP, and reduced the ARR (*Kappos et al 2018*). First dose cardiac monitoring is recommended for patients with a heart rate < 55 bpm or a history of cardiac disease. Siponimod shares many of the same warnings as fingolimod.
- Zeposia (ozanimod) is another sphingosine 1-phosphate receptor modulator that was approved by the FDA in March 2020. Clinical trials have shown ozanimod to significantly decrease ARR compared to IFNβ-1a; however, unlike other drugs in this class it does not require first dose cardiac monitoring (*Comi 2019, Cohen 2019*).
- Tecfidera (dimethyl fumarate) has efficacy similar to that of fingolimod; its benefit-risk profile makes it a reasonable initial or later stage DMT option for most patients with RRMS *(CADTH 2013, Wingerchuk et al 2014)*. Gastrointestinal intolerance and flushing are common side effects that may wane with time; slow titration to maintenance doses, taking the medication with food, and premedication with aspirin may reduce their severity.
- Vumerity (diroximel fumarate) is a recently approved oral agent for MS and is rapidly converted to monomethyl fumarate, which is also the active metabolite of Tecfidera (dimethyl fumarate). Diroximel fumarate may offer improved GI tolerability as compared to dimethyl fumarate (*Naismith et al 2019, Selmaj et al 2019).*
- Bafiertam (monomethyl fumarate) was approved by the FDA in April 2020 and is considered to be a “bioequivalent alternative” to dimethyl fumarate (*Drugs@FDA 2020*).
- Aubagio (teriflunomide) inhibits dihydroorotate dehydrogenase, a mitochondrial enzyme involved in de novo pyrimidine synthesis. Although its exact mechanism of action is unknown, it may involve a reduction in the number of activated lymphocytes in the CNS. Patients treated with teriflunomide in a clinical trial experienced a reduction in the ARR and improved MRI outcomes compared to placebo. Patients in the higher dose group (14 mg) also had a lower likelihood of disability progression, but this difference was not statistically significant in the lower dose group (7 mg) as compared to placebo *(O’Connor et al, 2011)*. Teriflunomide has boxed warnings for the possibility of severe liver injury and teratogenicity. The most common adverse reactions include increases in ALT, alopecia, diarrhea, influenza, nausea, and paresthesia.
- Mavenclad (cladribine) is a purine antimetabolite indicated for the treatment of relapsing forms of MS, to include relapsing-remitting disease and active secondary progressive disease. In a trial comparing Mavenclad to placebo, both Mavenclad 3.5 mg/kg and 5.25 mg/kg treatment groups had reduced ARRs and disability progression vs placebo (*Giovannoni et al 2010*). Mavenclad carries a boxed warning for risk of malignancies and teratogenicity. Lymphopenia is the most common adverse effect.
- Tysabri (natalizumab) is a recombinant monoclonal antibody indicated for the treatment of relapsing forms of MS and is also approved for use in the treatment of moderately to severely active CD in patients with an inadequate response to or who are unable to tolerate conventional CD therapies and TNF inhibitors.
    - In a 2011 systematic review of trials evaluating natalizumab for RRMS, pooled efficacy data from 2 RCTs (AFFIRM and SENTINEL) showed that natalizumab significantly reduced the risk for having a relapse during 2 years of treatment. In addition, natalizumab significantly reduced the risk for experiencing 12-week CDP at 2 years (RR, 0.74, 95% CI: 0.62 to 0.89) *(Pucci et al 2011)*. Natalizumab has been associated with an increased risk of PML; however, the overall incidence of PML has remained low (0.4%). Natalizumab can only be obtained through a restricted distribution program.
- Lemtrada (alemtuzumab) is a highly efficacious DMT that has demonstrated superiority in reducing relapses when compared to Rebif in both treatment-naïve and treatment-experienced patients. The dosing schedule of 2 annual treatment courses is counterbalanced by the need for regular monitoring of the increased risk for autoimmunity. Lemtrada is best reserved for patients who have failed at least 2 other DMTs and are not candidates for natalizumab (*Garnock-Jones 2014*).
- Ocrevus (ocrelizumab) is a recombinant monoclonal antibody designed to selectively target CD20-positive B cells. As a humanized form of Rituxan (rituximab), ocrelizumab is expected to be less immunogenic with repeated infusions and may have a more favorable benefit-to-risk profile than Rituxan *(Sorensen et al 2016)*.

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

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Therapeutic Class Overview
Anticonvulsants

INTRODUCTION

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

- When possible, monotherapy with a single AED is the preferred treatment approach. Combination therapy may be associated with decreased patient adherence to therapy and an increased incidence of AEs and drug interactions. When combination therapy is needed, it is recommended to select products with different mechanisms of action and AE profiles. There is little comparative clinical data to support the use of specific combinations (*Schachter 2019*).
- Several broad classes of AEDs are available, including barbiturates, benzodiazepines, hydantoins, and miscellaneous agents (see Table 1).
- Cannabidiol (Epidiolex) was FDA-approved in June 2018 for use in pediatric patients 2 years of age and older with LGS or Dravet syndrome (*FDA news release 2018*). It was the first FDA-approved drug for treatment of patients with Dravet syndrome and the first approved drug that contains a purified substance, cannabidiol, derived from marijuana. In July 2020, cannabidiol was FDA-approved for the treatment of seizures associated with tuberous sclerosis complex (TSC) in pediatric patients 1 year of age and older (*Epidiolex prescribing information 2020, FDA news release 2020)*. The age range for the indications of treatment of seizures associated with LGS or Dravet syndrome was also expanded to include pediatric patients 1 year of age and older (*Epidiolex prescribing information 2020)*. Initially designated as a schedule V controlled substance, cannabidiol has been descheduled and is no longer classified as a controlled substance.
- Stiripentol (Diacomit) capsules and powder for oral suspension were FDA-approved in August 2018 for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam. In June 2020, fenfluramine oral solution (Fintepla) was approved for the same indication without the requirement for concomitant clobazam (*Fintepla prescribing information 2020*).
- Everolimus tablets for oral suspension (Afinitor Disperz) received an expanded indication in April 2018 for use in partial-onset seizures associated with TSC. This product is a kinase inhibitor that also has several oncology indications.
- Midazolam nasal spray (Nayzilam) was approved in May 2019 for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 12 years of age (*Nayzilam prescribing information 2019*). In January 2020, diazepam nasal spray (Valtoco) was approved for the same indication in patients as young as 6 years of age (*Valtoco prescribing information 2020*).
- Several of the AEDs are used for additional indications beyond the management of epilepsy, including (but not limited to) bipolar disorder, migraine prophylaxis, and several types of neuropathic pain. These additional indications are listed in Table 2; however, this review primarily focuses on the use of AEDs for the management of epilepsy. Additionally, brands and formulations FDA-approved and marketed only for non-epilepsy indications are not included within this review; these include gabapentin tablets (Gralise), FDA-approved only for the management of postherpetic neuralgia, gabapentin enacarbil extended-release tablets (Horizant), FDA-approved only for management of postherpetic neuralgia and treatment of moderate-to-severe restless leg syndrome, and pregabalin extended-release tablets (Lyrica CR), FDA-approved only for the management of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia.
- Medispan class: Antianxiety agents, benzodiazepines; Anticonvulsants, AMPA glutamate receptor antagonists; Anticonvulsants, anticonvulsants – misc; Anticonvulsants, carbamates; Anticonvulsants, GABA modulators; Anticonvulsants, hydantoins; Anticonvulsants, succinimides; Anticonvulsants, valproic acid; Hypnotics/Sedatives/Sleep Disorder Agents, barbiturate hypnotics

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Barbiturates	
Pentobarbital (Nembutal)	✔
Phenobarbital* (Luminal†, Solfoton†)	✔
Primidone (Mysoline)	✔
Benzodiazepines	
Clobazam (Onfi; Sympazan)	✔ ***
Clonazepam (Klonopin§)	✔
Clorazepate (Tranxene T-Tab§)	✔
Diazepam (Diastat¶, Valium,§ Valtoco)	✔ ‖
Midazolam (Nayzilam)	-
Hydantoins	
Ethotoin (Peganone)	-

Drug	Generic Availability
Fosphenytoin (Cerebyx)	✔
Phenytoin (Dilantin§, Phenytek)	✔ ‖
Miscellaneous	
Brivaracetam (Briviact)	-
Cenobamate (Xcopri)	-
Cannabidiol (Epidiolex)	-
Carbamazepine (Carbatrol, Epitol**, Equetro, Tegretol§, Tegretol-XR)	✔
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	✔
Eslicarbazepine (Aptiom)	-
Ethosuximide (Zarontin)	✔
Everolimus (Afinitor Disperz)	-
Felbamate (Felbatol)	✔
Fenfluramine (Fintepla)	-
Gabapentin (Neurontin)	✔
Lacosamide (Vimpat)	-
Lamotrigine (Lamictal, Lamictal ODT, Lamictal XR, Subvenite**)	✔
Levetiracetam (Keppra, Keppra XR, Roweepra**, Roweepra XR**, Spritam, Elepsia XR)	✔ ‖
Methsuximide (Celontin)	-
Oxcarbazepine (Oxtellar XR, Trileptal)	✔ ‖
Perampanel (Fycompa)	-
Pregabalin (Lyrica)	✔
Rufinamide (Banzel)	- ¶¶
Stiripentol (Diacomit)	-
Tiagabine (Gabitril)	✔
Topiramate (Topamax, Topamax Sprinkle, Topiragen††, Trokendi XR, Qudexy XR¶)	✔ ‖
Valproic acid/valproate sodium (Depacon†, Depakene†)	✔
Vigabatrin (Sabril, Vigadrone**)	✔ ‖
Zonisamide (Zonegran§)	✔

* Not FDA approved
† Brand product not currently marketed; generic is available
§ Brand marketing status may vary by strength and/or formulation
‖ Generic availability may vary by strength and/or formulation
¶ Authorized generic available; no A-rated generics approved via abbreviated new drug application
** Branded generic
†† Branded generic; not currently marketed
***Generic available for Onfi tablets and oral suspension; only brand name available for Sympazan oral film
¶¶ Generic product has been FDA-approved, but not currently marketed

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

INDICATIONS

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

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

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

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

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

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

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

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

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

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

- Brivaracetam:
  - Treatment of partial-onset seizures in patients ≥ 4 years of age (oral formulations); ≥ 16 years of age (IV formulation)
- Cannabidiol:
  - Treatment of seizures associated with LGS, Dravet syndrome, or TSC in patients ≥ 1 year of age
- Carbamazepine:
  - Partial seizures with complex symptomatology (psychomotor, temporal lobe); patients with these seizures appear to show greater improvement than those with other types; generalized tonic-clonic seizures (grand mal); mixed seizure patterns which include the above, or other partial or generalized seizures
  - Absence seizures (petit mal) do not appear to be controlled; carbamazepine has been associated with increased frequency of generalized convulsions in these patients
  - Treatment of pain associated with true trigeminal neuralgia; beneficial results also reported in glossopharyngeal neuralgia
  - Bipolar indication is for an extended-release capsule formulation (Equetro) only: treatment of patients with acute manic or mixed episodes associated with bipolar I disorder
- Cenobamate:
  - Partial-onset seizures in adult patients
- Clobazam:
  - Seizures associated with LGS in patients ≥ 2 years of age
- Clonazepam:
  - In patients with absence seizures who have failed to respond to succinimides, clonazepam may be useful
- Diazepam:
  - Oral diazepam may be used adjunctively in convulsive disorders; it has not proved useful as sole therapy.
  - Rectal diazepam is indicated in the management of selected, refractory patients with epilepsy on stable regimens of AEDs who require intermittent use of diazepam to control bouts of increased seizure activity
  - Injectable diazepam is a useful adjunct in status epilepticus and severe recurrent convulsive seizures
  - Diazepam nasal spray is indicated for the acute treatment of intermittent, stereotypic episodes of frequent seizure activity (ie, seizure clusters, acute repetitive seizures) that are distinct from a patient's usual seizure pattern in patients with epilepsy ≥ 6 years of age
- Divalproex sodium:

- Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures (≥ 10 years of age for all formulations)
- Monotherapy and adjunctive therapy in the treatment of simple and complex absence seizures (≥ 10 years of age for extended-release tablets; age not specified for tablets/sprinkle capsules)
- The tablets and extended-release tablets have indications in bipolar disorder and migraine prophylaxis; the sprinkle capsule formulation does not. For bipolar disorder, safety and effectiveness for long-term use (> 3 weeks) has not been demonstrated in controlled clinical trials. Bipolar disorder indications are as follows:
  - Treatment of the manic episodes associated with bipolar disorder (tablets)
  - Treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic features (extended-release tablets)

- Eslicarbazepine:
  - Treatment of partial-onset seizures in patients ≥ 4 years of age
- Ethotoin:
  - Complex partial (psychomotor) seizures
- Everolimus:
  - Adjunctive treatment of adult and pediatric patients ≥ 2 years of age with TSC-associated partial-onset seizures (tablets for oral suspension only)
- Felbamate:
  - Not first-line; recommended only in patients who respond inadequately to alternative treatments and whose epilepsy is so severe that a substantial risk of aplastic anemia and/or renal failure is deemed acceptable
  - Monotherapy or adjunctive therapy in the treatment of partial seizures, with and without generalization, in adults with epilepsy
  - Adjunctive therapy of partial and generalized seizures associated with LGS in children (age not specified)
- Fenfluramine:
  - Treatment of seizures associated with Dravet syndrome in patients ≥ 2 years of age
- Fosphenytoin:
  - Treatment of generalized tonic-clonic status epilepticus
  - Prevention and treatment of seizures occurring during neurosurgery
  - Can be substituted short-term for oral phenytoin when oral phenytoin administration is not possible
- Gabapentin:
  - Adjunctive therapy in the treatment of partial-onset seizures, with and without secondary generalization, in adults and pediatric patients ≥ 3 years of age with epilepsy.
  - Management of postherpetic neuralgia in adults
- Lacosamide:
  - Treatment of partial-onset seizures in patients ≥ 4 years of age (tablet and oral solution)
  - Treatment of partial-onset seizures in patients ≥ 17 years of age (injection)
- Lamotrigine immediate-release formulations:
  - Age ≥ 2 years for adjunctive therapy for partial-onset seizures, primary generalized tonic-clonic seizures, and generalized seizures of LGS
  - Age ≥ 16 years for conversion to monotherapy in patients with partial-onset seizures who are receiving treatment with carbamazepine, phenytoin, phenobarbital, primidone, or valproate as the single AED
  - Maintenance treatment of bipolar disorder to delay the time to occurrence of mood episodes in patients treated for acute mood episodes with standard therapy (treatment of acute manic or mixed episodes is not recommended)
- Lamotrigine extended-release tablets:
  - Age ≥ 13 years for adjunctive therapy for primary generalized tonic-clonic seizures and partial-onset seizures with or without secondary generalization, and age ≥13 years for conversion to monotherapy in patients with partial-onset seizures who are receiving treatment with a single AED
  - The extended-release formulation is not FDA-approved for bipolar disorder
- Levetiracetam:
  - Tablets, oral solution, injection, and tablets for oral suspension:
    - Treatment of partial-onset seizures in patients ≥ 1 month of age (tablets, oral solution, and injection [Keppra]); adjunctive treatment for partial-onset seizures in patients ≥ 4 years of age and weighing > 20 kg (tablets for oral suspension [Spritam])

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

- Initial monotherapy in patients with partial-onset or primary generalized tonic-clonic seizures (age ≥ 2 years for tablets, immediate-release sprinkle capsules, and Qudexy XR extended-release capsules; age ≥ 6 years for Trokendi XR extended-release capsules)
- Adjunctive therapy for adults and pediatric patients with partial-onset seizures or primary generalized tonic-clonic seizures and in patients with seizures associated with LGS (age ≥ 2 years for tablets, immediate-release sprinkle capsules, and Qudexy XR extended-release capsules; age ≥ 6 years for Trokendi XR extended-release capsules)
- Prophylaxis of migraine headache in patients ≥ 12 years of age

- Valproic acid/valproate sodium:
  - Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures; sole and adjunctive therapy in the treatment of simple and complex absence seizures, and adjunctively in patients with multiple seizure types which include absence seizures
- Vigabatrin:
  - Adjunctive therapy for patients ≥ 2 years of age with refractory complex partial seizures who have responded inadequately to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss
  - Monotherapy for patients with infantile spasms 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss
- Zonisamide:
  - Adjunctive therapy in the treatment of partial seizures in adults with epilepsy

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

CLINICAL EFFICACY SUMMARY

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

- As initial monotherapy for adults with newly diagnosed or untreated generalized-onset tonic-clonic seizures:
  - Carbamazepine, lamotrigine, oxcarbazepine, phenobarbital, phenytoin, topiramate, and valproate are possibly efficacious/effective.
  - Gabapentin, levetiracetam, and vigabatrin are potentially efficacious/effective.
  - Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.
- For children with newly diagnosed or untreated generalized-onset tonic-clonic seizures:
  - Carbamazepine, phenobarbital, phenytoin, topiramate, and valproate are possibly efficacious/effective.
  - Oxcarbazepine is potentially efficacious/effective.
  - Carbamazepine and phenytoin may precipitate or aggravate generalized-onset tonic-clonic seizures.
- As initial monotherapy for children with newly diagnosed or untreated absence seizures:
  - Ethosuximide and valproate are established as efficacious/effective.
  - Lamotrigine is possibly efficacious/effective.
  - Gabapentin is established as inefficacious/ineffective.
  - Carbamazepine, oxcarbazepine, phenobarbital, phenytoin, tiagabine, and vigabatrin may precipitate or aggravate absence seizures (based on scattered reports).
- As initial monotherapy for children with benign childhood epilepsy with centrotemporal spikes (BECTS):
  - Carbamazepine and valproate are possibly efficacious/effective.
  - Gabapentin, levetiracetam, oxcarbazepine, and sulthiame (not available in the United States) are potentially efficacious/effective.
- For patients with newly diagnosed JME:
  - Topiramate and valproate are potentially efficacious/effective.
  - Carbamazepine, gabapentin, oxcarbazepine, phenytoin, tiagabine, and vigabatrin may precipitate or aggravate absence, myoclonic, and in some cases generalized tonic-clonic seizures. There has also been a report that lamotrigine may exacerbate seizures in JME.
- There is a lack of well-designed randomized trials in epilepsy, particularly for generalized seizures and in the pediatric population.

- A Cochrane systematic review evaluated the efficacy of AED monotherapy for epilepsy (*Nevitt et al 2017*). The review included the use of carbamazepine, phenytoin, valproate, phenobarbital, oxcarbazepine, lamotrigine, gabapentin, topiramate, levetiracetam, and zonisamide for the treatment of partial-onset seizures (simple partial, complex partial or secondarily generalized) or generalized tonic-clonic seizures with or without other generalized seizure types.
  - This network meta-analysis showed that for the primary outcome, the time to withdrawal of allocated treatment:
    - For individuals with partial seizures, levetiracetam performed better than carbamazepine and lamotrigine; lamotrigine performed better than all other treatments (aside from levetiracetam); and carbamazepine performed better than gabapentin and phenobarbital.
    - For individuals with generalized onset seizures, valproate performed better than carbamazepine, topiramate and phenobarbital.
    - For both partial and generalized onset seizures, phenobarbital seems to perform worse than all other treatments.
  - For the secondary outcome, time to first seizure:
    - For individuals with partial seizures, phenobarbital performed better than both carbamazepine and lamotrigine; carbamazepine performed better than valproate, gabapentin, and lamotrigine; and phenytoin performed better than lamotrigine.
    - For both partial and generalized seizure types, phenytoin and phenobarbital generally performed better than other treatments.
  - Few notable differences were shown for either partial or generalized seizure types for the secondary outcomes of time to 6-month or 12-month remission of seizures.
  - Overall, direct evidence and network meta-analysis estimates were numerically similar, and effect sizes had overlapping confidence intervals.
  - Data for individuals with generalized seizures are still limited and additional randomized trials are needed.
- The relative efficacy among valproate, lamotrigine, phenytoin, carbamazepine, ethosuximide, topiramate, levetiracetam, and phenobarbital as monotherapy for generalized (n = 7 studies) or absence seizures (n = 3 studies) was evaluated in a systematic review and network meta-analysis (*Campos et al 2018*). The outcomes analyzed were seizure freedom and withdrawal due to inefficacy. Compared to valproate, phenytoin had a lower odds of seizure freedom (odds ratio, 0.50;

95% credible Interval [CrI] 0.27 to 0.87) in patients with generalized tonic-clonic seizures. Lamotrigine had the highest probability of seizure freedom and valproate had the highest probability of withdrawal due to inefficacy in these patients. For absence seizures, ethosuximide and valproate were found to have a higher probability of seizure freedom compared to lamotrigine.

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

Cannabidiol, along with use of other agents, demonstrated a significant reduction in seizure frequency compared to placebo (*Thiele et al 2018*; *Devinsky et al 2018; Devinsky et al 2017*). In July 2020, cannabidiol was FDA-approved for a third indication, treatment of seizures associated with TSC, and the age range for all 3 indications was aligned to include pediatric patients 1 year of age and older (*FDA news release 2020, Epidiolex prescribing information 2020)*. In a placebo-controlled trial of 224 patients with TSC and seizures inadequately controlled with ≥ 1 concomitant AED, cannabidiol resulted in a significant reduction in seizure frequency compared to placebo (*Epidiolex prescribing information 2020*). To date, no comparative trials have been published.

- Everolimus tablets for oral suspension (Afinitor Disperz) received an expanded indication for adjunctive use in TSC-associated partial-onset seizures in April 2018. Results of a randomized, double-blind, placebo-controlled study of 366 patients with inadequately controlled seizures on 2 or more AEDs demonstrated a significant reduction in seizure frequency compared to placebo (*French et al 2016*).
- In August 2018, the FDA approved a second drug, stiripentol (Diacomit), for use in the treatment of seizures associated with Dravet syndrome. Two multicenter placebo-controlled studies evaluated the addition of stiripentol to clobazam and valproate therapy in patients 3 years to less than 18 years of age with Dravet syndrome. Responder rates (seizure frequency reduced by 50%) with respect to generalized tonic-clonic seizures were significantly lower with stiripentol compared to placebo (*Diacomit prescribing information 2018).*
- In May 2019, a nasal spray formulation of midazolam (Nayzilam) was approved for the acute treatment of cluster seizures in adults and adolescents. In one randomized controlled trial in patients with seizure clusters while receiving a stable AED regimen, the proportion of patients who experienced treatment success (seizure termination within 10 minutes and no recurrence for the next 6 hours) was significantly higher with midazolam nasal spray compared to placebo (53.7% vs 34.4%, p = 0.0109) with similar tolerability (*Detyniecki et al 2019*).
- Cenobamate was approved in late 2019 and its efficacy has yet to be compared to other AEDs. The approval of this agent was based on 2 multicenter, randomized, double-blind, placebo-controlled studies that enrolled 655 adults with partial-onset seizures with or without generalization who were not adequately controlled with 1 to 3 other AEDs. The results of these trials demonstrated that cenobamate significantly reduced the frequency of seizures occurring in a 28-day period. In the first trial, the median percent change in seizure frequency from baseline was -55.6% with cenobamate and -21.5% with placebo. In the second trial, the median percent change ranged from -36.3% to -55.3% with cenobamate and was -24.3% with placebo (*Xcopri package insert 2019, Krauss et al 2020*).
- In June 2020, the FDA approved a third drug, fenfluramine (Fintepla), for use in the treatment of seizures associated with Dravet syndrome. Two randomized, double-blind, placebo-controlled studies evaluated fenfluramine in patients 2 to 18 years of age with Dravet syndrome who were inadequately controlled with 1 to 4 other AEDs. In both trials, fenfluramine significantly reduced the frequency of convulsive seizures occurring in a 28-day period as compared to placebo. In the first trial, in patients not receiving stiripentol, fenfluramine at a dose of 0.7 mg/kg/day demonstrated a 62.3% greater reduction in mean monthly convulsive seizure frequency (MCSF) over 14 weeks compared with placebo. In the second trial, in patients who were receiving a stiripentol-inclusive AED regimen, fenfluramine at a dose of 0.4 mg/kg/day showed a 54% greater reduction in MCSF over 15 weeks compared with placebo (*Fintepla package insert 2020, Lagae et al 2020, Nabbout et al 2019*).
- A 2019 randomized controlled trial of children and adults with benzodiazepine-refractory convulsive status epilepticus compared the efficacy of intravenous levetiracetam (n = 145 patients), fosphenytoin (n = 118), or valproate (n = 121) in this setting. Results demonstrated that each agent led to seizure cessation and improved alertness by 1 hour in approximately 50% of patients, with no significant differences between groups (*Kapur et al 2019*).
- A meta-analysis of 9 randomized controlled trials evaluated the efficacy and safety of levetiracetam vs phenytoin as second-line treatment for benzodiazepine-resistant status epilepticus in children and adults. The efficacy outcomes included seizure cessation and seizure recurrence within 24 hours. The authors did not find a significant difference in efficacy between levetiracetam and phenytoin in the overall population or in the subgroup analysis of pediatric patients. AEs were similar across both groups except for a higher incidence of cardiac instability, reported mainly as hypotension, in the phenytoin group (*DeMott et al 2020).*

CLINICAL GUIDELINES

- **Efficacy and tolerability of the new antiepileptic drugs I: treatment of new-onset epilepsy**. American Academy of Neurology and American Epilepsy Society (*French et al 2004A, Kanner et al, 2018A*).
  - A 2018 update to the 2004 guideline focuses on treatment of new-onset epilepsy with second and third generation AEDs. The 2004 publication summarizes the efficacy, tolerability, and safety of gabapentin, lamotrigine, topiramate,

