Nevada Medicaid Drug Use Review Board Meeting

January 27, 2022

OPTUMRx®

Table of Contents

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

3rd REVISED NOTICE OF PUBLIC MEETING – DRUG USE REVIEW BOARD

Date of Publication:	~~December 15, 2021~~
Date of Revision:	~~December 22, 2021~~
Date of 2nd Revision:	~~December 28, 2021~~
Date of 3rd Revision:	January 03, 2022
Date and Time of Meeting:	January 27, 2022, at 1:00 PM
Name of Organization:	The State of Nevada, Department of Health and Human Services (DHHS), Division of Health Care Financing and Policy (DHCFP), Drug Use Review Board (DUR)
Place of Meeting:	The physical location for this meeting which is open to the public is at: Surestay Plus Hotel by Best Western Reno Airport 1981 Terminal Way Reno, NV 89502 (775) 348-6370 Space is limited at the physical location and subject to any applicable social distancing or mask wearing requirements as maybe in effect at the time of the meeting for the county in which the physical meeting is held. Note: If at any time during the meeting an individual who has been named on the agenda or has an item specifically regarding them included on the agenda is unable to participate because of technical or other difficulties, please email rxinfo@dhcfp.nv.gov and note at what time the difficulty started so that matters pertaining specifically to their participation may be continued to a future agenda if needed or otherwise addressed.
Webinar:	~~Microsoft Teams~~ **Microsoft Teams** (See final agenda page for full link or employ the shortened link directly below) ~~OR~~ ~~https://tinyurl.com/DURJAN2022~~ https://tinyurl.com/Jan-2022-DUR

Audio Only: (952) 222-7450

Event Number: ~~576 588 668#~~
920 295 021#

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

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

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

AGENDA

1. Call to Order and Roll Call

2. General Public Comment

Public comment is encouraged to be submitted in advance so that it may be included in meeting materials and given attention. No action may be taken upon a matter raised through public comment unless the matter itself has been specifically included on an agenda as an action item. Please provide your name in any comment for record keeping purposes. You may submit comments in writing via email to (rxinfo@dhcfp.nv.gov). Written comments will not be read into the record, but written comments are encouraged to be accessible to screen readers. There may be opportunity to take public comment via telephone or the meeting's virtual platform as well as in person opportunities, but phone participants should disconnect their call and re-join if they must take another call. Do not place your phone on hold or you may disrupt the meeting for other participants. Public comment will be limited to three minutes per person. Persons making comment will be asked to begin by stating their name for the record. **Note: this guidance applies for all periods of public comment referenced further in the agenda, such as those related to clinical presentations**.

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

3. Administrative

a. **For Possible Action:** Review and Approve Meeting Minutes from October 26, 2021.
b. Status Update by DHCFP.

4. Clinical Presentations

a. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Calcitonin Gene-Related Peptide (CGRP) Receptor Inhibitor Medications.

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.

iv. Proposed adoption of updated prior authorization criteria.

b. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Cystic Fibrosis Agents.

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.
iv. Proposed adoption of updated prior authorization criteria.

c. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Topical Immunomodulators.

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.
iv. Proposed adoption of updated prior authorization criteria.

d. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Cabenuva (cabotegravir; rilpivirine).

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.
iv. Proposed adoption of updated prior authorization criteria.

e. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Targeted Immunomodulators.

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.
iv. Proposed adoption of updated prior authorization criteria.

f. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Monoclonal Antibodies for the treatment of respiratory conditions.

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.
iv. Proposed adoption of updated prior authorization criteria.

g. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Neuropathic Pain/Fibromyalgia Agents.

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.
iv. Proposed adoption of updated prior authorization criteria.

h. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for Duchenne Muscular Dystrophy Agents.

i. Public comment on proposed clinical prior authorization criteria.
ii. Presentation of utilization and clinical information.
iii. Discussion by Board and review of utilization data.
iv. Proposed adoption of updated prior authorization criteria.

5. DUR Board Requested Reports

a. **For Possible Action**: Opioid utilization – top prescribers and members.

i. Presentation of opioid criteria.
ii. Discussion by the Board and review of utilization data.
iii. Requests for further evaluation or proposed clinical criteria to be presented at a later date.
~~iii.~~iv. Request for communication by the Board related to utilization, any reporting related to general outcomes for prior communication, if applicable.

6. Standard DUR Reports

a. Review of Prescribing/Program Trends.

i. Top 10 Therapeutic Classes for Q2 2021 and Q3 2021 (by Payment and by Claims).

b. Concurrent Drug Utilization Review (ProDUR).

i. Review of Q3 2021.
ii. Review of Top Encounters by Problem Type.

c. Retrospective Drug Utilization Review (RetroDUR).

i. Status of previous quarter.
ii. Status of current quarter.
iii. Review and discussion of responses.

7. Centers for Medicare and Medicaid Services (CMS) Annual Drug Utilization Review Surveys

a. Fee-for-Service Annual DUR Survey presented by OptumRx.
b. Anthem Blue Cross Blue Shield Healthcare Solutions Annual DUR Survey presentation.
c. Health Plan of Nevada (HPN) Annual DUR Survey presentation.
d. Silver Summit Health Plan Annual DUR Survey presentation.

8. Closing Discussion

a. Public comment.

(No action may be taken upon a matter raised under public comment period unless the matter itself has been specifically included on an agenda as an action item. Comments will be limited to

three minutes per person. Persons making comment will be asked to begin by stating their name for the record and to spell their last name.)

b. **For Possible Action**: Date and location of the next meeting.

c. Adjournment.

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

This notice and agenda have been posted online at http://dhcfp.nv.gov and http://notice.nv.gov as well as Carson City, Las Vegas, and Reno central offices for the Division of Health Care Financing and Policy. Email notice has been made to such individuals as have requested notice of meetings (to request notifications please contact rxinfo@dhcfp.nv.gov, or at 1100 East William Street, Suite 101, Carson City, Nevada 89701).

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

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

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 ideally at least ten days in advance of the meeting, by email at rxinfo@dhcfp.nv.gov in writing, at 1100 East William Street, Suite 101, Carson City, Nevada 89701.

Full Microsoft Teams Link:

https://teams.microsoft.com/dl/launcher/launcher.html?url=%2F_%23%2Fl%2Fmeetup-join%2F19%3Ameeting_YjI0ZmNjNWQtMmY0NS00OGIwLTgwNzQtZGViNWE4MzY5ZDJi%40thread.v2%2F0%3Fcontext%3D%257b%2522Tid%2522%253a%2522db05faca-c82a-4b9d-b9c5-0f64b6755421%2522%252c%2522Oid%2522%253a%25222311bd22-e984-4bae-84b9-bedd149b3c85%2522%257d%26anon%3Dtrue&type=meetup-join&deeplinkId=07ade02f-b94a-491a-8dae-3bec2d4fca56&directDl=true&msLaunch=true&enableMobilePage=false&suppressPrompt=true

Summary of the DUR Board

Drug Use Review Board

The Drug Use Review Board (DUR) is a requirement of the Social Security Act, Section 1927 and operates in accordance with Nevada Medicaid Services Manual, Chapter 1200 – Prescribed Drugs and Nevada Medicaid Operations Manual Chapter 200.

The DUR Board consists of no less than five members and no more than ten members appointed by the State Director of Health and Human Resources. Members must be licensed to practice in the State of Nevada and either an actively practicing physician or an actively practicing pharmacist.

The DUR Board meets quarterly to monitor drugs for:

- therapeutic appropriateness,
- over or under-utilization,
- therapeutic duplications,
- drug-disease contraindications
- quality care

The DUR Board does this by establishing prior authorization and quantity limits to certain drugs/drug classes based on utilization data, experience, and testimony presented at the DUR Board meetings. This includes retrospective evaluation of interventions, and prospective drug review that is done electronically for each prescription filled at the Point of Sale (POS).