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

        - Ezogabine (no longer marketed) use should be considered to reduce seizure frequency, but carries a serious risk of skin and retinal discoloration.
        - Clobazam and extended-release oxcarbazepine may be considered to decrease seizure frequency.
    - As monotherapy in patients with TRAFE:
        - Eslicarbazepine use may be considered to decrease seizure frequency.
        - Data are insufficient to recommend use of second- and the other third-generation AEDs.
    - For add-on therapy for generalized epilepsy, immediate-release and extended-release lamotrigine should be considered as add-on therapy to decrease seizure frequency in adults with treatment-resistant generalized tonic-clonic seizures secondary to generalized epilepsy. Levetiracetam use should be considered to decrease seizure frequency as add-on therapy for treatment-resistant generalized tonic-clonic seizures and for treatment-resistant juvenile myoclonic epilepsy.
    - Rufinamide is effective to reduce seizure frequency as add-on therapy for LGS. Clobazam use should be considered as add-on therapy for LGS.
    - For add-on therapy in pediatric patients with treatment-resistant focal epilepsy:
        - Levetiracetam use should be considered to decrease seizure frequency (ages 1 month to 16 years).
        - Zonisamide use should be considered to decrease seizure frequency (age 6 to 17 years).
        - Oxcarbazepine use should be considered to decrease seizure frequency (age 1 month to 4 years).
        - Data are unavailable on the efficacy of clobazam, eslicarbazepine, lacosamide, perampanel, rufinamide, tiagabine, or vigabatrin.
    - The guideline does not address newly approved agents including cannabidiol, everolimus, or stiripentol.
- **Evidence-based guideline: management of an unprovoked first seizure in adults.** Guideline Development Subcommittee of the American Academy of Neurology and the American Epilepsy Society (*Krumholz et al 2015; reaffirmed in 2018*).
    - This practice guideline makes recommendations based on a consideration of the evidence for prognosis and treatment of adults with an unprovoked first seizure.
    - Recommendations include the following:
        - Adults presenting with an unprovoked first seizure should be informed that the chance for a recurrent seizure is greatest within the first 2 years after a first seizure (21% to 45%).
        - Clinicians should also advise such patients that clinical factors associated with an increased risk of seizure recurrence include a prior brain insult such as a stroke or trauma, an EEG with epileptiform abnormalities, a significant brain-imaging abnormality, or a nocturnal seizure.
        - Clinicians should advise patients that, although immediate AED therapy, as compared with delay of treatment pending a second seizure, is likely to reduce the risk of a seizure recurrence in the 2 years subsequent to a first seizure, it may not improve quality of life.
        - Clinicians should advise patients that over the longer term (> 3 years), immediate AED treatment is unlikely to improve the prognosis for sustained seizure remission.
        - Patients should be advised that their risk for AED AEs ranges from 7% to 31% and that these AEs are predominantly mild and reversible.
    - Immediate AED therapy after an unprovoked first seizure is likely to reduce seizure recurrence risk. A reduction in risk may be important, particularly for adults, for whom seizure recurrences may cause serious psychological and social consequences such as loss of driving privileges and limitations on employment. However, immediate AED treatment is not well accepted and is debated. Decisions should be based on weighing the risk of recurrence against the AEs of AED therapy, and should take patient preferences into account.
    - It is accepted that when a patient has a second or additional seizures, an AED should be initiated because the risk of subsequent seizures is very high.
- **Evidence-based guideline: treatment of convulsive status epilepticus in children and adults.** Guideline Committee of the American Epilepsy Society (*Glauser et al 2016*).
    - This publication provides conclusions and a treatment algorithm based on a structured literature review of randomized trials of anticonvulsant treatments for seizures lasting longer than 5 minutes. A total of 38 trials were included.
    - For treatment in the adult population, conclusions included the following:
        - Intramuscular (IM) midazolam, intravenous (IV) lorazepam, IV diazepam (with or without phenytoin), and IV phenobarbital are established as efficacious at stopping seizures lasting at least 5 minutes.
        - IV lorazepam is more effective than IV phenytoin in stopping seizures lasting at least 10 minutes.

        - There is no difference in efficacy between IV lorazepam followed by IV phenytoin, IV diazepam plus phenytoin followed by IV lorazepam, and IV phenobarbital followed by IV phenytoin.
        - IV valproic acid has similar efficacy to IV phenytoin or continuous IV diazepam as second therapy after failure of a benzodiazepine.
        - Insufficient data exist in adults about the efficacy of levetiracetam as either initial or second therapy.
        - In adults with status epilepticus without established IV access, IM midazolam is established as more effective compared with IV lorazepam.
        - No significant difference in effectiveness has been demonstrated between lorazepam and diazepam in adults with status epilepticus.
    - For treatment in the pediatric population, conclusions included the following:
        - IV lorazepam and IV diazepam are established as efficacious at stopping seizures lasting at least 5 minutes.
        - Rectal diazepam, IM midazolam, intranasal midazolam, and buccal midazolam are probably effective at stopping seizures lasting at least 5 minutes.
        - Insufficient data exist in children about the efficacy of intranasal lorazepam, sublingual lorazepam, rectal lorazepam, valproic acid, levetiracetam, phenobarbital, and phenytoin as initial therapy.
        - IV valproic acid has similar efficacy but better tolerability than IV phenobarbital as second therapy after failure of a benzodiazepine.
        - Insufficient data exist in children regarding the efficacy of phenytoin or levetiracetam as second therapy after failure of a benzodiazepine.
        - In children with status epilepticus, no significant difference in effectiveness has been established between IV lorazepam and IV diazepam.
        - In children with status epilepticus, non-IV midazolam (IM/intranasal/buccal) is probably more effective than diazepam (IV/rectal).
    - Conclusions included the following (age not specified):
        - Insufficient data exist about the comparative efficacy of phenytoin and fosphenytoin. Fosphenytoin is better tolerated compared with phenytoin. When both are available, fosphenytoin is preferred based on tolerability, but phenytoin is an acceptable alternative.
    - The overall treatment algorithm directs that:
        - A benzodiazepine (IM midazolam, IV lorazepam, or IV diazepam) is recommended as the initial therapy of choice in the first phase of treatment (5 to 20 minutes after the beginning of the seizure). Although IV phenobarbital is established as efficacious and well tolerated as initial therapy, its slower rate of administration positions it as an alternative initial therapy. For prehospital settings or where first-line benzodiazepine options are not available, rectal diazepam, intranasal midazolam, and buccal midazolam are reasonable initial therapy alternatives.
        - In the second phase of treatment (from 20 to 40 minutes after the beginning of the seizure), reasonable options include fosphenytoin, valproic acid, and levetiracetam. There is no clear evidence that any of these options is better than the others. Because of AEs, IV phenobarbital is a reasonable second-therapy alternative if none of the 3 recommended therapies are available.
        - There is no clear evidence to guide therapy in the third phase of therapy (≥ 40 minutes after the beginning of the seizure).
- **Evidence-based guideline update: medical treatment of infantile spasms.** Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (*Go et al 2012*; reaffirmed in 2018)
    - This publication provides updated recommendations for the treatment of infantile spasms. The literature review included an evaluation of 26 published articles on this topic.
    - Recommendations include the following:
        - Evidence is insufficient to recommend the use of prednisolone, dexamethasone, and methylprednisolone as being as effective as adrenocorticotropic hormone (ACTH) for short-term treatment of infantile spasms.
        - Low-dose ACTH should be considered as an alternative to high-dose ACTH for treatment of infantile spasms.
        - ACTH or vigabatrin may be offered for short-term treatment of infantile spasms; evidence suggests that ACTH may be offered over vigabatrin.

        - Evidence is insufficient to recommend other therapies (valproic acid, vitamin B6, nitrazepam [not available in the United States], levetiracetam, zonisamide, topiramate, the ketogenic diet, or novel/combination therapies) for treatment of infantile spasms.
        - Hormonal therapy (ACTH or prednisolone) may be considered for use in preference to vigabatrin in infants with cryptogenic infantile spasms, to possibly improve developmental outcome.
        - A shorter lag time to treatment of infantile spasms with either hormonal therapy or vigabatrin may be considered to improve long-term cognitive outcomes.
    - There is a lack of sufficient randomized trials to provide definitive answers to key questions related to treatment of infantile spasms.
- **Practice parameter: treatment of the child with a first unprovoked seizure.** Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society (*Hirtz et al 2003*; reaffirmed in 2018)
    - This parameter reviews published literature relevant to the decision to begin treatment after a child or adolescent experiences a first unprovoked seizure and presents evidence-based practice recommendations. Treatment during the neonatal period is not addressed.
    - Recommendations include the following:
        - Treatment with AEDs is not indicated for the prevention of the development of epilepsy.
        - Treatment with AEDs may be considered in circumstances where the benefits of reducing the risk of a second seizure outweigh the risks of pharmacologic and psychosocial AEs.
    - The majority of children who experience a first unprovoked seizure will have few or no recurrences. Treatment with AEDs after a first seizure as opposed to after a second seizure has not been shown to improve prognosis for long-term seizure remission.
    - Treatment has been shown in several studies combining both children and adults to reduce the risk of seizure recurrence; however, there is a relative paucity of data from studies involving only children after a first seizure.
- **Summary of recommendations for the management of infantile seizures**. Task force report for the ILAE Commission of Pediatrics (*Wilmshurst et al 2015*).
    - This publication recommends an approach to the standard and optimal management of infants with seizures. When possible, recommendations are evidence-based; however, when no evidence was available, recommendations are based on expert opinion and standard practice.
    - Recommendations/findings include the following:
        - There is no indication for initiation of chronic AEDs for simple febrile seizures. However, in the acute treatment of febrile seizures, it is important to treat seizures lasting 10 minutes or longer.
        - In an otherwise healthy infant, a policy of “wait and see” is reasonable after the first afebrile seizure. However, this is a rare event and close monitoring is essential.
        - Treatment options with established or probable efficacy include the following:
            - Focal seizures: levetiracetam
            - Epileptic spasms: High-dose or low-dose ACTH
            - Dravet syndrome: stiripentol
        - Treatment options with possible efficacy include the following:
            - Generalized seizures: levetiracetam, valproate, lamotrigine, topiramate, clobazam
            - Epileptic spasms: prednisone, vigabatrin
            - Benign infantile convulsions: carbamazepine, phenobarbital, valproate
            - Dravet syndrome: topiramate, zonisamide, valproate
            - Benign myoclonic epilepsy of infancy: valproate, topiramate, lamotrigine, clonazepam
            - Provoked or situational seizures: carbamazepine
        - There is no clear evidence supporting an optimal duration of treatment; this is dependent on seizure type.
- **Guidelines on neonatal seizures**. World Health Organization (WHO) (*WHO 2011*).
    - This document was prepared based on a systematic review of the literature and involved cooperation between the WHO, the ILAE, and the International Bureau of Epilepsy (IBE).
    - Recommendations include the following:
        - Phenobarbital should be used as the first-line agent for treatment of neonatal seizures and should be made readily available in all settings.

        - In neonates who continue to have seizures despite administering the maximum tolerated dose of phenobarbital, either a benzodiazepine, phenytoin, or lidocaine may be used as the second-line agent for control of seizures (use of phenytoin or lidocaine requires cardiac monitoring).
        - In neonates with a normal neurological examination and/or normal EEG, stopping AEDs may be considered if the neonate has been seizure-free for > 72 hours; the drug(s) should be reinstituted if seizures recur.
        - In neonates in whom seizure control is achieved with a single AED, the drug can be discontinued abruptly without tapering the dose. In neonates requiring > 1 AED for seizure control, the drugs may be stopped one at a time, with phenobarbital being the last drug to be withdrawn.
- **Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): teratogenesis and perinatal outcomes.** Quality Standards Subcommittee and Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and American Epilepsy Society (*Harden et al 2009A*; reaffirmed in 2013; Update in progress)
    - This publication summarizes evidence for selected issues regarding the clinical management of women with epilepsy (WWE) who are pregnant or planning to be pregnant.
    - Recommendations include the following:
        - If possible, avoidance of the use of valproate as part of polytherapy during the first trimester of pregnancy should be considered to decrease the risk of major congenital malformations (MCMs).
        - If possible, avoidance of the use of valproate monotherapy during the first trimester of pregnancy may be considered to decrease the risk of MCMs.
        - To reduce the risk of MCMs, the use of valproate during the first trimester of pregnancy should be avoided, if possible, compared to the use of carbamazepine.
        - To reduce the risk of MCMs, avoidance of the use of polytherapy with valproate during the first trimester of pregnancy, if possible, should be considered, compared to polytherapy without valproate.
        - To reduce the risk of MCMs, avoidance of the use of valproate during the first trimester of pregnancy, if possible, may be considered, compared to the use of phenytoin or lamotrigine.
        - To reduce the risk of MCMs, avoidance of the use of AED polytherapy during the first trimester of pregnancy, if possible, compared to monotherapy should be considered.
        - Limiting the dosage of valproate or lamotrigine during the first trimester, if possible, should be considered to lessen the risk of MCMs.
        - Avoidance of the use of valproate, if possible, should be considered to reduce the risk of neural tube defects and facial clefts, and may be considered to reduce the risk of hypospadias.
        - Avoidance of phenytoin, carbamazepine, and phenobarbital, if possible, may be considered to reduce the risk of specific MCMs: cleft palate for phenytoin use, posterior cleft palate for carbamazepine use, and cardiac malformations for phenobarbital use.
        - Carbamazepine exposure probably does not produce cognitive impairment in offspring of WWE.
        - Avoiding valproate in WWE during pregnancy, if possible, should be considered to reduce the risk of poor cognitive outcomes.
        - Avoiding phenytoin and phenobarbital in WWE during pregnancy, if possible, may be considered to reduce the risk of poor cognitive outcomes.
        - Monotherapy should be considered in place of polytherapy, if possible, for WWE who take AEDs during pregnancy to reduce the risk of poor cognitive outcomes.
        - For WWE who are pregnant, avoidance of valproate, if possible, should be considered compared to carbamazepine to reduce the risk of poor cognitive outcomes.
        - For WWE who are pregnant, avoidance of valproate, if possible, may be considered compared to phenytoin to reduce the risk of poor cognitive outcomes.
    - Valproate has the most data showing an association with risk from in utero exposure. If a change from valproate to another AED is planned, it is prudent to make this change well before pregnancy.
    - Although many of the recommendations in this parameter suggest minimizing AED exposure during pregnancy, for most WWE, discontinuing AEDs is not a reasonable or safe option. Discontinuing AEDs may expose the mother and fetus to physical injury from accidents due to seizure activity.
- **Practice parameter update: management issues for women with epilepsy – focus on pregnancy (an evidence-based review): vitamin K, folic acid, blood levels, and breastfeeding.** Quality Standards Subcommittee and

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

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

SAFETY SUMMARY

- Tolerability and safety are as important as efficacy in determining the overall effectiveness of epilepsy treatment (*Schachter 2019*).

- Common AEs among AEDs include the following (*Fintepla prescribing information 2020, Schachter 2019*):
  - Systemic AEs:
    - nausea, vomiting, constipation, diarrhea, anorexia
    - rash
    - hyponatremia (carbamazepine, eslicarbazepine, oxcarbazepine)
    - weight gain (pregabalin, perampanel, valproate), weight loss (felbamate, topiramate, stiripentol, fenfluramine)
  - Neurologic AEs:
    - headache
    - somnolence, sedation, drowsiness, lethargy, fatigue
    - dizziness, vertigo
    - tremor, anxiety, nervousness, insomnia
    - aggression, irritability, hyperactivity
    - depression, mood alteration
    - confusion
    - ataxia
    - blurred or double vision
- Examples of rare but serious AEs include the following (*Schachter 2019, individual package inserts*):
  - suicidal ideation and behavior (AEDs as a class, except everolimus)
  - neutropenia, leukopenia, pancytopenia, agranulocytosis, thrombocytopenia, and/or aplastic anemia (brivaracetam, carbamazepine, ethosuximide, felbamate, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, primidone, stiripentol, valproate, vigabatrin, zonisamide)
  - anaphylaxis or angioedema (brivaracetam, fosphenytoin, gabapentin, levetiracetam, phenytoin, pregabalin)
  - severe skin rashes, Stevens-Johnson syndrome (SJS), and/or toxic epidermal necrolysis (TEN) (carbamazepine, clobazam, eslicarbazepine, ethosuximide, fosphenytoin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, primidone, rufinamide, tiagabine, topiramate, valproate, zonisamide)
  - hepatic failure (carbamazepine, ethosuximide, felbamate, phenytoin, phenobarbital, primidone, valproate)
  - hepatocellular injury (cannabidiol)
  - prolonged PR interval, atrioventricular block, and/or changes in QT interval (cenobamate, eslicarbazepine, lacosamide, rufinamide)
  - serum sickness (carbamazepine, ethosuximide, phenytoin, phenobarbital, primidone, valproate)
  - multiorgan hypersensitivity (carbamazepine, cenobamate, ethosuximide, gabapentin, lacosamide, lamotrigine, oxcarbazepine, perampanel, phenytoin, rufinamide, valproate, zonisamide)
  - severe neuropsychiatric effects/hostility/aggression (brivaracetam, levetiracetam, perampanel)
  - hemophagocytic lymphohistiocytosis (HLH) (lamotrigine)
  - cardiac AEs, including bradycardia and cardiac arrest (phenytoin)
  - abnormal magnetic resonance imaging signals in infants (vigabatrin)
  - intramyelinic edema (vigabatrin)
  - serotonin syndrome (fenfluramine)
  - significant elevation in blood pressure including hypertensive crisis (fenfluramine)
- A number of AEDs carry boxed warnings related to potentially serious AEs; these include the following:
  - Carbamazepine:
    - Serious and sometimes fatal dermatologic reactions, including TEN and SJS, have been reported. Studies in patients of Chinese ancestry have found a strong association between the risk of developing SJS/TEN and the presence of HLA-B*1502, an inherited allelic variant of the HLA-B gene. Patients with ancestry in genetically at-risk populations (across broad areas of Asia) should be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine.
    - Aplastic anemia and agranulocytosis have been reported. If a patient exhibits low or decreased white blood cell or platelet counts, the patient should be monitored closely, and discontinuation of the drug should be considered if any evidence of significant bone marrow depression develops.
  - Clobazam, clonazepam, clorazepate, diazepam, and midazolam:
    - Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Concomitant prescribing should be reserved for use in patients for whom alternative

treatment options are inadequate, and patients should be followed for signs and symptoms of respiratory depression and sedation.

- Felbamate:
  - Use is associated with a marked increase in the incidence of aplastic anemia. Felbamate should only be used in patients whose epilepsy is so severe that the risk of aplastic anemia is deemed acceptable. Routine blood testing cannot be reliably used to reduce the incidence of aplastic anemia, but it will in some cases allow detection of hematologic changes before the syndrome declares itself clinically. Felbamate should be discontinued if any evidence of bone marrow depression occurs.
  - Cases of acute liver failure have been reported. Felbamate should not be prescribed for anyone with a history of hepatic dysfunction. Treatment should be initiated only in individuals without active liver disease and with normal baseline serum transaminases. It has not been proven that periodic serum transaminase testing will prevent serious injury, but it is generally believed that early detection of drug-induced hepatic injury along with immediate withdrawal of the suspect drug enhances the likelihood for recovery. Serum transaminases should be monitored at baseline and periodically thereafter. Felbamate should be discontinued if either aspartate aminotransferase (AST) or alanine aminotransferase (ALT) become increased to ≥ 2 times the upper limit of normal, or if clinical signs and symptoms suggest liver failure, and should not be considered for retreatment.
- Fenfluramine:
  - Use of serotonergic drugs with 5-HT2B receptor agonist activity (eg, fenfluramine) is associated with valvular heart disease and pulmonary arterial hypertension. Echocardiogram assessments are required before, during, and after treatment with fenfluramine, and the benefits vs risks of initiating or continuing treatment with this product must be considered based on echocardiogram findings.
  - Due to the risks of valvular heart disease and pulmonary arterial hypertension, fenfluramine is available only through a risk evaluation and mitigation strategy (REMS) program (*FDA REMS 2020*). Healthcare providers who prescribe fenfluramine and pharmacies that dispense the product must be certified. Each patient must be enrolled in the REMS program. Prescribers must ensure that periodic cardiovascular monitoring is performed and report any AE suggestive of valvular heart disease and/or pulmonary hypertension to the fenfluramine REMS program.
- Fosphenytoin and phenytoin:
  - There is a cardiovascular risk associated with rapid IV infusion rates. The rate of administration should not exceed recommendations, and careful cardiac monitoring is required.
- Lamotrigine:
  - Cases of life-threatening serious skin rashes, including SJS and TEN, and/or rash-related death have been caused by lamotrigine. Benign rashes are also caused by lamotrigine; however, it is not possible to predict which rashes will prove to be serious. Lamotrigine should be discontinued at the first sign of a rash, unless the rash is clearly not drug related.
- Perampanel:
  - Serious or life-threatening psychiatric and behavioral AEs including aggression, hostility, irritability, anger, and homicidal ideation and threats have been reported. Patients should be monitored for these reactions and for changes in mood, behavior, or personality. The dose should be reduced if these symptoms occur, and it should be discontinued if symptoms are severe or worsening.
- Valproic acid and divalproex sodium:
  - Hepatotoxicity, including fatalities, have been reported, usually during the first 6 months of treatment. Serum liver tests are required and patients should be monitored closely. There is an increased risk of valproate-induced acute liver failure and resultant deaths in patients with mitochondrial disease. Valproic acid and divalproex sodium are contraindicated in patients known to have mitochondrial disorders caused by polymerase gamma (POLG) gene mutations, and in children < 2 years of age who are suspected of having a mitochondrial disorder.
  - There is a risk to fetuses exposed in utero, particularly neural tube defects, other major malformations, and decreased intelligence quotient (IQ). Valproate should not be given to a woman of childbearing potential unless the drug is essential to the management of her medical condition, and women should use effective contraception while using valproate.
  - Pancreatitis, including fatal hemorrhagic cases, has occurred. Patients and guardians should be warned that abdominal pain, nausea, vomiting, and/or anorexia can be symptoms of pancreatitis that require prompt medical evaluation.

- Vigabatrin:
  - Vigabatrin can cause permanent bilateral concentric visual field constriction, including tunnel vision that can result in disability. In some cases, vigabatrin may also damage the central retina and may decrease visual acuity. Baseline and periodic vision assessment are recommended. However, this assessment cannot always prevent vision damage, and once detected, vision loss due to vigabatrin is not reversible. Vigabatrin should be withdrawn from patients who fail to show substantial clinical benefit.
  - Due to the risks of vision loss, vigabatrin is available only through a REMS program (*FDA REMS 2020*). Healthcare providers who prescribe vigabatrin and pharmacies that dispense the product must be specially certified. Each patient must be enrolled in the REMS program. Prescribers must ensure that periodic visual monitoring is performed and report any AE suggestive of vision loss to the vigabatrin REMS program.

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

DOSING AND ADMINISTRATION

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

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Barbiturates				
Pentobarbital (Nembutal)	injection	IV, IM	Single dose	Acute use only. If needed, additional small increments may be given after the initial dose.
Phenobarbital* (Luminal†, Solfoton†)	tablets, elixir, injection	oral, IV, IM	2 to 3 times per day	
Primidone (Mysoline)	tablets	oral	3 to 4 times per day	
Benzodiazepines				
Clobazam (Onfi, Sympazan)	tablets, oral suspension, oral film	oral	1 or 2 times per day	Daily doses > 5 mg should be given in divided doses 2 times per day. Sympazan should be applied on top of the tongue where it adheres and dissolves.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Clonazepam (Klonopin)	tablets, orally disintegrating tablets (wafers)	oral	3 times per day	
Clorazepate (Tranxene T-Tab)	tablets	oral	2 to 3 times per day	
Diazepam (Diastat, Valium, Valtoco)	tablets, oral solution, oral concentrate, rectal gel, injection, nasal spray	oral, rectal, IV, IM, intranasal	2 to 4 times per day	For the rectal gel (for acute use), a second dose may be given 4 to 12 hours after the initial dose when required. The injection and nasal spray are also for short-term acute use. For the nasal spray, a second dose may be given 4 hours after the initial dose when required. The product should be used to treat no more than 1 episode every 5 days and no more than 5 episodes per month.
Midazolam (Nayzilam)	nasal spray	intranasal	Up to 2 doses per seizure cluster, with the second dose given at least 10 minutes after the first dose	Should be used to treat no more than 1 episode every 3 days and no more than 5 episodes per month.
Hydantoins				
Ethotoin (Peganone)	tablets	oral	4 to 6 times per day	
Fosphenytoin (Cerebyx)	injection	IV, IM	2 times per day or other divided doses based on drug levels	Generally used in acute situations as a loading dose; may be given in divided doses when substituted for oral phenytoin.
Phenytoin (Dilantin, Phenytek)	extended-release capsules, chewable tablets, oral suspension, injection	oral, IV, IM	2 to 4 times per day	Capsules are extended-release and may be suitable for once-daily dosing in some adults.
Miscellaneous				
Brivaracetam (Briviact)	tablets, oral solution, injection	oral, IV	2 times per day	The injection may be used when oral administration is temporarily not feasible.
Cannabidiol (Epidiolex)	oral solution	oral	2 times per day	The provided oral syringe should be used to measure an accurate dose.
Carbamazepine (Carbatrol, Epitol, Equetro, Tegretol, Tegretol-XR)	tablets, chewable tablets, oral suspension, extended-release tablets, extended-release capsules	oral	2 to 4 times per day	Immediate-release tablets are given 2 to 3 times per day and the suspension is given 4 times per day. Carbatrol and Equetro are twice-daily

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				extended-release capsule formulations; these capsules may be opened and sprinkled on soft food. Tegretol-XR is a twice-daily extended-release tablet formulation; these tablets must be swallowed whole.
Cenobamate (Xcopri)	tablets	oral	once daily	The recommended titration schedule should not be exceeded.
Divalproex sodium (Depakote, Depakote ER, Depakote Sprinkle)	delayed-release tablets, delayed-release sprinkle capsules, extended-release tablets	oral	2 to 3 times per day (once daily for extended-release tablets)	Delayed-release tablets and extended-release tablets should be swallowed whole. Sprinkle capsules may be opened and sprinkled on soft food. Delayed-release tablet and capsule doses > 250 mg per day should be given in divided doses.
Eslicarbazepine (Aptiom)	tablets	oral	once daily	Tablets may be crushed.
Ethosuximide (Zarontin)	capsules, oral solution/syrup	oral	once daily or in divided doses	
Everolimus (Afinitor Disperz)	tablets for oral suspension	oral	once daily	Should be taken at the same time each day with or without food. Suspension should be prepared using water only and administered immediately after preparation. The suspension should be discarded if not taken within 60 minutes of preparation. Dose adjustments are made based on trough drug concentration.
Felbamate (Felbatol)	tablets, oral suspension	oral	3 or 4 times per day	
Fenfluramine (Fintepla)	oral solution	oral	2 times per day	
Gabapentin (Neurontin)	tablets, capsules, oral solution	oral	3 times per day	Capsules should be swallowed whole.
Lacosamide (Vimpat)	tablets, oral solution, injection	oral, IV	2 times per day	
Lamotrigine (Lamictal, Lamictal ODT,	tablets, chewable dispersible tablets, orally disintegrating tablets, extended-release tablets	oral	2 times per day (once daily for extended-release tablets)	Only whole tablets should be administered. Extended-release tablets must not be chewed or crushed.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Lamictal XR, Subvenite)				
Levetiracetam (Keppra, Keppra XR, Roweepra, Roweepra XR, Spritam, Elepsia XR)	tablets, tablets for oral suspension, oral solution, extended-release tablets, injection	oral, IV	2 times per day (once daily for extended-release tablets)	Tablets and extended-release tablets should not be chewed or crushed. Tablets for oral suspension (Spritam) can be dissolved in liquid and swallowed or allowed to disintegrate in the mouth.
Methsuximide (Celontin)	capsules	oral	3 to 4 times per day (*Lexicomp 2020*)	
Oxcarbazepine (Oxtellar XR, Trileptal)	tablets, oral suspension, extended-release tablets	oral	2 times per day (once daily for extended-release tablets)	In conversion of oxcarbazepine immediate-release to Oxtellar XR, higher doses of Oxtellar XR may be necessary. Extended-release tablets must not be chewed or crushed.
Perampanel (Fycompa)	tablets, oral suspension	oral	once daily at bedtime	
Pregabalin (Lyrica)	capsules, oral solution	oral	2 to 3 times per day	
Rufinamide (Banzel)	tablets, oral suspension	oral	2 times per day	Tablets can be administered whole, as half tablets, or crushed.
Stiripentol (Diacomit)	capsules, powder for oral suspension	oral	2 to 3 times per day	Capsules must be swallowed whole with a glass of water during a meal. Powder should be mixed with water and taken immediately after mixing during a meal.
Tiagabine (Gabitril)	tablets	oral	2 to 4 times per day	
Topiramate (Topamax, Topamax Sprinkle, Topiragen, Trokendi XR, Qudexy XR)	tablets, sprinkle capsules, extended-release capsules, extended-release sprinkle capsules	oral	2 times per day (once daily for extended-release capsule formulations)	Sprinkle capsules may be opened and sprinkled on soft food. Extended-release capsules (Trokendi XR) must not be chewed or crushed, but extended release sprinkle capsules (Qudexy XR) may be sprinkled on soft food.
Valproic acid/ valproate sodium (Depakene†, Depacon†)	capsules, oral solution/ syrup, injection	oral, IV	1 to 3 times per day (*Lexicomp 2020*)	Capsules should be swallowed whole without chewing to avoid local irritation of the mouth and throat. If the total dose exceeds 250 mg, it should be given in divided doses.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Vigabatrin (Sabril, Vigadrone)	tablets, powder for oral solution	oral	2 times per day	Powder for oral solution is supplied in individual dose packets to be mixed with water before administration.
Zonisamide (Zonegran)	capsules	oral	1 or 2 times per day	Capsules must be swallowed whole.

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

CONCLUSION

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

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Therapeutic Class Overview
Respiratory Beta-Agonist Combination Agents

INTRODUCTION

- Respiratory beta$_2$-agonist combination agents include a beta$_2$-agonist combined with an inhaled corticosteroid (ICS), inhaled anticholinergic, or both. Beta$_2$-agonists can be short-acting beta$_2$-agonists (SABA) or long-acting beta$_2$-agonists (LABA); most combinations contain a LABA. Similarly, inhaled anticholinergics, also known as muscarinic antagonists, can be short-acting muscarinic antagonists (SAMA) or long-acting muscarinic antagonists (LAMA); most combinations contain a LAMA.
- Individual beta$_2$-agonist combinations are Food and Drug Administration (FDA) approved for the treatment of asthma, chronic obstructive pulmonary disease (COPD), or both.
  - All combinations of a beta$_2$-agonist and an ICS are indicated for the treatment of asthma, and some are additionally indicated for the treatment of COPD.
  - Combinations of a beta$_2$-agonist and an anticholinergic medication are indicated for COPD.
  - The 2 available triple combination agents (consisting of LAMA/LABA/ICS) are indicated for COPD and one is also indicated for asthma.
  - Refer to Tables 2A, 2B, and 2C for specific indications for each product.
- Asthma is a chronic lung disease that inflames and narrows the airways in the lungs. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing. Asthma affects people of all ages, but most often starts during childhood. In 2018, asthma affected an estimated 19.2 million adults and 5.5 million children in the United States (U.S.) (*Centers for Disease Control and Prevention [CDC] 2020, National Heart, Lung, and Blood Institute [NHLBI] Web site*).
- COPD is characterized by persistent respiratory symptoms and airflow limitation due to airway and/or alveolar abnormalities. The abnormalities are usually caused by exposure to noxious particles or gases, and cigarette smoking is a key risk factor. Airflow limitation is caused by a combination of small airway disease (eg, obstructive bronchiolitis) and parenchymal destruction (emphysema). The most common symptoms of COPD include dyspnea, cough, and sputum production (*Global Initiative for Chronic Obstructive Lung Disease [GOLD] 2020a*). COPD affects 6.4% of the U.S. population and is a major contributor to mortality from chronic lower respiratory diseases, the fourth leading cause of death in the U.S. (*CDC 2019*).
- Medispan class/subclass: Sympathomimetics/Adrenergic Combinations

Table 1. Medications Included Within Class Review*

Drug	Generic Availability
Beta$_2$-agonist & corticosteroid combinations	
Advair Diskus & Advair HFA (fluticasone propionate/salmeterol)	✔ ‡
AirDuo RespiClick & AirDuo Digihaler (fluticasone propionate/salmeterol)	✔ †
Breo Ellipta (fluticasone furoate/vilanterol)	-
Dulera (mometasone furoate/formoterol fumarate dihydrate)	-
Symbicort (budesonide/formoterol fumarate dihydrate)	✔ †
Wixela Inhub (fluticasone propionate/salmeterol)	✔ ‡
Beta$_2$-agonist & anticholinergic combinations	
Anoro Ellipta (umeclidinium/vilanterol)	-
Bevespi Aerosphere (glycopyrrolate/formoterol fumarate)	-
Combivent Respimat (ipratropium/albuterol)	-
Duaklir Pressair (aclidinium/formoterol fumarate)	-
ipratropium/albuterol solution	✔
Stiolto Respimat (tiotropium/olodaterol)	-

Drug	Generic Availability
Utibron Neohaler (glycopyrrolate/indacaterol)§	-
Triple combination	
Breztri Aerosphere (glycopyrrolate/formoterol/budesonide)	-
Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol)	-

* Branded product DuoNeb is no longer marketed.
† Authorized generic (for AirDuo RespiClick and Symbicort only)
‡ Wixela Inhub is the generic of Advair Diskus.
§ The inhaled LABA and anticholinergic combination, Utibron Neohaler (indacaterol/glycopyrrolate), was discontinued by the manufacturer effective April 1, 2020 for business reasons. (*OINDP news 2020*). At the time of this review, Utibron Neohaler was active in Medispan.

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

INDICATIONS

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

Indication	Advair Diskus	Advair HFA	AirDuo RespiClick & Digihaler	Breo Ellipta	Dulera	Symbicort	Wixela Inhub
Treatment of asthma	✔ (age ≥ 4 years)	✔ (age ≥ 12 years)	✔ (age ≥ 12 years)	✔ (age ≥ 18 years)	✔ (age ≥ 5 years)	✔ (age ≥ 6 years)	✔ (age ≥ 4 years)
Maintenance treatment of airflow obstruction in patients with COPD, including chronic bronchitis and/or emphysema	✔ (250/50 strength only)			✔ (100/25 strength only)		✔ (160/4.5 strength only)	✔ (250/50 strength only)
To reduce exacerbations of COPD in patients with a history of exacerbations	✔ (250/50 strength only)			✔ (100/25 strength only)		✔ (160/4.5 strength only)	✔ (250/50 strength only)

(*Prescribing information: Advair HFA 2019, Advair Diskus 2019, AirDuo Digihaler 2020, AirDuo RespiClick 2020, Breo Ellipta 2019, Dulera 2019, Symbicort 2019, Wixela Inhub 2019*)

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

Indication	Anoro Ellipta	Bevespi Aerosphere	Combivent Respimat	Duaklir Pressair	ipratropium/ albuterol solution	Stiolto Respimat	Utibron Neohaler
Long-term, once-daily, maintenance treatment of patients with COPD	✔					✔	
Long-term, twice-daily, maintenance treatment of airflow obstruction in patients with COPD				✔			✔
Long-term, twice-daily, maintenance treatment of patients with COPD, including chronic bronchitis and/or emphysema		✔					
For use in patients with COPD on a regular aerosol bronchodilator who continue to have evidence of bronchospasm and who require a second bronchodilator			✔				

Indication	Anoro Ellipta	Bevespi Aerosphere	Combivent Respimat	Duaklir Pressair	ipratropium/ albuterol solution	Stiolto Respimat	Utibron Neohaler
For the treatment of bronchospasm associated with COPD in patients requiring more than 1 bronchodilator					✔		

(*Prescribing information: Anoro Ellipta 2019, Bevespi Aerosphere 2019, Combivent Respimat 2016, Duaklir Pressair 2020, ipratropium/albuterol solution 2018, Stiolto Respimat 2019, Utibron Neohaler 2019*)

Table 2C. FDA-Approved Indications for Triple Combination Agents

Indication	Breztri Aerosphere	Trelegy Ellipta
Maintenance treatment of patients with COPD	✔	✔ (100/62.5/25 strength only)
Maintenance treatment of asthma		✔ (age ≥ 18 years)

(*Prescribing information: Breztri Aerosphere 2020, Trelegy Ellipta 2020*)

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

CLINICAL EFFICACY SUMMARY

Beta$_2$-agonist/corticosteroid combinations for asthma and COPD

Comparisons to placebo, monotherapy, combined use of individual components, varied treatments, or usual care:

- Numerous trials have compared the combination ICS/LABA products to their respective individual components as monotherapy, and in general, results have demonstrated that administration of the combination product is more effective than monotherapy for improving lung function and/or achieving control of symptoms in asthma and COPD (*Bateman et al 2001, Bateman et al 2004, Bateman et al 2006, Bateman et al 2014, Bateman et al 2018, Berger et al 2010, Bernstein et al 2015, Bleecker et al 2014, Calverley et al 2003, Corren et al 2007, Eid et al 2010, FDA AirDuo RespiClick Medical Review 2017, Gappa et al 2009, Hanania et al 2003, Jenkins et al 2006, Kerwin et al 2009, Kerwin et al 2013, Kuna et al 2006, Lalloo et al 2003, Lundback et al 2006, Martinez et al 2013, Meltzer et al 2012, Morice et al 2007, Murphy et al 2008, Nathan et al 2006, Nelson et al 2003a, Noonan et al 2006, O'Byrne et al 2014, Pearlman et al 2004, Pearlman et al 2017, Pohl et al 2006, Raphael et al 2018, Rennard et al 2009, Rodrigo et al 2016, Rodrigo et al 2017, Sharafkaneh et al 2012, Sher et al 2017, Tal et al 2002, Tang et al 2019, Tashkin et al 2008, Vaessen-Verberne et al 2010, Vestbo et al 2005, Weinstein et al 2010*). Results for reducing COPD exacerbations have been inconsistent (*Dransfield et al 2013, Ohar et al 2014*).
- A randomized, double-blind, double-dummy trial showed therapeutic bioequivalence of Wixela Inhub (generic fluticasone/salmeterol) to Advair Diskus (brand fluticasone/salmeterol) in 1227 patients with asthma. The trial revealed least-squares mean (LSM) Wixela Inhub to Advair Diskus ratios of 1.120 (90% confidence interval [CI], 1.016 to 1.237) for day 1 forced expiratory volume in 1 second (FEV_1) area under the curve and 1.069 (90% CI, 0.938 to 1.220) for day 29 trough FEV_1 (*Ng et al 2019*).
- The efficacy of the AirDuo Digihaler (fluticasone propionate/salmeterol) was based primarily on the dose-ranging trials and the confirmatory trials for the AirDuo RespiClick (fluticasone propionate/salmeterol). The AirDuo Digihaler contains a built-in electronic module which detects, records, and stores data on inhaler events, including peak inspiratory flow rate (L/minute), for transmission a mobile App. There is no evidence the use of the App leads to improved clinical outcomes, including safety and effectiveness (*AirDuo Prescribing information 2020*)
- Although a synergistic effect of combination inhalers has been suggested by some data, overall there are similar efficacy between the administration of the combination ICS/LABA products and their individual components used in combination (*Chapman et al 1999, Jenkins et al 2006, Marceau et al 2006, Nelson et al 2003b, Noonan et al 2006, Perrin et al 2010, Rosenhall et al 2002*). Improved adherence with combination inhalers has also been suggested but not been shown conclusively (*Marceau et al 2006, Perrin et al 2010*).

- A multicenter clinical trial (N = 181) compared mometasone furoate/formoterol 50/5 mcg to mometasone furoate 50 mcg in patients with asthma 5 to less than 12 years of age. The primary efficacy endpoint, defined as the change from baseline to week 12 in 60-minute morning post-dose % predicted FEV_1, was significantly improved with mometasone furoate/formoterol compared with mometasone furoate (5.21; 95% CI, 3.22 to 7.20) (*Dulera Prescribing Information 2019*).
- A large, double-blind, randomized trial (N = 6112) compared fluticasone propionate/salmeterol 500/50 mcg twice daily to its individual components and to placebo over a 3-year period in patients with COPD (*Calverley et al 2007*). The primary endpoint, time to death from any cause, for the combination vs placebo failed to reach statistical significance (12.6% vs 15.2%; p = 0.052). However, the difference in mortality between the combination therapy and fluticasone monotherapy did reach statistical significance (12.6% vs 16%; p = 0.007). Treatment with the combination regimen resulted in significantly fewer exacerbations, improved health status, and improved lung function compared with placebo.
- A large, double-blind, randomized trial (SUMMIT; N = 16,590) evaluated the use of fluticasone furoate/vilanterol vs fluticasone furoate alone, vilanterol alone, or placebo in a population of patients with moderate COPD and heightened cardiovascular risk (age ≥ 60 years and receiving medication for >2 of the following: hypercholesterolemia, hypertension, diabetes mellitus, or peripheral arterial disease) (*Vestbo et al 2016a*). Compared with placebo, there was no significant benefit or worsening in all-cause mortality with combination therapy (hazard ratio [HR], 0.88; 95% CI, 0.74 to 1.04; p = 0.137]) or with the components (fluticasone furoate HR, 0.91 [95% CI, 0.77 to 1.08; p = 0.284]; vilanterol HR, 0.96 [95% CI, 0.81 to 1.14; p = 0.655]). Composite cardiovascular events were also similar in the 4 groups (3.9% to 4.4%). All treatments reduced the risk of moderate to severe COPD exacerbations compared to placebo, with percent reductions of 29% (95% CI, 22 to 35), 12% (95% CI, 4 to 19), and 10% (95% CI, 2 to 18) in the fluticasone furoate/vilanterol, fluticasone furoate, and vilanterol groups, respectively.
- A 12-month, randomized, open-label trial (Salford Lung Study; N = 2799) compared the use of fluticasone furoate/vilanterol 100/25 mcg daily to continuation of usual care in a real-world patient population in the United Kingdom (*Vestbo et al 2016b*). Enrolled patients had COPD, had experienced ≥ 1 exacerbations in the previous 3 years, and were taking regular maintenance inhaler therapy (≥ 1 long-acting bronchodilators; ICS alone or in combination with a long-acting bronchodilator; or a combination of ICS, LABA, and LAMA). The primary endpoint, the rate of moderate or severe exacerbations among patients who had experienced an exacerbation within 1 year before the trial, was 1.74 per year in the fluticasone furoate/vilanterol group and 1.90 per year in the usual-care group, for a difference of 8.4% (95% CI, 1.1 to 15.2; p = 0.02). Serious adverse events, including pneumonia, were similar between the 2 groups.
- A meta-analysis of 19 trials evaluated the use of ICS/LABA combinations compared to placebo in patients with COPD, and demonstrated a significant reduction in exacerbation rate between fluticasone propionate/salmeterol and placebo and between budesonide/formoterol and placebo (*Nannini et al 2013a*). For the number of patients who experienced ≥ 1 exacerbations, the differences between fluticasone propionate/salmeterol vs placebo and mometasone furoate/formoterol 200/10 mcg strength vs placebo were not statistically significant; however, the mometasone furoate/formoterol 400/10 mcg strength was associated with a lower proportion of patients experiencing ≥ 1 exacerbation. This meta-analysis also demonstrated that when results for all combined inhalers vs placebo were pooled, there was an overall reduction in mortality (odds ratio [OR], 0.82; 95% CI, 0.68 to 0.99).
- A meta-analysis of 14 trials evaluated the use of ICS/LABA combinations compared to use of the same LABA as monotherapy in patients with COPD (*Nannini et al 2012*). This analysis demonstrated that exacerbation rates were reduced with ICS/LABA combination therapy compared to LABA monotherapy (rate ratio, 0.76; 95% CI, 0.68 to 0.84). However, there was a significant increase in the incidence of pneumonia with combination therapy compared to LABA monotherapy (OR, 1.55; 95% CI, 1.2 to 2.01).
- A meta-analysis of 15 trials evaluated the use of ICS/LABA combinations compared to use of ICS monotherapy in patients with COPD (*Nannini et al 2013b*). This analysis demonstrated that exacerbation rates were significantly reduced with ICS/LABA combination therapy vs ICS monotherapy (rate ratio, 0.87; 95% CI, 0.80 to 0.94). Adverse events were similar between treatments; pneumonia rates as diagnosed by chest x-ray were lower than those reported in earlier trials.
- A meta-analysis of 14 trials (total N = 6641) compared fluticasone furoate/vilanterol to placebo, fluticasone furoate monotherapy, fluticasone propionate monotherapy, vilanterol monotherapy, or fluticasone propionate/salmeterol in patients with asthma (*Dwan et al 2016*). Primary endpoints included health-related quality of life (HRQoL) and severe asthma exacerbations (defined by hospital admission or treatment with oral corticosteroids). Fewer than half of the studies reported on these primary endpoints, and there were few opportunities to combine results from the included studies. One of the 14 studies evaluated HRQoL (as measured by the Asthma Quality of Life Questionnaire [AQLQ]) for

fluticasone furoate/vilanterol 100/25 mcg vs placebo; it identified a significant advantage of fluticasone furoate/vilanterol (mean difference, 0.30; 95% CI, 0.14 to 0.46). Two studies compared fluticasone furoate/vilanterol 100/25 mcg vs placebo with respect to exacerbations; both studies reported no exacerbations in either treatment arm. No comparisons relevant to the primary outcomes were found for fluticasone furoate/vilanterol at a higher dose (200/25 mcg) vs placebo. There was insufficient evidence to assess whether once-daily fluticasone furoate/vilanterol had better or worse safety or efficacy compared to twice-daily fluticasone propionate/salmeterol. The authors stated that firm conclusions could not be drawn due to the limited number of studies, variety of endpoints, and short duration of most trials.

- Several large studies focused primarily on safety endpoints, with efficacy endpoints as secondary (*Peters et al 2016, Stempel et al 2016a, Stempel et al 2016b*). The studies compared the use of ICS/LABA combinations to ICS monotherapy in patients with asthma. These studies each demonstrated non-inferiority of the ICS/LABA combination to ICS monotherapy for the risk of serious asthma-related events, offering reassurance for the safety of these agents.
  - A randomized, double-blind study (AUSTRI; N = 11,679) enrolled adults and adolescents (age ≥ 12 years) with persistent asthma and a history of exacerbation within the previous year (*Stempel et al 2016a*). Patients were randomized to receive fluticasone propionate/salmeterol or fluticasone propionate monotherapy for 26 weeks. Patients were stratified by their baseline asthma control questionnaire (ACQ)-6 score and current asthma medication to determine the fluticasone propionate dose (100, 250, or 500 mcg twice daily) and were randomized to receive this dose with or without concomitant salmeterol.
    - The primary safety endpoint was the first serious asthma-related event, a composite endpoint that included death, endotracheal intubation, and hospitalization. There were 36 events in 34 patients in the fluticasone propionate/salmeterol group and 38 events in 33 patients in the fluticasone propionate group (HR, 1.03; 95% CI, 0.64 to 1.66). Fluticasone propionate/salmeterol was shown to be non-inferior to fluticasone propionate for this endpoint. There were no asthma-related deaths.
    - The main efficacy endpoint was the first severe asthma exacerbation, defined as asthma deterioration leading to the use of systemic glucocorticoids for ≥ 3 days or an asthma-related hospitalization or emergency department visit leading to the use of systemic glucocorticoids. At least 1 severe asthma exacerbation was reported in 480 patients (8%) in the fluticasone propionate/salmeterol group and in 597 patients (10%) in the fluticasone propionate group (HR, 0.79; 95% CI, 0.70 to 0.89; p < 0.001).
  - A similarly designed trial (VESTRI; N = 6208) enrolled pediatric patients 4 to 11 years of age (*Stempel et al 2016b*). Enrolled patients had a history of exacerbation within the previous year and consistent use of asthma medication during the 4 weeks before enrollment. Patients were randomized, on the basis of pretrial medication, Childhood Asthma Control Test (C-ACT) score, and exacerbation history, to receive fluticasone propionate/salmeterol 100/50 mcg or 250/50 mcg or fluticasone propionate alone 100 mcg or 250 mcg twice daily for 26 weeks.
    - The primary safety endpoint, the first serious asthma-related event (death, intubation, or hospitalization), occurred in 27 patients in the fluticasone propionate/salmeterol group and 21 patients in the fluticasone propionate group (HR, 1.28; 95% CI, 0.73 to 2.27); this demonstrated non-inferiority for fluticasone propionate/salmeterol compared to fluticasone propionate (p = 0.006). All of the events were asthma-related hospitalizations; there were no deaths or asthma-related intubations in either group.
    - The primary efficacy endpoint was the first severe asthma exacerbation, defined as asthma deterioration leading to the use of systemic glucocorticoids for ≥ 3 days or a depot injection of glucocorticoids. One or more severe asthma exacerbations occurred in 8.5% of patients in the fluticasone propionate/salmeterol group and 10.0% of patients in the fluticasone propionate group (HR, 0.86; 95% CI, 0.73 to 1.01).
  - An additional randomized, double-blind trial (N = 11,693) compared the safety of formoterol/budesonide to budesonide alone in patients ≥ 12 years of age (*Peters et al 2016*). Enrolled patients were receiving daily asthma medication and had experienced ≥ 1 exacerbation in the previous year. Patients were stratified to a dose level of budesonide on the basis of asthma control and prior treatment. Patients were then randomized to receive budesonide/formoterol (2 actuations of 80/4.5 mcg or 160/4.5 mcg) or budesonide alone (2 actuations of 80 mcg or 160 mcg) twice daily for 26 weeks.
    - The primary safety endpoint, the first serious adverse event (death, intubation, or hospitalization), occurred in 43 of 5,846 patients receiving budesonide/formoterol and 40 of 5,847 patients receiving formoterol alone (HR, 1.07; 95% CI, 0.70 to 1.65); this demonstrated non-inferiority for budesonide/formoterol vs budesonide alone. Two of the events (both in the budesonide/formoterol group) were asthma-related deaths; the remaining events were asthma-related hospitalizations.
    - The primary efficacy endpoint, the first asthma exacerbation (defined as a deterioration of asthma requiring systemic glucocorticoids for ≥ 3 days, inpatient hospitalization for asthma, or an emergency department visit for

asthma that resulted in receipt of systemic glucocorticoids) occurred in 9.2% of patients in the budesonide/formoterol group and 10.8% of patients in the budesonide group (HR, 0.84; 95% CI, 0.74 to 0.94).
  - A trial of 4215 patients ≥ 12 years of age with mild asthma found that budesonide/formoterol as needed was noninferior to budesonide twice daily for the reduction of severe asthma exacerbation. The annualized rate of severe exacerbations was 0.11 (95% CI, 0.10 to 0.13) and 0.12 (95% CI, 0.10 to 0.14), respectively (rate ratio, 0.97; upper one-sided 95% confidence limit, 1.16) However, budesonide/formoterol was inferior to budesonide for symptom control as the change in ACQ-5 score showed a difference of 0.11 units (95% CI, 0.07 to 0.15) in favor of budesonide maintenance therapy (*Bateman et al 2018*).
  - A 52-week randomized trial of adults with mild asthma (N = 675) revealed that budesonide/formoterol administered as needed was superior to albuterol as needed (relative rate, 0.49; 95% CI, 0.33 to 0.72; p < 0.001) and similar to budesonide with albuterol as needed (relative rate, 1.12; 95% CI, 0.70 to 1.79; p = 0.65) for prevention of asthma exacerbations. The rate of severe exacerbations was lower with budesonide/formoterol compared with albuterol as needed (relative risk, 0.40; 95% CI, 0.18 to 0.86) and budesonide with albuterol as needed (relative risk, 0.44; 95% CI, 0.20 to 0.96) (*Beasley et al 2019*).