Meetings are held quarterly and are open to the public. Anyone wishing to address the DUR Board may do so. Public comment is limited to three minutes per speaker/organization (due to time constraints). Anyone presenting documents for consideration must provide sufficient copies for each board member and a copy (electronic preferred) for the official record.

The mission of the Nevada DUR Board is to work with the agency to improve medication utilization in patients covered by Medicaid. The primary goal of drug utilization review is to enhance and improve the quality of pharmaceutical care and patient outcomes by encouraging optimal drug use.

Current Board Members:

Jennifer Wheeler, Pharm.D., Chair	Dave England, Pharm.D.
Netochi Adeolokun, Pharm.D., Vice Chair	Brian Le, DO
Mark Canty, MD	Michael Owens, MD
Crystal Castaneda, MD	Rebecca Sparks, PA-C
Jessica Cate, Pharm.D.	Jim Tran, Pharm.D.

Drug Use Review (DUR) Board Meeting Schedule for 2022

Date	Time	Location
April 28, 2022	1:00 PM	Surestay Plus Hotel – Reno, NV

Web References

Medicaid Services Manual (MSM) Chapter 1200:

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

Drug Use Review Board Bylaws:

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

Drug Use Review Board Meeting Material:

https://www.medicaid.nv.gov/providers/rx/dur/DURBoard.aspx

Social Security Act, 1927:

https://www.ssa.gov/OP_Home/ssact/title19/1927.htm

Meeting Minutes

Drug Use Review Board

Meeting Minutes

Date of Meeting: Thursday, October 26, 2021

Name of Organization: The State of Nevada, Department of Health and Human Services, Division of Health Care Financing and Policy (DHCFP), Drug Use Review Board

Agenda Item	Record	Notes
1. Call to Order and Roll Call	It was announced the meeting is being recorded. Chairwoman Wheeler called the meeting to order at 1:03 p.m. on October 26, 2021. Chairwoman Wheeler took the roll. Present / Absent Jennifer Wheeler, Pharm.D., Chair ☒ ☐ Netochi Adeolokun, Pharm.D., Vice Chair ☒ ☐ Mark Canty, MD ☒ ☐ Crystal Castaneda, MD ☒ ☐ Jessica Cate, Pharm.D. ☒ ☐ Dave England, Pharm.D. ☒ ☐	**The DHCFP Staff Present were as follows:** Woodrum, Homa, Senior Deputy Attorney General Capurro, Antonina, Deputy Administrator Gudino, Antonio, Social Services Program Specialist III Berntson, Kindra, Social Services Program Specialist II Flowers, Ellen, Program Officer I

Agenda Item	Record			Notes
	Brian Le, DO	☐	☒	**Managed Care Organization representatives present were as follows:** Bitton, Ryan, Pharm.D., Health Plan of Nevada Lim, Luke, Pharm.D., Anthem Blue Cross Beranek, Tom, RPh, SilverSummit Health Plan **Gainwell Technologies Staff Present were as follows:** Leid, Jovanna, Pharm.D. **OptumRx Staff Present were as follows:** LeCheminant, Jill, Pharm.D. Piccirilli, Annette Hansen, Sean Medina, Daniel Kiriakopoulos, Amanda, Pharm.D. **The public attendee list is included as attachment A.** **Note**: Participants may not have chosen to reveal their identity, and in the absence of a sign-in sheet, the attendee list's accuracy is not assured.
	Michael Owens, MD	☐	☒	
	Rebecca Sparks, PA-C	☐	☒	
	Jim Tran, Pharm.D.	☒	☐	
	A quorum was present.			