Comparisons between different ICS/LABA combinations

- There are some data available comparing different combination ICS/LABA products for the treatment of COPD.
  - One crossover study comparing budesonide/formoterol to fluticasone propionate/salmeterol demonstrated no significant difference between products for the primary endpoint, the increase from baseline in peak expiratory flow 5 minutes after the morning dose (*Partridge et al 2009*). However, the mean morning FEV_1 improved more with budesonide/formoterol at 5 minutes and 15 minutes post-dose compared to fluticasone propionate/salmeterol.
  - Several published trials compared fluticasone furoate/vilanterol to fluticasone propionate/salmeterol in patients with COPD. Three of the trials were published together; pooled results demonstrated a greater improvement with fluticasone furoate/vilanterol 100/25 mcg once daily compared to fluticasone propionate/salmeterol 250/50 mcg twice daily on the primary endpoint, the weighted mean (wm) FEV_1 (0 to 24 hr) (*Dransfield et al 2014*). However, 2 of these 3 trials did not demonstrate a significant difference on this endpoint. An additional trial compared fluticasone furoate/vilanterol 100/25 mcg daily to fluticasone propionate/salmeterol 500/50 mcg twice daily and found no significant difference between groups on the wm FEV_1 (0 to 24 hr) (*Agusti et al 2014*).
- There have been several trials comparing combination ICS/LABA products to one another for the treatment of asthma.
  - Several head-to-head trials have compared budesonide/formoterol to fluticasone propionate/salmeterol. The trials varied in their design and the doses of medications. In general, these head-to-head trials have failed to demonstrate that one product is consistently superior to the other. Some trials showed benefits for fluticasone propionate/salmeterol on some endpoints (*Dahl et al 2006, Fitzgerald et al 2005, Price et al 2007*); some showed benefits for budesonide/formoterol (*Aalbers et al 2004, Palmqvist et al 2001*), and another showed no significant differences between the 2 products (*Busse et al 2008*).
  - A meta-analysis of 5 trials comparing fluticasone propionate/salmeterol 250/50 mcg twice daily vs varied doses of budesonide/formoterol twice daily failed to demonstrate significant differences in exacerbations, asthma-related serious adverse events, FEV_1, rescue medication use, symptom scores, or peak expiratory flow (*Lasserson et al 2011*).
  - A head-to-head trial comparing mometasone/formoterol to fluticasone propionate/salmeterol demonstrated non-inferiority for mometasone/formoterol for the primary endpoint of FEV_1 area under the curve (AUC) (0 to 12 hr) (*Bernstein et al 2011*). Treatment with mometasone/formoterol demonstrated a rapid onset of action, with significantly greater effects on FEV_1 at all time points up to 30 minutes post-dose compared to fluticasone propionate/salmeterol. Other secondary endpoints were not significantly different between groups.
  - A head-to-head trial comparing fluticasone furoate/vilanterol 100/25 mcg daily to fluticasone propionate/salmeterol 250/50 mcg twice daily demonstrated no significant differences between treatments on the primary endpoint, the wm FEV_1 (0 to 24 hr) (*Woodcock et al 2013*). There were also no significant differences in key secondary endpoints, including the time to onset of bronchodilator effect, percentage of patients obtaining ≥ 12% and ≥ 200 mL increase from baseline in FEV_1 at 12 hours and 24 hours, and change from baseline in trough FEV_1. Another trial comparing fluticasone furoate/vilanterol with fluticasone propionate/salmeterol demonstrated noninferiority of fluticasone furoate/vilanterol to fluticasone propionate/salmeterol in evening trough FEV_1 at week 24 (*Bernstein et al 2018*).

ICS/LABA compared to tiotropium or in combination with tiotropium for COPD

- A double-blind, double-dummy, 2-year trial (N = 1323) compared the use of fluticasone propionate/salmeterol 250/50 mcg twice daily to tiotropium 18 mcg daily in patients with COPD (*Wedzicha et al 2008*). This trial demonstrated no significant difference between groups in the rate of exacerbations or post-dose FEV_1. The study demonstrated higher mortality in the tiotropium group (6%) compared to the fluticasone propionate/salmeterol group (3%). This study was limited by the high number of withdrawals, which were unevenly distributed between the study arms.
- A double-blind, double-dummy, 12-week trial (N = 623) evaluated the use of fluticasone furoate/vilanterol 100/25 mcg daily and tiotropium 18 mcg daily in patients with moderate-to-severe COPD and an increased cardiovascular risk (*Covelli et al 2016*). There was no significant difference in the primary endpoint, the change from baseline in wm FEV_1 (0 to 24 hr). Minor differences were noted in some secondary efficacy endpoints and in the safety profiles. Pneumonia occurred more frequently in the fluticasone furoate/vilanterol group, and 2 patients in the tiotropium group died following cardiovascular events. The duration of this trial was not long enough to allow any firm conclusions about the relative efficacy and safety of fluticasone furoate/vilanterol vs tiotropium.
- In a Cochrane review that included the *Covelli et al 2016* trial and 1 additional 12 week trial comparing tiotropium to fluticasone furoate/vilanterol (N = 880 across both trials), there were no differences between treatments when considering the following outcomes: mortality, COPD exacerbation, pneumonia, St. George's respiratory questionnaire (SGRQ) score, hospital admissions, or use of rescue medication (*Sliwka et al 2018*).
- Several trials have evaluated the potential benefits of adding a combination ICS/LABA to tiotropium vs the use of tiotropium alone in patients with COPD. These trials generally demonstrated an improvement in FEV_1 and some other lung function, symptom score, and quality-of-life endpoints (*Hanania et al 2012, Lee et al 2016, Rojas-Reyes et al 2016, Welte et al 2009*). Some trials (*Lee et al 2016, Welte et al 2009*) also demonstrated a reduction in the risk of COPD exacerbations or severe exacerbations; however, other trials and a meta-analysis have not confirmed a significant benefit for exacerbations (*Aaron et al 2007, Hanania et al 2012, Karner et al 2011, Rojas-Reyes et al 2016*).

Beta$_2$-agonist/anticholinergic combinations for COPD

Comparisons of combination beta$_2$-agonist/anticholinergic products to bronchodilator monotherapy:

- Numerous trials have compared the combination beta$_2$-agonist/anticholinergic products to their respective individual components as monotherapy, and in general, results have demonstrated that administration of the combination product is more effective than monotherapy for improving lung function and/or achieving control of symptoms in COPD (*Bateman et al 2015*, *Beeh et al 2015, Bone et al 1994, Buhl et al 2015, Celli et al 2014, Decramer et al 2014, Donohue et al 2013, Dorinsky et al 1999, D'Urzo et al 2014, Friedman et al 1999, Hanania et al 2017, Kerwin et al 2017a, Mahler et al 2015, Maltais et al 2019a, Martinez et al 2017, Sethi et al 2019, Singh et al 2014*).
- A randomized phase 3 study of patients with COPD (N = 1594) found that twice-daily aclidinium/formoterol improved lung function compared to once-daily tiotropium by week 24 (*Sethi et al 2019*).
- PINNACLE-4, a randomized phase 3 study of 1756 patients with moderate-to-severe COPD, showed that glycopyrrolate/formoterol significantly improved predose trough FEV_1 at week 24 compared with glycopyrrolate monotherapy, formoterol monotherapy, or placebo (all $p < 0.0001$). The combination therapy also improved other lung function endpoints compared with individual agents or placebo (*Lipworth et al 2018*).
- A double-blind, double-dummy, 12-week trial (N = 494) compared the use of umeclidinium/vilanterol 62.5/25 mcg daily to tiotropium 18 mcg daily in patients with COPD who had been treated with tiotropium monotherapy at the time of enrollment (*Kerwin et al 2017a*). The primary endpoint, trough FEV_1, showed improved efficacy in the group that stepped up to combination therapy, with a between-group difference of 88 mL (95% CI, 45 to 131; $p < 0.001$). Improvements with umeclidinium/vilanterol were also observed in some secondary endpoints, including the use of rescue medication use and transition dyspnea index (TDI) score.
- A Cochrane review (N = 7 trials; 5921 participants) found an improvement in dyspnea, lung function, and number of responders with fixed-dose aclidinium/formoterol compared to monotherapy with individual agents or placebo in patients with stable COPD. However, no significant differences in exacerbations, hospital admissions, mortality, and adverse events were found with fixed-dose aclidinium/formoterol compared to aclidinium, formoterol, or placebo monotherapy (*Ni et al 2018*).
- A post hoc pooled analysis of 3 studies (N = 1747) showed improved trough FEV_1 with umeclidinium/vilanterol compared with tiotropium ($p < 0.001$) in patients with COPD (*Maleki-Yazdi et al 2017*).
- A large, randomized-controlled trial (N = 7880) of patients with COPD and a history of exacerbations did not find a difference in the rate of exacerbations between LAMA/LABA therapy with tiotropium/olodaterol vs LAMA therapy with tiotropium (relative risk [RR], 0.93; 99% CI, 0.85 to 1.02; $p = 0.0498$) (*Calverley et al 2018*).

- In a meta-analysis of 6 randomized trials in patients with COPD, tiotropium/olodaterol resulted in similar changes in lung function and similar tolerability compared to tiotropium alone (*He and Lin 2020*).
- A systematic review of 23 studies of beta$_2$-agonist/anticholinergic combinations compared to their monocomponents and to other single-agent treatments in patients with COPD was conducted (*Price et al 2016*). The analysis demonstrated that beta$_2$-agonist/anticholinergic combinations significantly improved lung function compared to their individual components. These combinations generally improved other outcomes compared to monotherapies as well, including symptoms and health status, but there were some discrepancies between lung function results and these patient-reported outcomes.
- A systematic review and network meta-analysis (N = 74 trials; 74,832 participants) evaluated the efficacy of SAMAs, LABAs, LAMA/LABAs and LABA/ICSs for maintenance treatment of COPD. At 12 and 24 weeks, LAMA, LAMA/LABAs, and LABA/ICSs led to a significantly greater improvement in trough FEV_1 compared with placebo and SAMA monotherapy. With the exception of aclidinium/formoterol, all other LAMA/LABA therapies were superior to LAMA monotherapy and LABA/ICS therapy in improving trough FEV_1. Furthermore, LAMA/LABA therapy had the highest probability of being the best treatment for in FEV_1 improvement; similar trends were observed for the TDI and SGRQ scores. Authors concluded that there were no significant differences among the LAMAs and LAMA/LABAs within their respective classes (*Aziz et al 2018*).
- A systematic review and meta-analysis (N = 8 trials) compared tiotropium 5 or 18 mcg with LAMA/LABA therapy in patients with moderate-to-severe COPD; ICS therapy was also allowed and use ranged from 33.7% to 54.4% among included trials. Therapy with LABA/LAMA was superior to tiotropium monotherapy for all of the following outcomes at 12 and 24 weeks: FEV_1 peak and trough, SGRQ responder rate, mean SGRQ score, and use of rescue medication. At 12 weeks, LABA/LAMA improved FEV_1 trough by 63 mL compared to tiotropium alone (95% CI, 39.2 to 86.8; $p < 0.01$). During the same time period, LABA/LAMA improved mean SGRQ responder rate by 19% (rate ratio, 1.19; 95% CI, 1.09 to 1.28; $p < 0.01$) and reduced SGRQ total score by 1.87 points (95% CI, -2.72 to -1.02; $p < 0.01$) compared to tiotropium (*Han et al 2018).*

<u>Comparisons of combination beta$_2$-agonist/anticholinergic products to each other or to other bronchodilator combinations</u>

- Several head-to-head trials between different LAMA/LABA combinations have been published.
  - An 8-week, open-label, crossover trial compared umeclidinium/vilanterol and tiotropium/olodaterol in 236 patients with COPD (*Feldman et al 2017*). The primary endpoint, change from baseline in trough FEV_1, was shown to be greater for umeclidinium/vilanterol, with a difference of 52 mL (95% CI, 28 to 77; $p < 0.001$ for superiority in the intention-to-treat population). Effects on secondary endpoints were mixed, with umeclidinium/vilanterol demonstrating a small improvement in rescue medication use but no significant differences in COPD Assessment Test (CAT) scores (a health status questionnaire) or EXACT Respiratory Symptoms (E-RS) scores at most weekly assessments.
  - Two 12-week, double-blind, crossover trials compared glycopyrrolate/indacaterol to umeclidinium/vilanterol in a total of 712 patients with COPD (*Kerwin et al 2017b*). The primary endpoint, FEV_1 AUC (0 to 24 hr), was similar between treatment arms in both studies, with differences for glycopyrrolate/indacaterol vs umeclidinium/vilanterol of -11.5 mL (95% CI, -26.9 to 3.8) and -18.2 mL (95% CI, -34.2 to -2.3) in Studies 1 and 2, respectively. Although the trials failed to demonstrate noninferiority of glycopyrrolate/indacaterol to umeclidinium/vilanterol due to the noninferiority margin used in the study methodology, the differences between treatments were not considered clinically meaningful.
  - A 24-week, double-blind, double-dummy, randomized phase 3 trial compared glycopyrrolate/formoterol and umeclidinium/vilanterol in 1119 patients with moderate-to-very severe COPD (*Maltais et al 2019b*). One of the primary endpoints, peak change from baseline in FEV_1 within 2 hours post-dose over 24 weeks, was similar between glycopyrrolate/formoterol and umeclidinium/vilanterol (LSM difference, -3.4 mL; 97.5% CI, -32.8 to 25.9). Glycopyrrolate/formoterol showed improved outcomes for another primary endpoint, change from baseline in morning pre-dose trough FEV_1 over 24 weeks, compared with umeclidinium/vilanterol (LSM difference, - 87.2 mL; 97.5% CI, -117.0 to - 57.4). The trial did not reveal any clinically meaningful differences in symptoms between the 2 treatments.
- A 12-week, non-inferiority, randomized, double-blind, triple-dummy, parallel group study (N = 967) compared umeclidinium/vilanterol (62.5/25 mcg once daily) to tiotropium (18 mcg once daily) plus indacaterol (150 mcg once daily) (*Kalberg et al 2016*). When comparing trough FEV_1 on day 85, umeclidinium/vilanterol demonstrated non-inferiority to combination treatment with tiotropium and indacaterol. Other measures, including rescue medication use, TDI focal scores, and SGRQ scores, were also similar between both treatment groups on day 85 (p values not provided).

- A meta-analysis of 26 randomized controlled trials comparing the efficacy of umeclidinium/vilanterol, indacaterol/glycopyrrolate, formoterol plus tiotropium, salmeterol plus tiotropium, or indacaterol plus tiotropium to tiotropium alone found that umeclidinium/vilanterol was comparable to other LAMA/LABA fixed-dose combination agents with respect to trough FEV_1, SGRQ scores, TDI focal scores, and need for rescue medication use (*Huisman et al 2015*).
- Several systematic reviews/meta-analyses compared various LAMA/LABA combinations (*Calzetta et al 2016, Schlueter et al 2016, Siddiqui et al 2019, Sion et al 2017*). Limitations to these analyses included the fact that trials evaluated some formulations/dose regimens not available in the U.S. and did not include the more recently approved products in some cases. Additionally, comparisons between different combinations were based on indirect data.
  - Overall, these meta-analyses demonstrated that all LAMA/LABA combinations showed improved lung function vs monocomponents, with few differences among products across lung function and patient-reported endpoints.
  - The analysis by *Sion et al* noted that both glycopyrrolate/indacaterol and umeclidinium/vilanterol appeared to improve lung function to a greater extent than tiotropium/olodaterol at 12 weeks, with differences in trough FEV_1 of 52 mL (95% credible interval [CrI], 18 to 86) and 38 mL (95% CrI, 13 to 63), respectively.
  - The *Schlueter et al* meta-analysis of 27 trials (N = 30,361) including 4 LAMA/LABA fixed-dose combination agents (aclidinium/formoterol 400/12 mcg [not FDA approved for use in the U.S.], glycopyrrolate/indacaterol 110/50 mcg, tiotropium/olodaterol 5/5 mcg, and umeclidinium/vilanterol 62.5/25 mcg), and showed non-significant differences in efficacy, exacerbations, and discontinuation rates (*Schlueter et al 2016*). Safety profiles were also similar among the products. The only statistically significant result indicated that umeclidinium/vilanterol appeared to improve lung function to a greater extent than aclidinium/formoterol at 24 to 26 weeks (difference of 61 mL; 95% CrI, 18 to 103; in favor of umeclidinium/vilanterol).

ICS/LABA compared to LAMA/LABA combinations for COPD

- A randomized, double-blind, 12-week trial (N = 717) compared umeclidinium/vilanterol 62.5/25 mcg once daily to fluticasone propionate/salmeterol 500/50 mcg twice daily in patients with moderate to severe COPD and no exacerbations in the previous year (*Singh et al 2015*). It should be noted that the dose of fluticasone propionate was higher than what is recommended in the U.S. for treatment of COPD. Treatment with umeclidinium/vilanterol resulted in greater improvement in lung function than fluticasone propionate/salmeterol, with a difference of 80 mL (95% CI, 46 to 113) in the wm FEV_1 (0 to 24 hr) and a difference of 90 mL (95% CI, 55 to 125) in trough FEV_1. Effects on rescue bronchodilator use, mean TDI focal score, and SGRQ total scores, and the incidence of adverse events, were similar between groups.
- Two randomized, double-blind, 12-week trials (N = 707 and N = 700; reported together) compared umeclidinium/vilanterol 62.5/25 mcg daily to fluticasone propionate/salmeterol 250/50 mcg twice daily in patients with moderate to severe COPD without exacerbations in the previous year (*Donohue et al 2015*). These trials also demonstrated a greater improvement in lung function endpoints for umeclidinium/vilanterol compared to fluticasone propionate/salmeterol, with differences in wm FEV_1 (0 to 24 hr) and trough FEV_1 ranging from 74 to 101 mL ($p < 0.001$ for all comparisons). Adverse event rates and effects on TDI score and SGRQ were similar between groups.
- A randomized, double-blind, 26-week trial (ILLUMINATE; N = 523) compared indacaterol/glycopyrrolate 110/50 mcg daily to fluticasone propionate/salmeterol 500/50 mcg twice daily in patients with COPD and a history of ≥ 1 exacerbation during the previous year (*Vogelmeier et al 2013*). The dosing regimens for indacaterol/glycopyrrolate and fluticasone propionate/salmeterol evaluated in this study are different from those available and/or recommended for COPD in the U.S. The primary endpoint, FEV_1 AUC (0 to 12 hr), was significantly higher with indacaterol/glycopyrrolate than fluticasone propionate/salmeterol, with a treatment difference of 138 mL (95% CI, 100 to 176; $p < 0.0001$). Benefits were also seen for indacaterol/glycopyrrolate for some secondary endpoints, including additional lung function measures, change from baseline in rescue medication use, and TDI focal score; the difference in SGRQ was not statistically significant.
- A large, randomized, double-blind, 52-week trial (FLAME; N = 3362) compared indacaterol/glycopyrrolate 110/50 mcg daily to fluticasone propionate/salmeterol 500/50 mcg twice daily in patients with COPD and a history of ≥ 1 exacerbation during the previous year (*Wedzicha et al 2016*). Again, these dosing regimens varied from U.S. recommendations. The primary endpoint, the annual rate of all COPD exacerbations, was 11% lower in the indacaterol/glycopyrrolate group than in the fluticasone propionate/salmeterol group (3.59 vs 4.03; rate ratio, 0.89; 95% CI, 0.83 to 0.96; $p = 0.003$). Lung function was also improved to a greater extent with indacaterol/glycopyrrolate, with a difference in trough FEV_1 of 62 mL between groups ($p < 0.001$).

- A randomized, double-blind, crossover trial (N = 229) evaluated the use of tiotropium/olodaterol 2.5/5 mcg and 5/5 mcg once daily and fluticasone propionate/salmeterol 250/50 mcg and 500/50 mcg twice daily in patients with moderate to severe COPD; each patient received each of the 4 treatments for 6 weeks separated by 3-week washout periods (*Beeh et al 2016*). The lower dose of each combination is the dose available/recommended for COPD in the U.S. The primary endpoint, FEV_1 AUC (0 to 12 hr), was greater for the tiotropium/olodaterol regimens (range, 295 to 317 mL) than for the fluticasone propionate/salmeterol regimens (range, 188 to 192 mL) ($p < 0.0001$). FEV_1 AUC (12 to 24 hr) and FEV_1 AUC (0 to 24 hr) also favored tiotropium/olodaterol. Rates of adverse events were similar among the treatments.
- A network meta-analysis of 16 randomized controlled trials (N = 17,734) compared fixed-dose combinations of LABA/LAMA vs ICS/LABA. The analysis showed that umeclidinium/vilanterol, glycopyrrolate/indacaterol, and glycopyrrolate/formoterol were the most effective in improving FEV_1. Glycopyrrolate/indacaterol significantly decreased the risk of exacerbations compared with fluticasone/salmeterol (*Calzetta et al 2019*).

Triple combinations for COPD and asthma

- Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol) inhalation powder was the first FDA-approved "closed triple" inhaler – an inhaler containing 3 active ingredients from 3 different therapeutic classes: an ICS, a LAMA, and a LABA.
  - Two 12-week randomized studies (N = 619 and N = 620; published together) evaluated the efficacy and safety of double-blind treatment with umeclidinium 62.5 mcg, umeclidinium 125 mcg, or placebo when added to open-label fluticasone furoate/vilanterol 100/25 mcg for the treatment of patients with COPD (*Siler et al 2015*) . In both studies, the primary endpoint, trough FEV_1, was significantly improved with the addition of umeclidinium, with improvements ranging from 111 to 128 mL ($p < 0.001$ for all comparisons vs placebo). Improvement was also demonstrated on the secondary endpoint of wm FEV_1 (0 to 6 hr), with improvements ranging from 125 to 153 mL ($p < 0.001$ for all comparisons vs placebo). SGRQ results were inconsistent. No substantial benefit was observed with umeclidinium 125 mcg over 62.5 mcg, which is consistent with findings in the umeclidinium monotherapy studies.
  - Once-daily triple therapy with fluticasone furoate/umeclidinium/vilanterol has also been compared to twice-daily budesonide/formoterol 400/12 mcg in a 24-week, double-blind, double-dummy randomized trial in patients with COPD (FULFIL; N = 1810) (*Lipson et al 2017*). The formulation/dosing regimen of budesonide/formoterol in this trial is different from the formulation available in the U.S. The trial demonstrated improvements in the change from baseline in trough FEV_1 (difference, 171 mL; 95% CI, 148 to 194; $p < 0.001$), SGRQ (difference, -2.2; 95% CI, -3.5 to -1.0; $p < 0.001$), and the rate of moderate/severe exacerbations (rate ratio, 0.65; 95% CI, 0.49 to 0.86; $p = 0.002$). Although the comparator regimen is not available in the U.S., this trial further supports the efficacy of triple inhaler therapy for COPD with fluticasone furoate/umeclidinium/vilanterol.
  - Once-daily triple therapy with fluticasone furoate/umeclidinium/vilanterol was compared to fluticasone furoate/vilanterol and umeclidinium/vilanterol in a 52-week, double-blind, randomized trial among patients with COPD (IMPACT; *Lipson et al 2018*). The primary endpoint of moderate or severe exacerbations was significantly lower with triple therapy in comparison both with fluticasone furoate/vilanterol (rate ratio, 0.85; 95% CI, 0.80 to 0.90) and with umeclidinium/vilanterol (rate ratio, 0.75; 95% CI, 0.70 to 0.81). The annual rate of severe exacerbation resulting in hospitalization was also significantly lower with triple therapy vs umeclidinium/vilanterol (rate ratio, 0.66; 95% CI, 0.56 to 0.78), but not vs fluticasone furoate/vilanterol. The mean change from baseline in trough FEV_1 was significantly increased with triple therapy by 97 and 54 mL vs fluticasone furoate/vilanterol and umeclidinium/vilanterol, respectively. The risk of pneumonia was significantly higher with triple therapy vs umeclidinium/vilanterol (HR, 1.53; 95% CI, 1.22 to 1.92), but not vs fluticasone furoate/vilanterol. Significant improvements in SGRQ total scores also occurred with triple therapy vs fluticasone furoate/vilanterol (mean difference, -1.8; 95% CI, -2.4 to -1.1) and vs umeclidinium/vilanterol (mean difference, -1.8; 95% CI, -2.6 to -1.0).
    - An updated, post hoc mortality analysis of IMPACT was published after the collection of additional vital status data. With known vital status for 99.6% of the intention-to-treat population (n = 10,335), there were 98 deaths (2.36%) in patients on umeclidinium/vilanterol/fluticasone furoate, 109 (2.64%) on vilanterol/fluticasone furoate, and 66 (3.19%) on umeclidinium/vilanterol. For triple therapy, the HR for death was 0.72 (95% CI, 0.53 to 0.99; $p = 0.042$) vs umeclidinium/vilanterol and 0.89 (95% CI, 0.67 to 1.16; $p = 0.387$) vs vilanterol/fluticasone furoate (*Lipson et al 2020*). The FDA noted several statistical and clinical issues with respect to interpretation of the mortality data, and the FDA Pulmonary-Allergy Drugs Advisory Committee voted 14-1 against a proposed labeling claim that Trelegy Ellipta reduces all-cause mortality in patients with COPD (*FDA Trelegy Ellipta briefing document 2020, Healio 2020*).
  - The 24- to 52-week double-blind CAPTAIN trial evaluated the safety and efficacy of triple therapy with Trelegy Ellipta (umeclidinium/vilanterol/fluticasone furoate) for the treatment of asthma in adult patients.

Umeclidinium/vilanterol/fluticasone furoate was compared to Breo Ellipta (vilanterol/fluticasone furoate). For the comparison of triple vs dual therapy using the lower strength (100 mcg) of fluticasone furoate, there was a significant improvement in the primary endpoint of change in trough FEV_1 at week 24, with a difference of 110 mL (95% CI, 66 to 153; p < 0.0001). The corresponding improvement for the higher strength (200 mcg fluticasone furoate) was also significant at 92 mL (95% CI, 49 to 135) (*Lee et al 2020*).
    - A numerical improvement in the annualized rate of moderate/severe exacerbations was seen between triple and dual therapy with the lower strength, but the difference did not reach statistical significance (rate ratio, 0.78 [95% CI, 0.61 to 1.01]; p = 0.060). The exacerbation rate was comparable between triple and dual therapy for the higher strength comparison (rate ratio, 0.97; 95% CI, 0.73 to 1.28; p = 0.80).
- An additional triple therapy product, Breztri Aerosphere (glycopyrrolate/formoterol/budesonide) inhalation aerosol, was FDA-approved in 2020. Safety and efficacy were demonstrated in 2 double-blind trials comparing triple therapy to dual therapy with glycopyrrolate/formoterol (Bevespi Aerosphere) or formoterol/budesonide in patients with COPD (*Ferguson et al 2018, Rabe et al 2020*).
    - In the 24-week KRONOS study (N = 1902), the FEV_1 AUC (0 to 4 hr) was significantly improved for triple therapy vs formoterol/budesonide, with a difference of 116 mL (95% CI, 80 to 152; p < 0.0001); the difference in change from baseline in pre-dose trough FEV_1 was nominally significant, with a difference of 74 mL (95% CI, 47 to 102; p < 0.0001). These lung function endpoints were not significantly improved for the triple therapy vs glycopyrrolate/formoterol; however, improvements were demonstrated in some secondary endpoints including SGRQ and the incidence of moderate or severe COPD exacerbations for this comparison (*Ferguson et al 2018*).
    - The 52-week ETHOS study (N = 8588) enrolled patients with a documented history of COPD exacerbation(s) in the preceding year. The primary endpoint of annualized rate of moderate or severe COPD exacerbations was significantly improved for triple therapy (with the marketed dose) compared to the corresponding doses of either dual therapy. For triple therapy vs glycopyrrolate/formoterol, the rate ratio was 0.76 (95% CI, 0.69 to 0.83; p < 0.001), and for triple therapy vs formoterol/budesonide, the rate ratio was 0.87 (95% CI, 0.79 to 0.96; p = 0.003) (*Rabe et al 2020*).

CLINICAL GUIDELINES

Asthma

- The National Asthma Education and Prevention Program (NAEPP) guideline from the NHLBI states that the initial treatment of asthma should correspond to the appropriate asthma severity category, and it provides a stepwise approach to asthma management. Long-term control medications such as ICS, long-acting bronchodilators, leukotriene modifiers, cromolyn, theophylline, and immunomodulators should be taken daily on a long-term basis to achieve and maintain control of persistent asthma. ICS are the most potent and consistently effective long-term asthma control medication. Quick-relief medications such as SABAs and anticholinergics are used to provide prompt relief of bronchoconstriction and accompanying acute symptoms such as cough, chest tightness, and wheezing. Systemic corticosteroids are important in the treatment of moderate or severe exacerbations because these medications prevent progression of the exacerbation, speed recovery, and prevent relapses (*NHLBI 2007*).
    - LABAs are used in combination with ICS for long-term control and prevention of symptoms in moderate or severe persistent asthma.
    - Of the adjunctive treatments available, a LABA is the preferred option to combine with an ICS in patients 12 years of age and older. This combination is also an option in selected patients 5 to 12 years of age.
- The 2020 Global Initiative for Asthma (GINA) Global Strategy for Asthma Management and Prevention report also provides a stepwise approach to asthma management. It recommends as-needed low-dose ICS-formoterol as a preferred controller medication to prevent exacerbations and control symptoms in adult or adolescent patients with infrequent asthma symptoms (eg, < twice a month). If patients remain uncontrolled, an ICS or ICS/LABA is the next preferred controller option. The choice of a specific dose and combination depends on the age of the patient and step within the therapy. As-needed ICS-formoterol is also the preferred reliever medication for adults and adolescents, while as-needed SABAs are the only option for reliever medications in children; of note, a low dose ICS should be taken whenever a SABA is taken. At the highest step of therapy, the patient should be referred for add-on treatment (eg, tiotropium, azithromycin, omalizumab, mepolizumab, benralizumab, reslizumab, dupilumab) (*GINA 2019, GINA 2020*).
- The 2020 GINA report provides interim guidance on the management of asthma in the context of the coronavirus disease 2019 (COVID-19) pandemic. Patients with asthma should continue their prescribed asthma medications, including ICS with or without LABA and add-on therapies, during the pandemic. Use of nebulizers should be avoided when possible to prevent transmission of the virus to other patients or healthcare workers (*GINA 2020*).

- The available asthma guidelines are generally similar; however, one difference among them is the recommendation of ICS/formoterol as both maintenance and rescue therapy by the GINA guidelines. The NHLBI does not recommend LABA medications for the management of acute asthma symptoms or exacerbations (*GINA 2020, NHLBI 2007*).
  - A meta-analysis of 16 randomized controlled trials evaluating the use of a LABA/ICS as single maintenance and reliever therapy found that it was associated with a significant reduction in the risk of asthma exacerbations compared with controller therapy with the same dose of ICS and LABA (rate ratio, 0.68; 95% CI, 0.58 to 0.80) (*Sobieraj et al 2018*). Of the 16 trials, 15 studied budesonide/formoterol in a dry powder inhaler. Results were similar in comparisons with doses of ICS and LABA controller therapy that were higher than the combined LABA/ICS, and in comparison with ICS controller therapy only.
- For a step-down process when asthma is well-controlled, GINA recommends reducing the ICS dose or switching to as-needed low dose ICS/formoterol (*GINA 2020*). *Chipps et al* propose using ICS/LABA combination with lower doses of ICS or switching from ICS to low-dose ICS/LABA combinations as patients move from higher to lower steps within asthma therapy (*Chipps et al 2019*).
- A European Respiratory Society/American Thoracic Society guideline on the management of severe asthma recommends the addition of tiotropium for patients with uncontrolled asthma despite GINA step 4 or 5 or NAEPP step 5 therapy, and a trial of chronic macrolide therapy to reduce exacerbations in patients who require additional control despite GINA step 5 or NAEPP step 5 therapy (*Holguin et al 2020*).

COPD

- The 2020 GOLD guidelines state that the management strategy for stable COPD should be predominantly based on an assessment of the patient's symptoms and risk of exacerbations; the risk of exacerbations is based on a patient's exacerbation history. Of note, the 2020 GOLD guidelines no longer recognize the phrase "asthma-COPD overlap," instead, emphasize that asthma and COPD are unique disease states with some similar signs and symptoms. Key recommendations from the GOLD guidelines are as follows (*GOLD 2020a*):
  - Inhaled bronchodilators are central to symptom management in COPD and commonly given on a regular basis to prevent or reduce symptoms. Inhaled bronchodilators are recommended over oral bronchodilators.
- LAMAs and LABAs significantly improve lung function, dyspnea, and health status, and reduce exacerbation rates.
  - LAMAs and LABAs are preferred over short-acting agents except for patients with only occasional dyspnea, and for immediate relief of symptoms in patients already receiving long-acting bronchodilators for maintenance therapy.
  - LAMAs have a greater effect on exacerbation reduction compared to LABAs and decrease hospitalizations.
- Patients may be started on single long-acting bronchodilator therapy or dual long-acting bronchodilator therapy. In patients with persistent dyspnea on 1 bronchodilator, treatment should be escalated to 2 bronchodilators.
  - Combination treatment with a LABA and LAMA:
    - Reduces exacerbations compared to monotherapy.
    - Increases FEV_1 and reduces symptoms compared to monotherapy.
- Key points for the use of inhaled medications include the following:
  - The choice of inhaler device must be individually tailored and will depend on factors including the patient's ability and preference.
  - It is essential to provide instructions and to demonstrate the proper inhalation technique when prescribing a device, ensure that inhaler technique is adequate, and re-check at each visit.
  - Inhaler technique and adherence to therapy should be assessed before concluding that the current therapy requires modification.
- Triple inhaled therapy of LAMA/LABA/ICS improves lung function, symptoms, and health status and reduces exacerbations compared to ICS/LABA, LABA/LAMA, or LAMA monotherapy.
- A number of recent studies have shown that blood eosinophil counts predict the magnitude of the effect of ICS in preventing exacerbations when added on top of regular maintenance bronchodilator treatment. ICS-containing regimens appear to have little or no effect at a blood eosinophil count < 100/mcL. The threshold of a blood eosinophil count > 300/mcL identifies the top of the continuous relationship between eosinophils and ICS and can be used to identify patients with the greatest likelihood of treatment benefit with ICS.
- Long-term monotherapy with ICS is not recommended. Long-term treatment with ICS may be considered in association with LABAs for patients with a history of exacerbations despite treatment with long-acting bronchodilators. Long-term treatment with ICS may cause pneumonia in patients with severe disease.
- Treatment recommendations are given for patients with COPD based on their GOLD patient group (see Table 3).

- Group A: Patients should be offered bronchodilator treatment (short- or long-acting), based on its effect on breathlessness. This should be continued if symptomatic benefit is documented.
- Group B: Initial therapy should consist of a long-acting bronchodilator (LAMA or LABA). For patients with persistent breathlessness on monotherapy, use of 2 bronchodilators is recommended (LAMA + LABA). For patients with severe breathlessness, initial therapy with 2 bronchodilators may be considered. If the addition of a second bronchodilator does not improve symptoms, it is suggested that treatment could be stepped down to a single bronchodilator; switching to another device or molecules can also be considered.
- Group C: Initial therapy should be a LAMA.
- Group D: In general, it is recommended to start therapy with a LAMA. For patients with more severe symptoms, especially dyspnea and/or exercise limitation, LAMA/LABA may be considered for initial treatment. In some patients, initial therapy with an ICS + LABA may be the first choice; these patients may have a history and/or findings suggestive of asthma or blood eosinophil count ≥ 300 cells/µL.
- Follow-up treatments: The follow-up treatments apply to any patients receiving maintenance treatment irrespective of the patient GOLD group.
  - For persistent dyspnea: The use of 2 bronchodilators is recommended in patients receiving 1 long-acting bronchodilator and experiencing persistent breathlessness or exercise limitation. Patients with persistent dyspnea symptoms on LABA + ICS may benefit from LAMA + LABA + ICS.
  - For exacerbations: Patients with persistent exacerbations on long-acting bronchodilator monotherapy may benefit from adding a second long-acting bronchodilator (LAMA + LABA, preferred) or using an ICS + LABA. For patients who have a history and/or findings suggestive of asthma or blood eosinophil count ≥ 300 cells/µL, ICS + LABA is preferred. In patients who develop further exacerbations on LAMA + LABA therapy, alternative pathways include escalation to a LAMA + LABA + ICS if eosinophil count ≥ 100 cells/µL or addition of roflumilast or azithromycin if eosinophil count < 100 cells/µL. In patients with additional exacerbations on LABA + ICS, patients should try LAMA + LABA + ICS therapy. If patients treated with a LAMA + LABA + ICS still have exacerbations, options for selected patients may include addition of roflumilast, addition of a macrolide, or stopping the ICS.
- Patients with COPD should continue their usual therapy, including inhaled or oral corticosteroids during the coronavirus disease 2019 (COVID-19) pandemic

- Patients with COPD should continue their regular therapy during the coronavirus disease 2019 (COVID-19) pandemic; GOLD is not aware of any scientific evidence to support that inhaled (or oral) corticosteroids should be avoided during this epidemic (*GOLD 2020b*).

Table 3. Assessment of Symptoms and Risk of Exacerbations to Determine GOLD Patient Group

Moderate/Severe Exacerbation history	Symptoms	
	mMRC 0 to 1 CAT <10	mMRC ≥ 2 CAT ≥10
≥ 2 (or ≥ 1 leading to hospital admission)	C	D
0 or 1 (not leading to hospital admission)	A	B

Abbreviations: CAT = COPD assessment test; mMRC = modified Medical Research Council questionnaire

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

- Guidelines from the American College of Chest Physicians and the Canadian Thoracic Society for prevention of acute exacerbations of COPD state that LAMA/LABA combinations are effective in reducing acute COPD exacerbations, but do not state that this combination is superior to LAMA monotherapy (*Criner et al 2015*).

SAFETY SUMMARY

Beta$_2$-agonist/corticosteroid combinations

- Beta$_2$-agonist/ICS combinations are generally contraindicated for the primary treatment of status asthmaticus or other acute episodes of asthma/COPD where intensive measures are required.
- Advair Diskus, AirDuo RespiClick, Breo Ellipta, and Wixela Inhub are contraindicated in patients with a severe hypersensitivity to milk proteins.
- Previously, ICS/LABA combinations had a boxed warning about an increased risk of asthma-related death, which had been observed with the LABA salmeterol. However, the boxed warning was removed from the prescribing information for ICS/LABA combinations in December 2017 based on an FDA review of 4 large clinical safety trials, which demonstrated that these combinations do not result in a significantly increased risk of asthma-related death, hospitalizations, or the need for intubation compared to ICS alone. There is still a warning/precaution in the prescribing information of ICS/LABA combinations related to the increased risk of asthma-related death with LABA monotherapy. A description of the clinical safety trials with ICS/LABA combinations has been added to the prescribing information for these products (*FDA 2017*).
- Other key warnings and precautions include:
  - Significant cardiovascular effects and fatalities with excessive use of beta$_2$-agonists
  - Cardiovascular and/or central nervous system effects from beta-adrenergic stimulation (seizures, angina, hypertension or hypotension, tachycardia, arrhythmias, nervousness, headache, tremor, palpitation, nausea, dizziness, fatigue, malaise, and insomnia)
  - Paradoxical bronchospasm
  - Hypercorticism and adrenal suppression due to systemic absorption of the corticosteroid
  - The need for caution when transferring patients from systemic corticosteroid therapy (deaths due to adrenal insufficiency have occurred)
  - Lower respiratory tract infections/pneumonia
  - Local infections of the mouth and pharynx with *Candida albicans*
  - Reduced growth velocity in pediatric patients
  - The potential for drug interactions with strong CYP3A4 inhibitors; concomitant use is not recommended due to the potential for increased systemic effects
  - The potential for developing glaucoma, increased intraocular pressure, blurred vision, central serous chorioretinopathy, or cataracts
  - Immunosuppression
  - Hypersensitivity
  - Reduction in bone mineral density
- It is also important to note that ICS/LABA combinations should not be initiated in the setting of disease deterioration or potentially life-threatening episodes.
- Commonly reported adverse events (≥ 5% for at least 1 medication in the class) include oral candidiasis, hoarseness/dysphonia, nasopharyngitis/pharyngitis, pharyngolaryngeal/oropharyngeal pain, sinusitis, upper respiratory tract infection, upper respiratory tract inflammation, bronchitis, cough, headache, gastrointestinal discomfort, and nausea/vomiting.

Beta$_2$-agonist/anticholinergic combinations

- Both albuterol/ipratropium combination products are contraindicated in patients with hypersensitivity to atropine or its derivatives. Anoro Ellipta and Duaklir Pressair are contraindicated in patients with hypersensitivity to any component of the product, as well as in patients with severe hypersensitivity to milk proteins. Anoro Ellipta, Bevespi Aerosphere, Duaklir Pressair, Stiolto Respimat, and Utibron Neohaler are contraindicated without ICS in patients with asthma.
- Anoro Ellipta, Bevespi Aerosphere, Duaklir Pressair, Stiolto Respimat, and Utibron Neohaler have a warning stating that LABAs increase the risk of asthma-related death. Data from a large placebo-controlled U.S. trial that compared the safety of another LABA (salmeterol) with placebo added to usual asthma therapy showed an increase in asthma-related

deaths in subjects receiving salmeterol. This finding with salmeterol is considered a class effect of all LABA, including formoterol (an active ingredient in Bevespi Aerosphere and Duaklir Pressair), indacaterol (an active ingredient in Utibron Neohaler), vilanterol (an active ingredient in Anoro Ellipta), and olodaterol (an active ingredient in Stiolto Respimat). The safety and efficacy of Anoro Ellipta, Bevespi Aerosphere, Duaklir Pressair, Stiolto Respimat, and Utibron Neohaler in patients with asthma have not been established, and these products are not indicated for the treatment of asthma.

- Warnings and precautions are very similar among products, and include the following:
  - Paradoxical bronchospasm: May produce paradoxical bronchospasm, which can be life-threatening. If it occurs, the product should be discontinued and alternative therapy instituted.
  - Cardiovascular effect: Beta$_2$-agonists can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, and/or symptoms. If these symptoms occur, the product may need to be discontinued. In addition, electrocardiogram (ECG) changes may occur. These products should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.
  - Ocular effects: Ipratropium and other anticholinergic agents may increase intraocular pressure, which may precipitate or worsen narrow-angle glaucoma. They should be used with caution in patients with narrow-angle glaucoma. In addition, patients should avoid spraying product into eyes, as this can cause eye pain and visual symptoms.
  - Urinary retention: Ipratropium and other anticholinergic agents may cause urinary retention. Caution is advised when administering to patients with prostatic hyperplasia or bladder-neck obstruction.
  - The recommended dose should not be exceeded: Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs in patients with asthma.
  - Hypersensitivity reactions: Urticaria, angioedema, rash, pruritus, bronchospasm, laryngospasm, oropharyngeal edema, and anaphylaxis may occur. If such a reaction occurs, therapy should be discontinued and alternative treatment considered.
  - Coexisting conditions: Due to the beta$_2$-agonist component, caution is advised in patients with convulsive disorders, hyperthyroidism, or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines.
  - Hypokalemia: β-agonists may produce significant hypokalemia in some patients, which has the potential to produce adverse cardiovascular effects. The decrease in serum potassium is usually transient, not requiring supplementation.
  - Drug interactions with strong CYP3A4 inhibitors; increased cardiovascular effects may occur (Anoro Ellipta only).
  - Reports of anaphylactic reactions in patients with severe milk protein allergy (Anoro Ellipta only).
  - Deterioration of disease and acute episodes; drug has not been studied in this setting and is not to relieve acute symptoms (Anoro Ellipta, Duaklir Pressair, and Stiolto Respimat only).
- Adverse reactions are similar among products and include back pain, bronchitis, upper respiratory infection, lung disease, headache, dyspnea, nasopharyngitis/pharyngitis, and cough.
- In a 12-week trial comparing Combivent Respimat to Combivent inhalation aerosol, rates of adverse reactions were very similar between groups. In a 48-week safety trial, most adverse reactions were similar in type and rate between treatment groups; however, cough occurred more frequently in patients enrolled in the Combivent Respimat group (7%) than the Combivent inhalation aerosol group (2.6%).
- The choice of a specific LAMA/LABA fixed-dose combination product is not based on any difference in the safety profile (*Matera et al 2016*).

Triple combination (beta$_2$-agonist/anticholinergic/corticosteroid [LAMA/LABA/ICS])

- Contraindications with Trelegy Ellipta include:
  - Severe hypersensitivity to milk proteins or any ingredients in the formulation.
  - Primary treatment of status asthmaticus or acute episodes of COPD or asthma requiring intensive measures
- Similar to other combination agents for COPD (and/or asthma), Trelegy Ellipta and Breztri Aerosphere have a number of additional warnings and precautions including:
  - Increased risk of asthma-related death
  - Not indicated for treatment of asthma
  - Not initiating in patients with rapidly deteriorating COPD
  - Avoiding excess use
  - Local effects of ICS
  - Risk of pneumonia
  - Immunosuppression
  - Using caution when transferring patients from systemic corticosteroid therapy

- Hypercorticism and adrenal suppression
- Drug interactions with strong cytochrome P450 (CYP) 3A4 inhibitors
- Paradoxical bronchospasm
- Hypersensitivity reactions
- Cardiovascular effects
- Reduction in bone mineral density
- Glaucoma and cataracts
- Urinary retention
- Using caution in patients with certain coexisting conditions such as convulsive disorders or thyrotoxicosis
- Hypokalemia and hyperglycemia

- The most common adverse reactions with Trelegy Ellipta include:
  - COPD (incidence ≥ 1%): upper respiratory tract infection, pneumonia, bronchitis, oral candidiasis, headache, back pain, arthralgia, influenza, sinusitis, pharyngitis, rhinitis, dysgeusia, constipation, urinary tract infection, diarrhea, gastroenteritis, oropharyngeal pain, cough, and dysphonia.
  - Asthma (incidence ≥ 2%): pharyngitis/nasopharyngitis, upper respiratory tract infection/viral upper respiratory tract infection, bronchitis, respiratory tract infection/viral respiratory tract infection, sinusitis/acute sinusitis, urinary tract infection, rhinitis, influenza, headache, and back pain.
- The most common adverse reactions (incidence ≥ 2%) with Breztri Aerosphere include upper respiratory tract infection, pneumonia, back pain, oral candidiasis, influenza, muscle spasm, urinary tract infection, cough, sinusitis, and diarrhea.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency
Beta$_2$-agonist & corticosteroid combinations			
Advair Diskus (fluticasone propionate/salmeterol)	Inhalation powder	Inhalation	2 times daily
Advair HFA (fluticasone propionate/salmeterol)	Aerosol inhaler	Inhalation	2 times daily
AirDuo RespiClick (fluticasone propionate/salmeterol)	Inhalation powder	Inhalation	2 times daily
AirDuo Digihaler (fluticasone propionate/salmeterol)*	Inhalation powder	Inhalation	2 times daily
Breo Ellipta (fluticasone furoate/vilanterol)	Inhalation powder	Inhalation	Once daily
Dulera (mometasone furoate/formoterol fumarate dihydrate)	Aerosol inhaler	Inhalation	2 times daily
Symbicort (budesonide/formoterol fumarate dihydrate)	Aerosol inhaler	Inhalation	2 times daily
Wixela Inhub (fluticasone propionate/salmeterol)	Inhalation powder	Inhalation	2 times daily
Beta$_2$-agonist & anticholinergic combinations			
Anoro Ellipta (umeclidinium/vilanterol)	Inhalation powder	Inhalation	Once daily
Bevespi Aerosphere (glycopyrrolate/formoterol fumarate)	Inhalation spray	Inhalation	2 times daily
Combivent Respimat (ipratropium bromide/albuterol)	Inhalation spray	Inhalation	4 times daily
Duaklir Pressair (aclidinium/formoterol fumarate)	Inhalation powder	Inhalation	2 times daily
ipratropium bromide/albuterol	Nebulizer solution	Inhalation (nebulizer)	4 times daily
Stiolto Respimat (tiotropium bromide/olodaterol)	Inhalation spray	Inhalation	Once daily
Utibron Neohaler (indacaterol/glycopyrrolate)	Inhalation powder	Inhalation	2 times daily
Triple combination			
Trelegy Ellipta (fluticasone furoate/umeclidinium/vilanterol)	Inhalation powder	Inhalation	Once daily
Breztri Aerosphere (glycopyrrolate/formoterol/budesonide)	Inhalation spray	Inhalation	2 times daily

*The AirDuo Digihaler contains a built-in electronic module which detects, records, and stores data on inhaler events, including peak inspiratory flow rate (L/minute), for transmission to mobile App. Use of the App is not required for administration of medication to the patient.

See the current prescribing information for full details.

CONCLUSION

- Respiratory medications, including bronchodilators and corticosteroids, are a mainstay of treatment for asthma and COPD, and a large amount of clinical evidence supports the safety and efficacy of combination beta$_2$-agonist agents for these indications.
  - Clinical trials have demonstrated that the combination products have superior efficacy compared with the individual separate components when given as monotherapy for the treatment of both asthma and COPD. The combination products are generally well tolerated.
- Several single-ingredient inhalers containing beta$_2$-agonists, ICS, or anticholinergics are also available. Beta$_2$-agonist combinations offer improved convenience over the use of multiple separate inhalers.
  - Trelegy Ellipta and Breztri Aerosphere are fixed-dose "triple therapy" combination inhalers combining a LAMA, a LABA, and an ICS. Both agents provide an alternative to the use of multiple inhalers for patients with COPD in whom triple therapy is indicated; Trelegy Ellipta is also an option for adult patients with asthma who require triple therapy.
- The GINA guideline supports the use of combination ICS/LABA products for long-term control and prevention of symptoms and exacerbations in patients with asthma.
  - Single-agent LABA therapy should not be used for asthma management due to the increased risk of asthma-related death, as well as asthma-related hospitalization in pediatric and adolescent patients. However, recent drug safety information from the FDA states that no significantly increased risk of serious asthma outcomes has been seen with the use of ICS/LABA combinations, and boxed warnings about this potential risk have been removed from the prescribing information for the ICS/LABA combinations.
  - An advantage of the ICS/LABA combination products is that their use ensures that patients are not using a LABA without a concomitant ICS.
  - In adults and adolescents, low dose ICS-formoterol is the preferred reliever medication. For chronic management of asthma, the preferred controller options consist of ICS-formoterol (on an as-needed basis), ICS, or ICS/LABA depending on the age of a patient and severity of symptoms.
- GOLD guidelines recommend the use of combination ICS/LABA products as an option for some patients at higher risk of exacerbations, a history and/or findings suggestive of asthma, or blood eosinophil count ≥ 300 cells/µL; however, the use of 1 or more bronchodilator without an ICS is recommended as first-line treatment for most COPD patients.
  - A LAMA is recommended as first-line treatment in most patients with COPD, with the exception of low-risk patients with milder symptoms, or patients with more severe symptoms.
- The current asthma and COPD treatment guidelines do not recommend the use of one specific combination product over another. The GINA guideline discusses the use of budesonide/formoterol as the preferred as-needed low-dose ICS/formoterol combination in lower steps of therapy.
  - Administration instructions and inhalation devices vary among products and should be considered in product selection.

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OPTUMRx®

Established Drug Classes

Therapeutic Class Overview
Calcitonin gene related peptide (CGRP) inhibitors

INTRODUCTION

- Migraine is a common, recurrent, incapacitating disorder characterized by moderate to severe headaches and disabling features, including nausea, vomiting, neurologic symptoms, photophobia, and phonophobia. Cluster headache is less prevalent than migraine and characterized by attacks of severe, unilateral pain with ipsilateral autonomic symptoms, which occur every other day to multiple times daily during a cluster period (*International Headache Society [IHS] 2018, Starling et al 2015).*
  - The goals for treatment of migraine are to reverse or stop the progression of a migraine attack. The goals for preventive treatment are to reduce the frequency, severity and duration of a migraine (*American Headache Society [AHS] 2019, Katsarava 2012*).
- The International Classification of Headache Disorders (ICHD) includes both cluster headache and migraine as part of a group of primary headache disorders (*IHS 2018*):
  - Chronic migraine is defined as ≥ 15 headache days per month for > 3 months with the features of migraine headache for at least 8 mean migraine days per month (MMD). The most common cause of symptoms suggestive of chronic migraine is medication overuse. According to the ICHD, around 50% of patients apparently with chronic migraine revert to an episodic migraine type after drug withdrawal; such patients are in a sense wrongly diagnosed with chronic migraine. In most clinical trials, migraine that is not chronic (ie, < 15 headache days per month) is considered to be episodic migraine, although the condition is not clearly defined in the ICHD.
  - Cluster headache is defined as ≥ 5 attacks lasting 15 to 180 minutes every other day to 8 times a day with severe unilateral orbital, supraorbital, and/or temporal pain. Episodic cluster headache attacks occur for a period of 7 days to 1 year and are separated by pain-free periods lasting at least 3 months. Common symptoms include nasal congestion, rhinorrhea, conjunctival injection and/or lacrimation, eyelid edema, sweating (forehead or face), miosis, ptosis, and/or a sense of restlessness or agitation.
- Cluster headache is more likely to occur in men, whereas migraines are more likely to occur in women. Migraines have a global prevalence of 15 to 18% and are a leading cause of disability worldwide. Chronic migraine is estimated to occur in 2 to 8% of patients with migraine, whereas episodic migraine occurs in more than 90% of patients. Cluster headache is rare compared to other primary headache disorders. It is estimated to have a prevalence of 0.1% within the general population (*Global Burden of Disease Study [GBD] 2016, Hoffman et al 2018, Lipton et al 2016, Ljubisavljevic et al 2019, Manack et al 2011*).
- Treatments for migraines and cluster headache are divided into acute and preventive therapies. Evidence and reputable guidelines clearly delineate appropriate therapies for episodic migraine treatment and prophylaxis; options stretch across a wide variety of therapeutic classes and are usually oral therapies. For the prevention of migraines, treatment options include oral prophylactic therapies, injectable prophylactic therapies, and neuromodulator devices. Oral prophylactic migraine therapies have modest efficacy, and certain oral therapies may not be appropriate for individual patients due to intolerability or eventual lack of efficacy. For the treatment of acute migraine, options include triptans, ergots, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, small molecule CGRP inhibitors, and a 5-hydroxytryptamine (5-HT)$_{1F}$ receptor agonist. For the treatment of cluster headache, subcutaneous sumatriptan, zolmitriptan nasal spray, and oxygen have the most positive evidence for acute therapy, and suboccipital steroid injections are most effective for prevention (*American Migraine Foundation [AMF] 2020, Marmura et al 2015, Robbins et al 2016, Silberstein et al 2012, Simpson et al 2016)*.
- The calcitonin gene-related peptide (CGRP) pathway is important in pain modulation and the Food and Drug Administration (FDA) has approved 6 CGRP inhibitors for prevention or treatment of migraine/headache disorder(s). Erenumab-aooe is a fully human monoclonal antibody, which potently binds to the CGRP receptor in a competitive and reversible manner with greater selectivity than to other human calcitonin family receptors. Fremanezumab-vfrm, eptinezumab-jjmr, and galcanezumab-gnlm are humanized monoclonal antibodies that bind to the CGRP ligand and block its binding to the receptor. Rimegepant and ubrogepant are small molecule oral CGRP receptor antagonists (*Dodick et al 2018[b], Edvinsson 2017, Goadsby et al 2017, Sun et al 2016, Tepper et al 2017*).
  - Two CGRP inhibitors known as the “gepants,” telcagepant and olcegepant, were previously investigated. In 2009, Merck withdrew the FDA application for telcagepant because of elevated liver enzymes and potential liver toxicity

observed with chronic use, which was likely related to the chemical structure of the compound. The manufacturer of olcegepant also ceased pursuing FDA approval; however, the manufacturer did not explicitly state the rationale. It has been widely speculated that olcegepant development ceased due to limitations associated with administration as an intravenous (IV)-only product (*Edvinsson et al 2017, Walker et al 2013*). No substantial issues with liver toxicity have been observed in trials with the currently marketed CGRP inhibitors.
  - Additional CGRP inhibitors early in their development include vazegepant, the first intranasally administered CGRP inhibitor, and atogepant, another oral CGRP inhibitor (*Biohaven press release 2019*, *Staines 2019*).
  - In April 2019, Teva announced that it would not pursue development of fremanezumab-vfrm for an episodic cluster headache indication due to results from the ENFORCE trial (*Teva Pharmaceuticals press release 2019*). Erenumab-aooe and eptinezumab-jjmr are not currently under clinical investigation for the indication of cluster headache (*Clinicaltrials.gov 2020*).
- Medispan class: Migraine products – monoclonal antibodies; Calcitonin gene−related peptide (CGRP) receptor antagonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Aimovig (erenumab−aooe)	–
Ajovy (fremanezumab-vfrm)	–
Nurtec ODT (rimegepant sulfate)	–
Emgality (galcanezumab-gnlm)	–
Ubrelvy (ubrogepant)	–
Vyepti (eptinezumab-jjmr)	–

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	**Aimovig** (erenumab−aooe)	**Ajovy** (fremanezumab-vfrm)	**Emgality** (galcanezumab-gnlm)	**Nurtec ODT** (rimegepant)	**Ubrelvy** (ubrogepant)	**Vyepti** (eptinezumab-jjmr)
Acute treatment of migraine with or without aura in adults	-	-	-	✔*	✔*	-
Preventive treatment of migraine in adults	✔	✔	✔	-	-	✔
Treatment of episodic cluster headache in adults	-	-	✔	-	-	-

* Limitation of use: Not indicated for the preventive treatment of migraine.

(*Prescribing information: Aimovig 2020, Ajovy 2020, Emgality 2019, Nurtec ODT, Ubrelvy 2019, Vyepti 2020*)

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

CLINICAL EFFICACY SUMMARY

- Rimegepant ODT has been studied as acute therapy in approximately 1466 patients in 1 Phase 3 trial of episodic migraine (with or without aura) patients and in 1 unpublished long-term safety trial. Three additional trials evaluating the efficacy and safety of rimegepant 75 mg in an oral tablet formulation were considered supportive for approval; 2 trials

included approximately 2348 patients with episodic migraine, and 1 dose-ranging study included 885 patients randomized to 6 dose groups of rimegepant, sumatriptan 100 mg, or placebo.

- Ubrogepant has been studied as acute therapy in approximately 3360 patients across 2 trials in patients with 2 to 8 migraines/month with moderate to severe pain intensity either with or without aura and in 1 unpublished, open-label extension (OLE) trial.
- Eptinezumab-jjmr has been studied in approximately 2019 patients across 2 trials in patients with episodic or chronic migraine subtypes for prevention, with data available in published formats.
- Erenumab-aooe has been studied as preventive therapy in approximately 2500 patients across 4 trials in patients with episodic or chronic migraine subtypes and 1 OLE trial, with data available in published and unpublished formats.
- Fremanezumab-vfrm has been studied as preventive therapy in approximately 2005 patients across 3 trials in patients with episodic or chronic migraine subtypes, with data available in published formats. In fremanezumab-vfrm trials, the definition of a headache or migraine day for the primary endpoint required a consecutive 2 hour (episodic) or 4 hour (chronic) duration of pain, compared to other CGRP inhibitor trials that required a duration of ≥ 30 minutes.
- Galcanezumab-gnlm has been studied as preventive therapy in approximately 2886 patients across 3 trials in patients with episodic or chronic migraine subtypes and 1 long-term safety trial with unpublished data to 1 year. The efficacy and safety of galcanezumab-gnlm was evaluated for treatment in one 8-week study with 106 adults with episodic cluster headache (maximum of 8 attacks/day).
- The definition of the primary and secondary endpoints differed in the prevention of episodic and chronic migraine trials. Additional differences included, but were not limited to, co-morbid conditions, concomitant medications, a requirement of stable doses of migraine prevention medication (if co-administered) for certain durations, and the definitions of headache, migraine headache, and migraine day. Some CGRP inhibitor trials allowed patients to receive concomitant preventive migraine medication during treatment. Also, some chronic migraine trials allowed for the inclusion of patients with medication overuse headache.

Prevention of episodic migraine

Eptinezumab-jjmr

- PROMISE-1 was a double-blind (DB), placebo-controlled (PC), multi-center (MC), Phase 3 trial in which adults with a history of episodic migraine were randomized to receive placebo (n = 222), eptinezumab-jjmr 100 mg (n = 221), or eptinezumab-jjmr 300 mg (n = 222) every 3 months for 12 months. The primary efficacy endpoint was the change in MMD from baseline to week 12. Eptinezumab-jjmr 100 mg and 300 mg significantly reduced MMDs across weeks 1 to 12 compared with placebo (placebo, −3.2; 100 mg, −3.9, p = 0.02; 300 mg, −4.3, p = 0.0001). The odds for a 50% reduction in MMD were approximately 1.7 to 2.2 times higher with eptinezumab-jjmr than placebo. Of note, the endpoints underwent a testing hierarchy and were not significant for 50% migraine responder rates in the 100 mg dose group (*Ashina et al 2020, Vyepti [dossier] 2020).*

Erenumab-aooe

- The STRIVE trial was a 6-month, DB, PC, MC, Phase 3 trial in which 955 patients with episodic migraine were randomized to placebo (n = 319), erenumab-aooe 70 mg (n = 317), or erenumab-aooe 140 mg (n = 319) once monthly. The primary endpoint was the change in mean MMD from baseline to months 4 to 6, which favored treatment with erenumab−aooe 70 mg (mean change vs placebo, −1.4; 95% confidence interval [CI], −1.9 to −0.9; p < 0.001) and erenumab−aooe 140 mg (mean change vs placebo, −1.9; 95% CI, −2.3 to −1.4; p < 0.001). Erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 70 mg vs placebo, 16.7%; odds ratio [OR], 2.13; difference for 140 mg vs placebo, 23.4%; OR, 2.81). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 70 mg vs placebo, −0.9; difference for 140 mg vs placebo, −1.4) (*Goadsby et al 2017*).
- The ARISE trial was a 12-week, DB, PC, MC, Phase 3 trial in which 577 patients with episodic migraine were randomized to placebo (n = 291) or erenumab-aooe 70 mg (n = 286) once monthly. The primary endpoint was the change in MMD from baseline to weeks 9 to 12, which favored treatment with erenumab−aooe 70 mg (mean change vs placebo, −1.0; 95% CI, −1.6 to −0.5; p < 0.001). Compared to placebo, erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference, 10.2%; OR, 1.59). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference, −0.6) (*Dodick et al 2018[a]*).

- The LIBERTY trial was a 12-week, DB, PC, MC, Phase 3b trial in which 246 patients with episodic migraine who failed 2 to 4 prior preventive migraine treatments were randomized to placebo (n = 125) or erenumab-aooe 140 mg (n = 121) once monthly. The primary endpoint was the proportion of patients with ≥ 50% reduction in MMD from baseline to the last 4 weeks of DB treatment (weeks 9 to 12), which erenumab−aooe significantly increased over placebo (difference, 16.6%; OR, 2.73; 95% CI, 1.43 to 5.19; p = 0.002). Compared to placebo, 5.9% more patients treated with erenumab−aooe 140 mg reported a 100% reduction in MMD, or migraine cessation. Erenumab-aooe 140 mg/month compared with placebo significantly reduced the MMD (difference, −1.61; 95% CI, −2.70 to −0.52; p = 0.004). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference, −1.73) (*Reuter et al 2018*).

Fremanezumab-vfrm

- The HALO-EM trial was a 12-week, DB, PC, MC, Phase 3 trial in which 875 patients with episodic migraine were randomized to placebo (n = 294), fremanezumab-vfrm 225 mg once monthly (n = 290), or fremanezumab-vfrm 675 mg once quarterly (n = 291). The primary endpoint was the change in mean MMD, which favored treatment with fremanezumab-vfrm 225 mg (mean change vs placebo, −1.5; 95% CI, −2.0 to −0.9; p < 0.001) and fremanezumab-vfrm 675 mg (mean change vs placebo, −1.3; 95% CI, −1.8 to −0.7; p < 0.001). Of note, HALO-EM was powered to detect a 1.6-day difference in the MMD between the fremanezumab-vfrm and placebo groups, but effect sizes resulted in a 1.5-day reduction for the fremanezumab-vfrm monthly dosing group and a 1.3-day reduction for the fremanezumab-vfrm quarterly dosing group. Although the threshold was not reached, a minimal clinically important difference has not been established for this particular outcome. Compared to placebo, greater MMD reductions were also observed in patients who were prescribed fremanezumab-vfrm 225 mg (mean change vs placebo, −1.3) and 675 mg (mean change vs placebo, −1.1) as monotherapy. Fremanezumab-vfrm significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 225 mg vs placebo, 19.8%; OR, 2.36; difference for 675 mg vs placebo, 16.5%; OR, 2.06). Additionally, fremanezumab-vfrm was associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 225 mg vs placebo, −1.4; difference for 675 mg vs placebo, −1.3) (*Dodick et al 2018[b]*).
- FOCUS was a DB, PC, Phase 3b trial that evaluated 838 patients with episodic (39%) or chronic migraine (61%) who had previously not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, approximately 40% were classified as having episodic migraines and randomized to fremanezumab-vfrm 225 mg administered monthly with no loading dose (n = 110/283), fremanezumab-vfrm 675 mg administered quarterly (n = 107/276), or placebo (n = 112/279) for 12 weeks. Failure was defined as no clinically meaningful improvement after at least 3 months of therapy at a stable dose, as per the treating physician's judgment, discontinuation because of adverse events that made treatment intolerable, or treatment contraindicated or unsuitable for the preventive treatment of migraine for the patient. At baseline, the MMD was approximately 14.2 days and the MMHD (of at least moderate severity) was 12.6 days. For the overall population, the MMD reduction over 12 weeks was 0.6 (standard error [SE], 0.3) days for placebo, 4.1 (SE, 0.34) days for the monthly fremanezumab-vfrm group (least squares mean difference [LSMD] vs placebo, -3.5; 95% CI, -4.2 to -2.8 days; p < 0.0001), and 3.7 (SE, 0.3) for days for the quarterly fremanezumab-vfrm group (LSMD vs placebo, -3.1; 95% CI, -3.8 to -2.4 days; p < 0.0001). For episodic migraine and compared to placebo, the LSMD in MMD reduction over 12 weeks was 3.1 days for both dose groups (fremanezumab-vfrm monthly: LSMD, -3.1; 95% CI, -4.0 to -2.3 days; fremanezumab-vfrm quarterly: LSMD, -3.1; 95% CI, -3.9 to -2.2 days; p < 0.0001 for both). In the overall population, the proportions of patients with a ≥ 50% response over 12 weeks were 34% in both the quarterly and monthly fremanezumab-vfrm groups vs 9% with placebo (p < 0.0001). Only the monthly fremanezumab-vfrm arm achieved a ≥ 75% sustained responder rate that was statistically different from placebo (OR, 8.6; 95% CI, 2.0 to 37.9; p = 0.0045). Adverse events were similar for placebo and fremanezumab-vfrm. Serious adverse events were reported in 4 (1%) of 277 patients with placebo, 4 (1%) of 285 with monthly fremanezumab-vfrm, and 2 (< 1%) of 276 with quarterly fremanezumab-vfrm (*Ferrari et al 2019*).

Galcanezumab-gnlm

- The EVOLVE-1 and EVOLVE-2 trials were 6-month, DB, PC, MC, Phase 3 trials in 858 and 915 patients with episodic migraine, respectively. Patients were randomized to placebo (EVOLVE-1, n = 433; EVOLVE-2, n = 461), galcanezumab-gnlm 120 mg once monthly (EVOLVE-1, n = 213; EVOLVE-2, n = 231), or galcanezumab-gnlm 240 mg once monthly (EVOLVE-1, n = 212; EVOLVE-2, n = 223). Patients in the galcanezumab-gnlm 120 mg group received a loading dose of 240 mg at the first injection only. The EVOLVE-1 trial included a North American population and the EVOLVE-2 trial included a global population. The primary endpoint was the change in mean monthly migraine headache days (MMHD) (*Stauffer et al 2018, Skljarevski et al 2018*).

- In EVOLVE-1, the primary endpoint outcome favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −1.9; 95% CI, −2.5 to −1.4; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.8; 95% CI, −2.3 to −1.2; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 23.7%; OR, 2.64; difference for 240 mg vs placebo, 22.3%; OR, 2.50). Compared to placebo, 9.4% more patients treated with galcanezumab-gnlm 120 mg and 9.4% more treated with galcanezumab-gnlm 240 mg reported a 100% reduction in MMHD, or migraine cessation. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −1.8; difference for 240 mg vs placebo, −1.6) (*Stauffer et al 2018*).
- In EVOLVE-2, the primary endpoint outcome favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −2.0; 95% CI, −2.6 to −1.5; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.9; 95% CI, −2.4 to −1.4; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 23.0%; OR, 2.54; difference for 240 mg vs placebo, 21.0%; OR, 2.34). Compared to placebo, 5.8% more patients treated with galcanezumab-gnlm 120 mg and 8.1% more treated with galcanezumab-gnlm 240 mg reported migraine cessation. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −1.8; difference for 240 mg vs placebo, −1.7) (*Skljarevski et al 2018*).
- In an analysis of persistence for patients with episodic migraine, 41.5 and 41.1% of galcanezumab-gnlm-treated patients (120 mg and 240 mg, respectively) had a ≥ 50% response for ≥ 3 months, which was greater than placebo (21.4%; p < 0.001). Approximately 6% of galcanezumab-gnlm-treated patients maintained ≥ 75% response all 6 months vs 2% of placebo-treated patients. Few galcanezumab-gnlm-treated patients maintained 100% response for all 6 months (< 1.5%) (*Förderreuther et al 2018*).

Prevention of chronic migraine

Eptinezumab-jjmr

- The PROMISE-2 trial was a 12-week, DB, PC, MC, Phase 3 trial in which 1121 patients with chronic migraine were randomized to placebo (n = 366), eptinezumab-jjmr 100 mg (n = 356), or eptinezumab-jjmr 300 mg (n = 350) once every 12 weeks (or quarterly). The primary endpoint was the change in mean MMD. Treatment with eptinezumab 100 and 300 mg was associated with significant reductions in MMDs across weeks 1 to 12 compared with placebo (placebo −5.6; 100 mg −7.7, p < 0.0001; 300mg −8.2, p < 0.0001). The odds for a 50% reduction in MMD were approximately 2.1 to 2.4 times higher with eptinezumab-jjmr than placebo (*Lipton et al 2020*).

Erenumab-aooe

- Erenumab-aooe was studied in a 12−week, DB, PC, MC, Phase 2 trial in which 667 patients with chronic migraine were randomized to placebo (n = 286), erenumab−aooe 70 mg (n = 191), or erenumab−aooe 140 mg (n = 190) once monthly. The primary endpoint was the change in MMD from baseline to weeks 9 to 12, which favored treatment with erenumab−aooe 70 mg and erenumab−aooe 140 mg (mean change for both doses vs placebo, −2.5; 95% CI, −3.5 to −1.4; p < 0.0001). Erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 70 mg vs placebo, 17%; OR, 2.2; difference for 140 mg vs placebo, 18%; OR, 2.3). Both erenumab−aooe 70 mg (difference, −1.9) and erenumab−aooe 140 mg (difference, −2.6) significantly reduced the mean acute migraine−specific medication days; however, the higher 140 mg dose had a greater reduction numerically over placebo and reductions may be dose−dependent (*Tepper et al 2017*).
  - An analysis of patient reported outcomes found patients with chronic migraine had clinically relevant improvements across a range of measures. Improvements were observed at month 3 for all endpoints regardless of erenumab−aooe dose, and minimally important clinical differences were achieved for certain measures with the erenumab−aooe 140 mg dose (*Lipton et al 2019[b]*).

Fremanezumab-vfrm

- Fremanezumab-vfrm was studied in a 12-week, DB, PC, MC, Phase 3 trial, HALO-CM, in which 1130 patients with chronic migraine were randomized to placebo (n = 375), fremanezumab-vfrm 225 mg once monthly (n = 379), or fremanezumab-vfrm 675 mg once quarterly (n = 376). Patients in the fremanezumab-vfrm 225 mg group received a loading dose of 675 mg at the first injection only. The primary endpoint was the change in mean headache days (MHD), which favored treatment with fremanezumab-vfrm 225 mg (mean change vs placebo, −2.1; SE, ± 0.3; p < 0.001) and fremanezumab-vfrm 675 mg (mean change vs placebo, −1.8; SE, ± 0.3; p < 0.001). Fremanezumab-vfrm significantly increased the proportion of patients achieving ≥ 50% reduction in MHD (difference for 225 mg vs placebo, 22.7%; OR,

2.73; difference for 675 mg vs placebo, 19.5%; OR, 3.13). Additionally, fremanezumab-vfrm was associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 225 mg vs placebo, −2.3; difference for 675 mg vs placebo, −1.8) (*Silberstein et al 2017*).

- FOCUS was previously described as including 838 patients overall who had not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, 61% were diagnosed with chronic migraine and were randomized to fremanezumab-vfrm 675 mg administered quarterly (n = 169/276), a fremanezumab-vfrm 675 mg loading dose followed by 225 mg administered monthly (n = 173/283), or placebo (n = 167/279). Among patients classified as having chronic migraine and compared to placebo, the LSMD in MMD reduction over 12 weeks was 3.8 days for the fremanezumab-vfrm monthly group and 3.2 days for the fremanezumab-vfrm quarterly group (fremanezumab-vfrm monthly: LSMD, -3.8; 95% CI, -4.8 to -2.8 days; fremanezumab-vfrm quarterly: LSMD, -3.2; 95% CI, -4.2 to -2.2 days; p < 0.0001 for both) (*Ferrari et al 2019*).

Galcanezumab-gnlm

- Galcanezumab-gnlm was evaluated in a 12-week, DB, PC, MC, Phase 3 trial, REGAIN, in which 1113 patients with chronic migraine were randomized to placebo (n = 558), galcanezumab-gnlm 120 mg once monthly (n = 278), or galcanezumab-gnlm 240 mg once monthly (n = 277). Patients in the galcanezumab-gnlm 120 mg group received a loading dose of 240 mg at the first injection only. The primary endpoint was the change in MMHD, which favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −2.1; 95% CI, −2.9 to −1.3; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.9; 95% CI, −2.7 to −1.1; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 12.2%; OR, 2.10; difference for 240 mg vs placebo, 12.1%; OR, 2.10). Compared to placebo, 0.2% more patients treated with galcanezumab-gnlm 120 mg and 0.8% more treated with galcanezumab-gnlm 240 mg reported migraine cessation; this was not statistically different for either dose group. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −2.5; difference for 240 mg vs placebo, −2.1) (*Detke et al 2018*).
  - In an analysis of persistence for patients with chronic migraine, 29% of galcanezumab-gnlm-treated patients maintained ≥ 30% response all 3 months compared to 16% of placebo-treated patients. A total of 16.8 and 14.6% of galcanezumab-gnlm-treated patients (120 mg and 240 mg, respectively) had a ≥ 50% response for ≥ 3 months, which was greater than placebo (6.3%; p < 0.001). Few patients maintained ≥ 75% response (< 3%) (*Förderreuther et al 2018*).

Treatment of episodic cluster headache

Galcanezumab-gnlm

- Galcanezumab-gnlm was evaluated in an 8-week, DB trial, in which 106 patients with episodic cluster headache were randomized to placebo (n = 57) or galcanezumab-gnlm 300 mg once monthly (n = 49). A total of 90 (85%) patients completed the DB phase. Patients were allowed to use certain specified acute/abortive cluster headache treatments, including triptans, oxygen, acetaminophen (APAP), and NSAIDs during the study. At baseline, patients had a mean of 17.5 headache attacks/week, maximum of 8 attacks/day, minimum of 1 attack every other day, and at least 4 attacks during the prospective 7-day baseline period. For the primary endpoint, galcanezumab-gnlm significantly decreased the mean change from baseline in weekly cluster headache attack frequency during weeks 1 to 3 vs placebo (-8.7 vs -5.2 attacks; p = 0.036). Galcanezumab-gnlm was also associated with a significantly greater proportion of responders (≥ 50% reduction in weekly cluster headache attack frequency) at week 3 (71.4 vs 52.6%; p = 0.046). Adverse events did not differ between groups, except for a significant increase in the incidence of injection-site pain with galcanezumab-gnlm treated patients (8 vs 0%; p = 0.04) (*Clinicaltrials.gov [NCT02397473] 2020, Emgality prescribing information 2019, Goadsby et al 2019*).

Treatment of acute migraine (with or without aura)

Rimegepant ODT

- Rimegepant ODT was evaluated in a Phase 3, DB, MC, PC, randomized controlled trial (RCT) in 1466 patients (modified intention to treat, n = 1351) with migraine with or without aura. Patients were randomized to placebo (n = 682) or rimegepant ODT 75 mg (n = 669) and were not allowed a second dose of study treatment. Rescue medications allowed 2 hours post-dose included aspirin, ibuprofen, naproxen (or any other type of NSAID), APAP up to 1000 mg/day, antiemetics (eg, metoclopramide or promethazine), or baclofen. Approximately 14% of patients were taking

preventive medications for migraine at baseline. The co-primary endpoints were pain freedom and most bothersome symptom (MBS) freedom at 2 hours post-dose. Among patients randomized, 92.2% were included in the efficacy analysis and 93.8% in the safety analysis (*Croop et al 2019, Nurtec ODT [dossier] 2020, Nurtec ODT prescribing information 2020*).
  - The percentage of patients achieving headache pain freedom and MBS freedom 2 hours after a single dose was statistically significantly greater in patients who received rimegepant ODT compared to those who received placebo.
    - *Pain-free at 2 hours*: 21.2% for rimegepant ODT 75 mg vs 10.9% for placebo ($p < 0.0001$)
    - *MBS-free at 2 hours*: 35.1% for rimegepant ODT 75 mg vs 26.8% for placebo ($p = 0.0009$)
  - Out of the 21 secondary endpoints tested hierarchically, significant results were achieved for the first 19 endpoints. Those endpoints that were considered not significant included freedom from nausea at 2 hours post-dose, and pain relapse from 2 to 48 hours.
  - The most common adverse events were nausea and urinary tract infection. No serious adverse events were reported.
- Three additional trials evaluating the efficacy and safety of rimegepant 75 mg in an oral tablet (non-ODT) formulation were considered supportive for approval.
  - A MC, DB, dose-ranging trial using an adaptive design was conducted to determine an effective and tolerable dose range of rimegepant for the acute treatment of migraine. A total of 885 adults with migraine with or without aura were randomized to 1 of 6 rimegepant dose groups (10, 25, 75, 150, 300, or 600 mg), sumatriptan 100 mg, or placebo. It was found that the proportion of patients who were pain-free 2 hours after receiving a single dose of rimegepant 75 mg oral tablet was significantly higher compared with placebo (31.4% [n = 27/86] vs 15.3% [n = 31/203]; $p = 0.002$). The most common adverse events were nausea, vomiting, and dizziness. No treatment-related serious AEs were reported (*Marcus et al 2014*).
  - A MC, DB, PC, Phase 3 trial (n = 1072 in efficacy analysis) evaluating rimegepant vs placebo for acute migraine treatment found that the proportion of patients who were pain-free 2 hours after receiving a single dose of rimegepant 75 mg oral tablet was significantly higher compared with placebo (19.6 vs 12.0%; absolute difference, 7.6%; 95% CI, 3.3 to 11.9; $p < 0.001$). In addition, the proportion of patients who were free from their MBS 2 hours post-dose was significantly higher with rimegepant 75 mg oral tablet compared with placebo (37.6 vs 25.2%; absolute difference, 12.4%; 95% CI, 6.9 to 17.9; $p < 0.001$). Nausea and urinary tract infection were the only AEs reported in > 1% of the patients in the rimegepant and placebo groups. A serious adverse event associated with rimegepant was back pain (n = 1) (*Lipton et al 2019[c]*, *Nurtec ODT [dossier] 2020*).
  - A MC, DB, PC, Phase 3 trial (n = 1084 in efficacy analysis) evaluating rimegepant vs placebo for acute migraine treatment found that the proportion of patients who were pain-free 2 hours after receiving a single dose of rimegepant 75 mg oral tablet was significantly higher compared with placebo (19.2 vs 14.2%; $p = 0.03$). In addition, the proportion of patients who were free from their MBS 2 hours post-dose was significantly higher with rimegepant 75 mg oral tablet compared with placebo (36.6 vs 27.7%; $p = 0.002$). Nausea and dizziness were the most common adverse events reported in the rimegepant and placebo treatment groups, respectively. Serious adverse events were reported in 2 patients treated with rimegepant and 1 patient treated with placebo (*Lipton et al 2018 [poster], Nurtec ODT [dossier] 2020*).

Ubrogepant

- Ubrogepant was evaluated in 2 Phase 3, PC, DB trials (ACHIEVE I and II), in which 3358 patients (ACHIEVE I, n = 1672; ACHIEVE II, n =1686) were randomized to take 1 dose of placebo (n = 1122), ubrogepant 50 mg (n = 1118), or ubrogepant 100 mg (n = 557) (100 mg was evaluated in the ACHIEVE I trial only, and a 25 mg group was included in the ACHIEVE II trial only [n = 561]). Patients had 2 to 8 migraines/month with moderate to severe pain intensity in the past 3 months either with or without aura and had a history of migraine for ≥ 1 year. A second dose of study treatment (placebo or ubrogepant), or the patient's usual acute treatment for migraine, was allowed between 2 to 48 hours after the initial treatment for a non-responding or recurrent migraine headache. At baseline, 23% of patients were taking preventive medications for migraine, and approximately 23 to 27% were insufficient triptan responders. In ACHIEVE I, 79% were included in the efficacy analysis and 86% in the safety analysis, and in ACHIEVE II, 91.7% had a qualifying migraine event and 88% were included in the analysis (*Dodick et al 2019, Lipton et al 2019[a], Ubrelvy prescribing information 2019*).
  - Compared to placebo, significant improvements were demonstrated for the co-primary endpoints of pain freedom and the MBS freedom at 2 hours post-dose in the ubrogepant arms. MBS was a collection of selective, self-identified symptoms (ie, photophobia, phonophobia, or nausea). The following differences from placebo were demonstrated:

  - *Pain-free at 2 hours*: 7.4% (p = 0.002) and 7.5% (p = 0.007) for the ubrogepant 50 mg dose in ACHIEVE I and II trials, respectively, and 9.4% (p < 0.001) for ubrogepant 100 mg dose in ACHIEVE I trial.
  - *MBS-free at 2 hours*: 10.8% and 11.5% (p < 0.001 for both) for the ubrogepant 50 mg dose in ACHIEVE I and II trials, respectively, and 9.9% (p < 0.001) for ubrogepant 100 mg dose in ACHIEVE I trial.
- The incidence of photo- and phonophobia was reduced following administration. Significantly more patients maintained pain freedom for 2 to 24 hours post-dose in the ubrogepant 100 mg arm (difference from placebo, 6.8%; p = 0.002) and the 50 mg arm for ACHIEVE II only (6.2%; p = 0.005).
- In ACHIEVE I, the most common adverse events included nausea (1.5 to 4.7%), somnolence (0.6 to 2.5%), and dry mouth (0.6 to 2.1%). In ACHIEVE II, the most common adverse events within 48 hours were nausea (≤ 2.5% for all arms) and dizziness (≤ 2.1% for all arms). No serious adverse events or adverse events leading to discontinuation were reported 48 hours after the initial dose. In ACHIEVE II, the serious adverse events at 30 days included appendicitis, spontaneous abortion, pericardial effusion, and seizure.

Open-label extensions (OLE) and long-term safety studies

- One published OLE with data to 1 year and 1 unpublished abstract with data to ≥ 3 years evaluated erenumab-aooe 70 mg (protocol amended to include 140 mg doses) in patients with episodic migraine. Of 472 patients in the parent study, 308 patients completed 1 year of open-label (OL) treatment. For the ≥ 3 year assessment, of the 383 patients enrolled in the OLE, 250 continued into the 140 mg once monthly dosing. At the time of interim analysis, 236 patients remained in the OLE (*Amgen [data on file] 2018, Ashina et al 2017, Ashina et al 2018*).
  - There may be greater improvements with sustained therapy based on a 1-year OLE interim analysis of episodic migraine patients treated with erenumab-aooe 70 mg once monthly. Patients had a mean value of 8.8 MMDs at parent study baseline. After 3 months of treatment in the parent study, the number of MMDs was reduced to 6.3 days (mean change of 2.5 days). After a total of 16 months of treatment, the number of MMDs was reduced to 3.7 days (mean change of 5.1 days). After 64 weeks, 65% (n = 184) of episodic migraine patients achieved a ≥ 50% reduction in MMDs and 26% (n = 73) had achieved a migraine-free status. The most frequently reported adverse events (≥ 4.0 per 100 patient-years) were viral upper respiratory tract infection, upper respiratory tract infection, sinusitis, influenza, and back pain.
- One unpublished OLE evaluated erenumab-aooe 70 mg (protocol amended to include 140 mg doses) with data to 1 year in patients with chronic migraine. A total of 609 patients with chronic migraine enrolled in the OLE. A total of 199 increased their dose from 70 mg to 140 mg by week 28 (*Amgen [data on file] 2018, Tepper et al 2018*).
  - Patients with chronic migraine had a mean value of 18.8 MMDs at parent study baseline. After a total of 1 year of treatment, the number of MMDs was reduced to 8.5 in the erenumab-aooe 70 mg group and 10.5 in the erenumab-aooe 140 mg group. After 1 year of erenumab-aooe 70 mg and 140 mg monthly dosing, a total of 53% and 67% of chronic migraine patients achieved a ≥ 50% reduction in MMDs and 6% and 13% had achieved a migraine-free status, respectively. The most frequently reported adverse events (≥ 2.0 per 100 patient-years) were viral upper respiratory tract infection, upper respiratory tract infection, sinusitis, and arthralgia.
- Another unpublished safety study, the CGAJ study, evaluated galcanezumab-gnlm 120 mg (plus 240 mg loading dose) and 240 mg monthly dosing to 1 year in patients with episodic or chronic migraine. At baseline, 80.7% of patients in the galcanezumab-gnlm 120 mg arm and 77.0% in the galcanezumab-gnlm 240 mg arm had episodic migraine. A total of 270 patients who had a history of ≥ 4 MMHDs and ≥ 1 headache-free day/month for the past 3 months continued galcanezumab-gnlm treatment (*Eli Lilly and Company [data on file] 2018, Emgality [dossier] 2018, Stauffer et al 2017*).
  - At baseline, patients had a mean value of 9.7 to 11.4 (standard deviation [SD], 6.0 to 6.6) MMHDs. After a total of 1 year of treatment, the number of MMHDs was reduced to 5.6 days in the galcanezumab-gnlm 120 mg group and 6.5 days in the galcanezumab-gnlm 240 mg group. After ≥ 12 consecutive months of treatment, 24.2% of patients treated with galcanezumab-gnlm 120 mg and 34.8% of patients treated with galcanezumab-gnlm 240 mg maintained response. The most frequently reported adverse events (incidence ≥ 15.0%) were injection site pain, nasopharyngitis, and upper respiratory tract infections. One patient discontinued due to suicidal ideation in the galcanezumab-gnlm 120 mg group. There were no overall concerns regarding safety or tolerability.
- The long-term safety of ubrogepant was evaluated in 813 patients with intermittent dosing administered for up to 1 year in an OLE. Of the 813 patients, 421 patients were exposed to ubrogepant 50 mg or 100 mg for ≥ 6 months, and 364 patients were exposed for ≥ 1 year. All patients were treated for ≥ 2 migraine attacks/month, on average. In the OLE, 2.5% of patients withdrew from ubrogepant treatment because of an adverse reaction. The most common adverse

reaction resulting in discontinuation in the OLE was nausea (*Clinicaltrials.gov [NCT02873221] 2020, Ubrelvy prescribing information 2019*).

- Rimegepant 75 mg was evaluated in an unpublished interim analysis of a long-term safety study which evaluated 1784 patients for up to 52 weeks. The most frequently reported adverse events were upper respiratory tract infection (8.5%) and nasopharyngitis (6.4%). There were no deaths, and the rates of serious adverse events and adverse events leading to discontinuation of rimegepant were low (2.5% and 2.7%, respectively). No clinically relevant trends in laboratory abnormalities were observed on-treatment or during follow up (*Nurtec ODT dossier 2020*).
- Caution should be exercised in applying results from extension trials. The OL design may contribute to biased reports. Extension trials may have biased outcomes because those experiencing benefit are included in extension trials; results are useful for reporting trends in treatment. Additionally, there is no comparator to account for placebo effects.

CLINICAL GUIDELINES

Acute treatment of migraine

- The American Headache Society (AHS) published updated consensus statement guidelines for migraine in 2018. The AHS recommends the use of APAP, NSAIDs, non-opioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans or dihydroergotamine (DHE) are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics. These guidelines do not differentiate the triptans, but recommend that non-oral routes be used when severe nausea or vomiting is present. Overall, the AHS designated the following drugs as having efficacy (*AHS 2019*):
  - Established efficacy:
    - Triptans
    - Ergotamine derivatives
    - NSAIDs (aspirin, diclofenac, ibuprofen, naproxen)
    - Opioids (butorphanol, although use is not recommended)
    - Combination medications
  - Probably effective
    - Ergotamine or other forms of DHE
    - NSAIDs (ketoprofen, ketorolac intramuscular or IV, flurbiprofen)
    - Magnesium IV
    - Isometheptene compounds
    - Combination medications (codeine/APAP, tramadol/APAP)
    - Antiemetics (prochlorperazine, promethazine, droperidol, chlorpromazine, metoclopramide)
  - The AHS recommends that rimegepant and ubrogepant may have a role in patients who have contraindications to the use of triptans or who have failed to respond to or tolerate ≥ 2 oral triptans, as determined by either a validated acute treatment patient reported outcome questionnaire or healthcare provider attestation. Coverage should be provided until ≥ 2 attacks are treated to determine efficacy and tolerability.
    - Other agents have had more established efficacy and safety relative to the newly FDA-approved migraine agents.
- There are a number of older guidelines/treatment recommendations for the treatment of migraine but, similar to the 2018 guidelines, they do not state a preference for a particular triptan or therapy (*Evers et al 2009, Francis et al 2010, Marmura et al 2015, Silberstein 2000, Silberstein et al 2012 [guideline reaffirmed in 2015]*).
- In 2019, the American Academy of Neurology (AAN) and the AHS published a guideline on the acute treatment of migraine in children and adolescents. The guideline states that there is evidence to support the efficacy of ibuprofen, APAP (in children and adolescents), and triptans (mainly in adolescents) for migraine relief, although confidence in the evidence varies between agents (*Oskoui et al 2019[a]*).
  - Of note, the CGRP inhibitors have not been adequately studied in children or adolescents and are not currently FDA-approved for use in these populations.

Prevention of migraine

- According to the AAN/AHS evidence−based guideline update on the pharmacologic treatment for episodic migraine prevention in adults, the following medications are effective preventive treatment options (see Appendix A for a definition of classifications) (*Silberstein et al 2012*):
  - Level A (established efficacy and > 2 Class I trials):
    - Antiepileptic drugs: divalproex sodium, sodium valproate, and topiramate

    - Beta blockers: metoprolol, propranolol, and timolol
    - Triptans (for menstrual related migraine [MRM]): for short−term prophylaxis, frovatriptan
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Antidepressants: amitriptyline and venlafaxine
    - Beta blockers: atenolol and nadolol
    - Triptans (for MRM): for short−term prophylaxis, naratriptan and zolmitriptan
  - Level C (possibly effective and 1 Class II trial):
    - Angiotensin−converting enzyme (ACE) inhibitors: lisinopril
    - Angiotensin II receptor blockers (ARBs): candesartan
    - Alpha agonists: clonidine and guanfacine
    - Antiepileptic drugs: carbamazepine
    - Beta blockers: nebivolol and pindolol
    - Antihistamines: cyproheptadine
- The AAN recommends onabotulinumtoxin A as an effective treatment option that should be offered for chronic migraine. However, onabotulinumtoxin A is considered ineffective for the treatment of episodic migraines and should not be offered. There is insufficient evidence to compare the effectiveness of botulinum neurotoxin A with that of oral prophylactic topiramate (*Simpson et al 2016*).
- In 2019, the AAN/AHS published a guideline on the preventive treatment of migraine in pediatric patients. The guideline states that the majority of preventive medications for pediatric migraine fail to demonstrate superiority to placebo. The guidelines make the following statements and recommendations for initial therapy (see Appendix B for a definition of classifications) (*Oskoui et al 2019[b]*):
  - It is possible that cognitive behavioral therapy (CBT) alone is effective in migraine prevention.
  - There is insufficient evidence to evaluate the effects of flunarizine, nimodipine, valproate, and onabotulinumtoxinA for use in migraine prevention in children and adolescents.
  - Acknowledging the limitations of currently available evidence, use of short-term treatment trials (a minimum of 2 months) may be warranted in those who could benefit from preventive treatment (Level B).
  - Consider amitriptyline combined with cognitive behavioral therapy (CBT) (inform of the potential adverse events, including risk of suicide) (Level B).
  - Consider topiramate (Level B). Inform of side effects including decreased efficacy when combined with oral contraceptives and the teratogenic effect in patients of childbearing potential (Level A). In patients of childbearing potential, daily folic acid is recommended (Level A).
  - Consider propranolol (Level B).
    - Of note, the CGRP inhibitors have not been adequately studied in children or adolescents and are not currently FDA-approved for use in these populations.

Cluster headache

- According to the AHS evidence-based guidelines for the treatment of cluster headache, there are a number of effective treatment options (AAN classifications were used for grading; see Appendix A for definitions) (*Robbins et al 2016*).
- For acute therapy of cluster headache, the following therapy options have positive evidence:
  - Level A (established efficacy and ≥ 2 Class I trials):
    - Certain triptans: sumatriptan subcutaneous and zolmitriptan nasal spray
    - Oxygen
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Certain triptans: sumatriptan nasal spray and zolmitriptan oral
    - Sphenopalatine ganglion stimulation
  - Level C (possibly effective and 1 Class II trial):
    - Cocaine/lidocaine nasal spray
    - Octreotide subcutaneous
- For preventive therapy of cluster headache, the following therapy options have positive evidence:
  - Level A (established efficacy and ≥ 2 Class I trials):
    - Suboccipital steroid injection
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Civamide nasal spray (not marketed in the US)

- Level C (possibly effective and 1 Class II trial):
  - Lithium
  - Verapamil
  - Warfarin
  - Melatonin

SAFETY SUMMARY

- Ubrogepant is contraindicated with concomitant use of strong CYP3A4 inhibitors.
- Eptinezumab-jjmr, erenumab-aooe, fremanezumab-vfrm, galcanezumab-gnlm, and rimegepant are contraindicated in patients with serious hypersensitivity to the active ingredient or any of the excipients. Mild to moderate hypersensitivity reactions (eg, rash, dyspnea, pruritus, urticaria) were reported in trials. Cases of anaphylaxis and angioedema have been reported post-marketing. Delayed serious hypersensitivity has occurred with rimegepant. In cases of serious or severe reactions, treatment should be discontinued.
- Warnings and precautions associated with the CGRP inhibitors include hypersensitivity reactions. Erenumab-aooe has additional warnings and precautions associated with the following:
  - Constipation with serious complications: Constipation with serious complications has been reported post-marketing. Some cases have required hospitalization, including surgery. Constipation was a common adverse event reported in up to 3% of patients. Concurrent use of medication associated with decreased gastrointestinal motility may increase the risk for severe constipation.
  - Hypertension: Post-marketing reports of the development or worsening of hypertension have emerged. Some cases required pharmacological treatment to manage or, in other cases, hospitalization. Incidences of hypertension were most frequently reported within 7 days of treatment, and most cases were reported after the first dose.
- The CGRP inhibitors generally have a similar incidence of adverse events as placebo. Very few severe adverse events and treatment discontinuations due to adverse events were reported. Across studies, adverse events were generally mild and/or similar to placebo. The most common adverse events observed in studies of injectable CGRP inhibitors included injection site reactions (subcutaneous CGRP inhibitors), constipation (erenumab-aooe only), and nasopharyngitis and hypersensitivity (eptinezumab-jjmr only). For the oral CGRP inhibitors, ubrogepant was associated with somnolence, and both ubrogepant and rimegepant were associated with nausea.
- CGRP is a vasodilator and is found at higher concentrations during a migraine attack. In the 1-year interim analysis of an OLE study with erenumab-aooe, 2 patients had severe adverse events (a fatal arteriosclerosis event and a myocardial ischemia event confounded by sumatriptan administration). No additional concerns were raised within the OLE at ≥ 3 years, including any CV events. In a long-term safety study of patients treated with galcanezumab-gnlm for 1 year, 1 patient discontinued due to suicidal ideation in the galcanezumab-gnlm 120 mg group. In a safety study of eptinezumab-jjmr in which 90.2% of patients were exposed to the drug for ≥ 6 months and 47.7% were exposed for ≥ 12 months, the most common adverse events observed were nasopharyngitis and hypersensitivity. A total of 9 patients reported serious adverse events with ubrogepant 50 mg (sinus tachycardia, intestinal obstruction, gait disturbance, cholelithiasis, acute cholecystitis, allergy, pneumonia, pelvic inflammatory disease, post-procedure infection, hypertensive crisis, and a substance-induced mood disorder) and 12 with ubrogepant 100 mg (colitis, hiatus hernia, acute pancreatitis, non-cardiac chest pain, cholelithiasis, acute cholecystitis, gastroenteritis, pneumonia, sepsis, subdural hematoma, ketoacidosis, hemiparesis, abortion, ectopic pregnancy, suicidal ideation, and acute respiratory failure); however, not all events may be related to treatment. In an interim analysis of an OL, 52-week safety study of rimegepant, the most frequently reported adverse events were upper respiratory tract infection and nasopharyngitis. There were no deaths, and the rates of serious adverse events and adverse events leading to discontinuation of rimegepant were low. The long-term implications of prolonged CGRP inhibition are not fully established and safety has not been fully characterized *(Amgen [data on file] 2018, Ashina et al 2017, Ashina et al 2018, Clinicaltrials.gov [NCT02873221] 2020, Eli Lilly and Company [data on file] 2018, Nurtec ODT [dossier] 2020,Stauffer et al 2017, Tepper et al 2018, Vyepti prescribing information 2020)*.
- There are no adequate data on the risks associated in patients who are pregnant or nursing, or in adolescent or pediatric populations.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Aimovig (erenumab−aooe)	Auto-injector (70 mg/mL or 140 mg/mL)	SC	Once monthly (70 or 140 mg)	May be self−administered by patients in the abdomen, thigh, or back of upper arm. Latex−sensitive patients may have an allergic reaction to the needle shield within the white cap and the gray needle cap of the syringe. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, erenumab-aooe has a limited stability of 7 days.
Ajovy (fremanezumab−vfrm)	Prefilled syringe (225 mg/1.5 mL)	SC	Once monthly (225 mg) or once every 3 months (675 mg)	May be self−administered by patients in the abdomen, thigh, or back of upper arm. The prefilled syringe cap is not made with natural rubber latex. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, fremanezumab-vfrm has a limited stability of 24 hours.
Emgality (galcanezumab−gnlm)	Auto-injector (120 mg/mL) Prefilled syringe (100 mg/mL or 120 mg/mL)	SC	*Prevention of migraine*: 2 consecutive injections (120 mg each) as a loading dose, then once monthly *Episodic cluster headache*: 3 consecutive injections (100 mg each) at onset, and then once monthly until the end of the cluster period	May be self−administered by patients in the abdomen, thigh, back of upper arm or buttocks. The cap is not made with natural rubber latex. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, galcanezumab-gnlm has a limited stability of 7 days.
Nurtec ODT (rimegepant sulfate)	ODT (75 mg)	PO	*Acute migraine treatment:* As needed. Maximum dose: 75 mg in 24 hours.	The safety of treating > 15 migraines in a 30-day period has not been established. Avoid concomitant administration with strong inhibitors of CYP3A4, moderate or strong inducers of CYP3A, or P-gp or BCRP inhibitors.
Ubrelvy (ubrogepant)	Oral tablets (50 and 100 mg)	PO	*Acute migraine treatment:* As needed. A second dose may be taken at least 2 hours after the	The safety of treating > 8 migraines in a 30 day period has not been established.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			initial dose. Maximum dose: 200 mg in 24 hours.	Dose adjustments are warranted with certain concomitant drugs or in cases of metabolic impairment. Avoid use in patients with end stage renal disease (CrCL < 15 mL/min). Take with or without food
Vyepti (eptinezumab-jjmr)	Single-dose vial (100 mg/mL)	IV	Once every 3 months (100 or 300 mg) The recommended dosage is 100 mg every 3 months; some patients may benefit from a dosage of 300 mg every 3 months.	Dilute with 0.9% sodium chloride injection. Following dilution, eptinezumab-jjmr must be infused within 8 hours. Infuse over approximately 30 minutes. Administered by a healthcare provider in a healthcare setting. Must be refrigerated and protected from light until time of use.

See the current prescribing information for full details
Abbreviations: CrCL = creatinine clearance; CYP = cytochrome P450; BCRP = breast cancer resistance protein; IV = intravenous; ODT = orally disintegrating tablet; P-gp = P-glycoprotein; PO = oral; SC = subcutaneous
Note: With all of the CGRP inhibitors, there are no data in pregnant women or breastfed infants. A benefit/risk assessment should be taken into consideration prior to administering.

CONCLUSION

- Migraine is a common, recurrent, incapacitating disorder characterized by moderate to severe headaches and disabling features, including nausea, vomiting, neurologic symptoms, photophobia, and phonophobia. Migraines have a spectrum of frequency and severity that can significantly affect the quality of life of patients. Cluster headache is less prevalent than migraine and characterized by attacks of severe, unilateral pain with ipsilateral autonomic symptoms, which occur every other day to multiple times daily during a cluster period. Cluster headache is more likely to occur in men, whereas migraines are more likely to occur in women.
- Rimegepant and ubrogepant are oral CGRP inhibitors indicated for acute treatment of migraine with or without aura. The injectable CGRP inhibitors eptinezumab-jjmr, erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm are indicated for the prevention of migraine. Galcanezumab-gnlm has an additional indication for the treatment of episodic cluster headache. No CGRP inhibitor is FDA-approved for use in patients aged < 18 years. Eptinezumab-jjmr is the only IV formulation and requires administration in a healthcare setting.
- Guidelines divide treatment recommendations according to age, prevention or treatment, and migraine type:
  - Current evidence−based prophylactic migraine treatment options and guidance are limited for chronic migraine, and oral prophylactic medications prescribed for episodic migraine are often used for the preventive treatment of chronic migraine. Prophylactic migraine treatment options include oral agents (mainly anti−seizure agents, antidepressants, and beta blockers), injectable agents (onabotulinumtoxin A for chronic subtypes only), or neuromodulation devices for migraine or headache attacks. Certain oral therapies may not be appropriate for individual patients due to intolerability or eventual lack of efficacy. There is no optimal prophylactic migraine therapy and head-to-head trials are lacking.
  - For the treatment of cluster headache, subcutaneous sumatriptan, zolmitriptan nasal spray, and oxygen have the most positive evidence for acute therapy according to the AHS guidelines. To date, only subcutaneous sumatriptan is FDA-approved for the acute treatment of cluster headache. Additionally, sumatriptan nasal spray, zolmitriptan oral formulations, and sphenopalatine ganglion stimulation are probably effective for acute treatment per guidelines. For prevention of cluster headaches, suboccipital steroid injections are most effective according to the guidelines; however, there is no preventive medication currently FDA-approved for cluster headache.

- For acute treatment of migraine in adults, guidelines generally recommend the use of APAP, NSAIDs, non-opioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans or DHE are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics. Recent AHS guidelines state that rimegepant and ubrogepant may have a role in patients who have contraindications to the use of triptans or who have failed to respond to or tolerate ≥ 2 oral triptans.

- There are no head-to-head studies with the CGRP inhibitors and no agent is clearly superior to others. Evidence for the CGRP inhibitors have demonstrated efficacy for the respective indications:
  - Like other preventive medications for migraine, the CGRP inhibitors are not likely to render patients migraine-free. Based on 3 to 6 month data, primary endpoint reductions are similar to many oral prophylactic therapies; however, comparisons are limited as endpoints have been inconsistently defined. There are limited analyses and trials examining efficacy in patients who failed ≥ 2 prior preventive therapies; however, available data suggest that these patients may achieve greater reductions in migraine/headache frequency. Further research is warranted.
    - Compared to placebo, the CGRP inhibitors when prescribed for prophylactic migraine therapy consistently demonstrated modest but statistically significant reductions in primary endpoint measures (eg, MMD, MMH, or MMHD) ranging from 0.7 to 3.5 days after 3 to 6 months of treatment. Overall, the odds for a 50% reduction in MM(H)D were approximately 1.6 to 5.8 times higher with the CGRP inhibitors than placebo with numbers-needed to treat (NNTs) ranging from 3 to 10.
  - For the treatment of cluster headaches, galcanezumab-gnlm demonstrated efficacy compared to placebo in an 8-week trial, which allowed for acute/abortive treatments during therapy. Galcanezumab-gnlm significantly decreased the mean change from baseline in weekly cluster headache attack frequency by 3.5 during weeks 1 to 3 vs placebo. Additionally, 18.8% more patients were classified as responders (≥ 50% reduction in weekly cluster headache attack frequency) with galcanezumab-gnlm at week 3 vs placebo (p = 0.046).
  - Ubrogepant and rimegepant are oral CGRP inhibitors FDA-approved for acute treatment of migraine with or without aura in adults. One differing characteristic is that ubrogepant allows for a second dose within 24 hours whereas rimegepant does not.
    - Rimegepant ODT demonstrated efficacy compared to placebo in a Phase 3, DB, RCT which evaluated acute response to migraine treatment after 2 hours. Patients were not allowed a second dose of study treatment (placebo or rimegepant). Rescue medications allowed 2 hours post-dose included aspirin, ibuprofen, naproxen (or any other type of NSAID), APAP up to 1000 mg/day, antiemetics (eg, metoclopramide or promethazine), or baclofen. Compared to placebo, significantly more patients treated with rimegepant 75 mg were pain-free at 2 hours (difference vs placebo, 10.3%). For the co-primary endpoint of MBS, significantly more rimegepant-treated patients reported being MBS-free at 2 hours post-dose (difference vs placebo, 8.3%). Three additional trials evaluating the efficacy and safety of rimegepant 75 mg in an oral tablet formulation were considered supportive for approval.
    - Ubrogepant demonstrated efficacy compared to placebo in 2 DB, RCTs, which reported acute response to migraine treatment after 2 hours. A second dose of study treatment (placebo or ubrogepant), or the patient's usual acute treatment for migraine, was allowed between 2 to 48 hours after the initial treatment for a non-responding or recurrent migraine headache. Compared to placebo, significantly more patients treated with ubrogepant were pain-free at 2 hours when administered the 50 mg (difference vs placebo, 7.4 to 7.5%) or 100 mg (difference vs placebo, 9.4%) dose. For the co-primary endpoint of MBS, significantly more ubrogepant-treated patients reported being MBS-free at 2 hours post dose for the 50 mg (difference vs placebo, 10.8 to 11.5%) and 100 mg (difference vs placebo, 9.9%) dose.

- Lack of information during pregnancy and breastfeeding is a consideration as many migraine patients are women of childbearing potential. The unknown risks of monoclonal antibodies and the effects on certain conditions are not fully characterized. Furthermore, rimegepant and ubrogepant have a number of drug interactions, and may not be appropriate with other medications. Important co-morbid populations were excluded from trials (eg, anxiety, depression, hypertension, and fibromyalgia), which also limits the generalizability to broader groups. There are no data in adolescents and children.

- The safety profiles of the subcutaneous CGRP inhibitors are generally mild with the most common adverse events observed being injection site reactions. Hypersensitivity and nasopharyngitis were the most commonly reported adverse events for the IV-administered agent, eptinezumab-jjmr. Mild to moderate hypersensitivity reactions, including rash, pruritus, drug hypersensitivity, and urticaria, were reported with all CGRP inhibitors. Post-marketing reports with erenumab-aooe have included hypertension and constipation with serious complications; some cases of constipation have required hospitalization and surgery. The oral CGRP inhibitors, ubrogepant and rimegepant, were associated with nausea; ubrogepant was additionally associated with somnolence.

- Overall, ubrogepant and rimegepant are alternatives to triptans and/or DHE in patients who are unable to tolerate or have an inadequate response or contraindication to established pharmacologic abortive migraine treatments. The injectable CGRP inhibitors represent another therapy option in the prevention of episodic or chronic migraine. Eptinezumab-jjmr and fremanezumab-vfrm are the only agents in the class that may be administered quarterly, which may fulfill a niche in patients who are non-adherent with treatment. Galcanezumab-gnlm is the only CGRP inhibitor indicated for the treatment of episodic cluster headaches. Dosage and administration vary by product and indication. Further long-term study is warranted.

APPENDICES

- **Appendix A. AAN levels of evidence classification** *(AAN 2017, Gronseth et al 2011)*

Rating of recommendation	
A	Established as effective, ineffective, or harmful for the given condition in the specified population
B	Probably effective, ineffective, or harmful for the given condition in the specified population
C	Possibly effective, ineffective, or harmful for the given condition in the specified population
U	Data inadequate or conflicting; given current knowledge, treatment is unproven.
Rating of therapeutic article	
Class I	RCT in representative population with masked outcome assessment. The following are required: a) concealed allocation; b) primary outcome(s) is/are clearly defined; c) exclusion/inclusion criteria are clearly defined; d) adequate accounting for dropouts and crossovers with numbers sufficiently low to have minimal potential for bias; e) certain requirements are needed for noninferiority or equivalence trials claiming to prove efficacy for 1 or both drugs.
Class II	Cohort study that meets a–e (Class I) or RCT that lacks 1 criterion from above (b−e).
Class III	Controlled trials (including well−defined natural history controls or patients serving as own controls), a description of major confounding differences between groups, and where outcome assessment is independent of patient treatment.
Class IV	Does not include patients with the disease, different interventions, undefined/unaccepted interventions or outcomes measures, and/or no measures of effectiveness or statistical precision presented or calculable.

- **Appendix B. AAN/AHS levels of evidence classification** *(Oskoui et al 2019[b])*

Level of obligation; magnitude of benefit	
A	Must; large benefit relative to harm
B	Should; moderate benefit relative to harm
C	May; small benefit relative to harm
U	No recommendation supported; too close to call

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OPTUMRx

Therapeutic Class Overview
Ophthalmic Immunomodulators

INTRODUCTION

- Dry eye syndrome refers to a group of disorders of the tear film that are due to reduced tear production or excessive tear evaporation (*American Academy of Ophthalmology [AAO] 2018, Shtein 2020*). The condition can be associated with discomfort and/or visual symptoms and may result in disease of the ocular surface. The ocular surface and tear-secreting glands are recognized to be responsible for the maintenance of tear production and to clear tears. Therefore, disease or dysfunction results in an unstable and poorly maintained tear film that causes ocular irritation symptoms and an epithelial disease known as keratoconjunctivitis sicca (KCS). Decreased tear secretion and clearance initiates an inflammatory response on the ocular surface, which plays a role in the pathogenesis of KCS. Symptoms of KCS include, but are not limited to, dryness, discomfort, irritation/pain, foreign body sensation, and blurred vision (*AAO 2018).*
- Rare complications of severe dry eyes include ocular surface keratinization; corneal scarring, thinning, or neovascularization; microbial or sterile corneal ulceration with possible perforation; and severe visual loss.
- Frequent instillation of ophthalmic medications (eg, natural tears) may cause dry eye symptoms by preventing the normal maintenance of the tear film. Other factors known to exacerbate symptoms of dry eye include environmental factors such as reduced humidity, air drafts, air conditioning, or heating. Associated systemic diseases include Sjögren's Syndrome, rosacea, and viral infection. Common drug-induced causes of dry eye symptoms include systemic medications such as anticholinergics, antidepressants, antihistamines, diuretics, and retinoids (*AAO 2018*).
- Medispan Therapeutic Classes: Ophthalmic Immunomodulators; Ophthalmic Integrin Antagonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Restasis, Restasis Multidose (cyclosporine ophthalmic emulsion)	-
Cequa (cyclosporine ophthalmic solution)	-
Xiidra (lifitegrast ophthalmic solution)	-

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

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

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

(*Restasis prescribing information 2017; Restasis Multidose prescribing information 2016, Xiidra prescribing information 2020, Cequa prescribing information 2019*)

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

CLINICAL EFFICACY SUMMARY

- The ophthalmic immunomodulator products have not been directly compared in clinical trials and have primarily been compared to vehicle.
- The pivotal trials for cyclosporine ophthalmic emulsion were 2 randomized, placebo-controlled trials that included 877 patients and an open-label, extension trial that included 412 patients (*Barber et al 2005, Sall et al 2000*). All patients were diagnosed with moderate-to-severe KCS and decreased tear production based on the Schirmer tear test. The combined results of the 2 placebo-controlled trials demonstrated that cyclosporine ophthalmic emulsion 0.05% and 0.1% were associated with significant improvements from baseline in corneal staining, Schirmer tear test scores, Ocular Surface Disease Index (OSDI) scores, Subjective Facial Expression Rating Scale scores, and various dry eye related symptoms (*Sall et al 2000*). Specifically compared to placebo, at 4 months, improvements in corneal staining were significant in both cyclosporine ophthalmic emulsion groups compared to placebo ($p \leq 0.044$), and at 6 months, only the cyclosporine ophthalmic emulsion 0.05% group demonstrated significance over placebo ($p = 0.008$). Additionally, at 6 months, improvements in Schirmer tear test scores were significantly greater for both cyclosporine ophthalmic emulsion groups compared to placebo ($p \leq 0.05$ for both) and from baseline scores (p values not reported). Improvements in OSDI and Subjective Facial Expression Rating Scale scores were significant compared to baseline for all treatment groups ($p < 0.001$), but there were no significant differences among these groups (p values not reported). Improvements in blurred vision were significantly greater in the cyclosporine ophthalmic emulsion 0.05% group than placebo at all follow-up visits ($p \leq 0.014$), and significant improvements were achieved at all time points within all treatment groups when compared to baseline for relief of dry eye symptoms including dryness ($p < 0.001$), sandy/gritty feeling ($p < 0.001$), and itching ($p \leq 0.038$). A Chinese, double-blind study used similar subjective ratings for dry eye symptoms and found that cyclosporine ophthalmic emulsion 0.05% improved measures over 8 weeks (*Chen et al 2010*).
- An open-label, extension trial was also conducted to determine the long-term safety of cyclosporine ophthalmic emulsion. After 3 consecutive 12-month periods, results demonstrated that cyclosporine ophthalmic emulsion was safe and well tolerated. Over 3 years, adverse events (AEs) were found in 65.3% (269/412) of patients with ocular burning reported most commonly (12.1%). This trial also demonstrated sustained efficacy of cyclosporine ophthalmic emulsion over an extended period of time (*Barber et al 2005*).
- A trial comparing cyclosporine ophthalmic emulsion to punctal plugs or a combination of both demonstrated that both treatments improved the symptoms of dry eye, but punctal plugs achieved results more rapidly than cyclosporine ophthalmic emulsion (*Roberts et al 2007*).
- A systematic review of 18 randomized controlled trials (RCTs) examined the efficacy and safety of topical cyclosporine for treatment of DED. All cyclosporine formulations proved safe for the treatment of DED. Symptoms improved in 100% (9/9 RCTs), tear function improved in 72% (13/18 RCTs) and ocular surface damage was ameliorated in 53% (9/17 RCTs) (*Saccheti et al 2014*).
    - Statistical comparison of cyclosporine efficacy through a meta-analysis of data was not possible due to a lack of standardized criteria and comparable outcomes among studies.
- A systematic review/meta-analysis of 30 randomized, controlled clinical studies (N = 4009) assessed the effectiveness and safety of topical cyclosporine in the treatment of DED. Eighteen studies compared cyclosporine 0.05% plus artificial tears (AT) vs AT alone. However, due to incomplete results data or considerable statistical heterogeneity, only a meta-analysis on mean conjunctival goblet cell density was conducted. The mean density (MD) was greater in the cyclosporine treated group (MD 22.5 cells per unit, 95% Confidence Interval [CI], 16.3 to 28.8). Additionally, the analysis could not demonstrate the benefit of cyclosporine for tear production and helping to reduce signs and symptoms of dry eye. The remaining 12 studies were not assessed due to inconsistent data reporting (*de Paiva et al 2019*).
- Two multicenter, randomized, controlled clinical studies evaluated the efficacy of cyclosporine ophthalmic solution 0.09% in 1048 patients with KCS. In both studies, there was a significantly ($p < 0.01$) higher percentage of eyes with increases of ≥ 10 mm from baseline in Schirmer wetting as compared to vehicle at day 84. This effect was seen in approximately 17% of patients treated with cyclosporine ophthalmic solution vs approximately 9% of patients treated with vehicle (*Cequa prescribing information 2018, Goldberg et al 2019, Luchs et al 2018, Sheppard et al 2020, Tauber et al 2018*).
- The safety and efficacy of lifitegrast ophthalmic solution for the treatment of DED were assessed in a total of 1181 patients (1067 of which received lifitegrast 5%) in four 12-week, randomized, multicenter, double-masked, vehicle-controlled studies (*Semba et al 2012, Sheppard et al 2014, Tauber et al 2015, Holland et al 2017*). The use of AT was not allowed during the studies. The clinical trials evaluated various endpoints related to signs and symptoms of DED. However, the Food and Drug Administration (FDA) approval relied on an assessment of symptoms based on change

from baseline in patient reported eye dryness score (EDS; 0 to 100 visual analogue [VAS] scale) and an assessment of signs based on the inferior corneal staining score (ICSS; 0 to 4 scale).
    - A larger reduction in EDS favoring lifitegrast was observed in all studies at day 42 and day 84.
        - EDS was used as a primary symptom endpoint in 2 of the 4 studies (OPUS-2 and OPUS-3); the other 2 evaluated EDS as a secondary endpoint.
        - In OPUS-1, the primary symptom endpoint was the visual-related function subscale score of the Ocular Surface Disease Index (VR-OSDI) questionnaire. No difference between lifitegrast and placebo was seen in the mean change from baseline to day 84 (p = 0.7894) (*Sheppard et al 2014*).
    - At day 84, a larger reduction in ICSS favoring lifitegrast was observed in 3 of the 4 studies (no statistically significant difference between lifitegrast and placebo was found in the OPUS-2 study).
    - In a 1-year safety study (N = 331: 220 lifitegrast; 111 placebo), there were no serious ocular treatment-emergent AEs. Overall, 53.6% of participants receiving lifitegrast experienced ≥ 1 ocular treatment-emergent AE vs 34.2% in the placebo group; most treatment-emergent AEs were mild to moderate in severity, with burning, instillation site reaction, reduced visual acuity, dry eye, and dysgeusia reported most commonly (*Donnenfeld et al 2016*).
    - Ocular comfort of lifitegrast was also assessed in OPUS-3 (N = 711). Drop comfort scores (0 = very comfortable, 10 = very uncomfortable) were assessed immediately after instillation and at 1, 2, and 3 minutes post-instillation. The results showed that drop comfort scores with lifitegrast improved within 3 minutes of instillation with scores approaching that of placebo (*Nichols et al 2018*).
- A pooled analysis of 5 randomized trials (lifitegrast N = 1287, placebo N = 1177) evaluated the safety and tolerability of lifitegrast ophthalmic solution 5.0% for the treatment of dry eye. Overall, the majority of treatment related adverse events reported (> 5%) were: instillation site irritation, instillation site reaction and instillation site pain; the most common non-ocular adverse event reported was dysgeusia in 14.5% of patients receiving lifitegrast vs 0.3% in the placebo group. The analysis also noted that drop comfort scores in the lifitegrast treatment group improved within 3 minutes of instillation and continued to improve across visits through 1 year (*Nichols et al 2019*).

CLINICAL GUIDELINES

- The American Academy of Ophthalmology (AAO) Preferred Practice Pattern for Dry Eye Syndrome makes treatment recommendations based on disease severity (*AAO 2018*).
    - For mild disease, education and environmental modifications, aqueous enhancement using artificial tears, gels or ointments, and eyelid therapy with warm compresses and eyelid scrubs are recommended.
    - For moderate disease, the AAO recommends in addition to the treatments for mild disease, anti-inflammatory agents such as topical cyclosporine, lifitegrast, and corticosteroids; punctal plugs; or spectacle side shields and moisture chambers.
        - Low-dose topical corticosteroid therapy should be used at infrequent intervals for short periods of time (ie, several weeks) to suppress ocular surface inflammation. Patients prescribed corticosteroids for dry eye should be monitored for AEs such as increased intraocular pressure and cataract formation.
    - For severe disease, the AAO recommends in addition to all the previously mentioned treatments, systemic cholinergic agonists or anti-inflammatory agents, mucolytic agents, autologous serum tears, contact lenses, permanent punctal occlusion, or tarsorrhaphy.
- Tear Film and Ocular Surface Society Dry Eye Workshop II (TFOS DEWS II) (*Jones et al 2017*)
    - A step-wise approach is recommended based on disease severity.
        - Step 1: education, lid hygiene, warm compress, modification of environmental factors, omega-3 fatty acid supplementation, or ocular lubricants. Ocular lubricants are considered mainstay of treatment, however, they only offer palliative relief with no disease modifying potential.
        - Step 2 (if above inadequate):
            - Non-pharmacological: punctual occlusion (most widely used tear conservation approach), pulsed light therapy, moisture goggles
            - Pharmacological: topical antibiotic for blepharitis, limited duration topical corticosteroid, topical cyclosporine, lifitegrast.
        - Step 3(if above inadequate): oral secretagogues, allogenic serum eye drops, or therapeutic contact lenses
        - Step 4(if above inadequate): longer duration topical steroid, membrane grafts, punctual occlusion or other surgical approaches.

SAFETY SUMMARY

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

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Restasis, Restasis Multidose (cyclosporine ophthalmic emulsion)	Ophthalmic emulsion	Ophthalmic	Instill 1 drop twice daily (approximately 12 hours apart)	Cyclosporine ophthalmic emulsion can be used concomitantly with artificial tears; however, patients should allow for a 15-minute interval between the products. To avoid contamination, care should be taken not to touch the bottle tip to the eye or other surfaces. Restasis (single-dose vial): Discard vial immediately after use. Restasis Multidose is packaged in a multi-dose preservative-free 10 mL bottle containing 5.5 mL.
Cequa (cyclosporine ophthalmic solution)	Ophthalmic solution	Ophthalmic	Instill 1 drop twice daily (approximately 12 hours apart)	Cyclosporine ophthalmic solution can be used concomitantly with artificial tears; however, patients should allow for a 15-minute interval between the products.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				To avoid contamination, care should be taken not to touch the bottle tip to the eye or other surfaces. Discard the vial immediately after use.
Xiidra (lifitegrast ophthalmic solution)	Ophthalmic solution	Ophthalmic	Instill 1 drop twice daily (approximately 12 hours apart)	Contact lenses should be removed prior to the administration of lifitegrast and may be reinserted 15 minutes following administration. Discard the single-use container immediately after using in each eye.

See the current prescribing information for full details

CONCLUSION

- Restasis (cyclosporine ophthalmic emulsion) is the first ophthalmic emulsion FDA-approved to increase tear production in patients with KCS. Although the exact mechanism of action of this agent is unknown, it is assumed that it acts as a partial immunomodulator.
- Xiidra (lifitegrast ophthalmic solution) is the second prescription treatment to receive FDA-approval for treatment of DED. Lifitegrast is a novel small molecule integrin antagonist that inhibits T cell-mediated inflammation by blocking the binding of 2 important cell surface proteins (lymphocyte function-associated antigen 1 [LFA-1] and intercellular adhesion molecule 1 [ICAM-1]), thus lessening overall inflammatory responses. However, the exact mechanism of action of lifitegrast in DED is unknown.
- In August 2018, the FDA approved Cequa (cyclosporine ophthalmic solution) to increase tear production in patients with KCS (*Cequa prescribing information 2018)*. This is the first cyclosporine product to utilize nanomicellar technology. This formulation allows the drug molecule to overcome solubility difficulties, penetrate the eye's aqueous layer, and prevent the release of active lipophilic molecule prior to penetration.
- In clinical trials, cyclosporine ophthalmic emulsion demonstrated significant increases in tear production and decreases in dry eye symptoms compared to placebo and demonstrated safety for up to 3 years (*Sall et al 2000, Barber et al 2005, Roberts et al 2007*). For the new nanomicellar cyclosporine ophthalmic solution, there was a significantly ($p < 0.01$) higher percentage of eyes with increases of ≥ 10 mm from baseline in Schirmer wetting as compared to vehicle at day 84 *(Cequa prescribing information 2018, Goldberg et al 2019, Luchs et al 2018, Sheppard et al 2020, Tauber et al 2018)*.
- Lifitegrast also demonstrated significant improvements in the signs and symptoms of DED compared with placebo in clinical trials. Lifitegrast was well tolerated with no unexpected AEs in a 1-year safety exposure study (*Donnenfeld et al 2016, Holland et al 2017, Semba et al 2012, Sheppard et al 2014, Tauber et al 2015*).
- Ophthalmic immunomodulators improve signs of DED in patients who are inadequately treated with AT and other therapies. Lifitegrast demonstrated improvement in symptoms of DED; however, cyclosporine has not consistently improved symptoms in DED compared to placebo. Direct comparative data between cyclosporine products and lifitegrast are lacking.

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