Agenda Item	Record	Notes
2. General Public Comment	Dr. Jill LeCheminant referenced submitted written public comment that was previously provided to the Board. Telephonic and web comment was called for, and the phone lines were opened. No public comment was offered.	
3. Administrative		
a. **For Possible Action**: Review and Approve Meeting Minutes from July 22, 2021	No corrections were offered. Board Member Adeolokun moved to approve the minutes as presented, and Board Member Canty seconded the motion. A vote was taken, the results were as follows from members in attendance (in favor, against, and abstentions where applicable): Jennifer Wheeler, Pharm.D., Chair — Yes ☒ No ☐ Abst. ☐ Netochi Adeolokun, Pharm.D., Vice Chair — Yes ☒ No ☐ Abst. ☐ Mark Canty, MD — Yes ☒ No ☐ Abst. ☐ Crystal Castaneda, MD — Yes ☒ No ☐ Abst. ☐ Jessica Cate, Pharm.D. — Yes ☒ No ☐ Abst. ☐ Dave England, Pharm.D. — Yes ☒ No ☐ Abst. ☐ Jim Tran, Pharm.D. — Yes ☒ No ☐ Abst. ☐	
b. Status Update by DHCFP	Dr. Antonina Capurro commented that a new managed care organization, Molina Healthcare, will be joining Nevada Medicaid beginning January 1, 2022. Medicaid recipients will be randomly distributed across the four managed care organizations, and the recipients will have 90 days to determine if they would like to change their MCO enrollment. Dr. Capurro informed the Board that the Synagis season began early due to a rise in RSV cases and the Synagis season is open from September 1, 2021, through	

Agenda Item	Record	Notes
	March 31, 2022. Dr. Capurro reviewed legislative updates, including Assembly Bill 177 that requires pharmacies to provide information regarding a prescription in languages other than English. Dr. Capurro noted that the Board of Pharmacy is working on adopting the regulations. She covered Assembly Bill 178, which addresses early prescription renewals by pharmacists due to natural disasters earlier this month. Dr. Capurro also provided information regarding the creation of a new provider type for pharmacists along with Senate Bill 190 that allows pharmacists to prescribe self-administered hormonal contraceptives and Senate Bill 325, which permits pharmacists to prescribe drugs to prevent the acquisition of human immunodeficiency virus (HIV) and perform specific laboratory tests related to HIV testing. The public hearing for the State Plan Amendment for the new provider type was September 28, and implementation is scheduled for January 1, 2022. She commented that the public notices are available on the website for additional information. Dr. Capurro announced that Magellan Medicaid Administration will start on July 1, 2022, as Nevada's new pharmacy benefit manager (PBM). She noted that Magellan would begin facilitating the Silver State Scripts Board meetings at that time. Dr. Tina Hawkins from Magellan was present at the meeting to introduce herself. Dr. Hawkins commented that they were joining today to listen to the current process of meetings. Chairwoman Wheeler announced the agenda item of the informational update from DHCFP counsel was moved to the DUR Board requested reports section.	
4. Clinical Presentations		
a. **For Possible Action**: Discussion and possible adoption of prior authorization criteria and/or quantity limits		

Agenda Item	Record	Notes
for sacubitril/valsartan (Entresto®).		
i. Public comment on proposed clinical prior authorization criteria.	Telephonic and web comment was called for, and the phone lines were opened. No written comment was received. Comment was made by Dr. Melissa Sommers, representing Novartis, requesting the requirement that Entresto is prescribed by a cardiologist be removed from the criteria.	
ii. Presentation of utilization and clinical information.	Dr. LeCheminant reviewed the updated indication for Entresto and highlighted key points from the 2021 Update to the ACC Expert Consensus Decision Pathway. Dr. LeCheminant reviewed the proposed criteria presented in the binder and discussed utilization. Dr. Luke Lim agreed with the proposed criteria and highlighted a trend of increasing Entresto utilization. Dr. Ryan Bitton proposed a policy update to require beta-blocker therapy only in specific populations. Dr. Bitton highlighted a trend of increasing Entresto utilization. Mr. Tom Beranek proposed a policy update of reduced left ventricular ejection fraction and concomitant use of aliskiren for any member diagnosed with diabetes. He highlighted steady utilization for Entresto.	
iii. Discussion by Board and review of utilization data.	Chairwoman Wheeler discussed the benefits of removing the requirement for Entresto to be prescribed by a cardiologist. She asked for comments from the Board Members. Board Member Canty and Board Member England agreed with the comments made by Chairwoman Wheeler.	

<table>
<tr><th>Agenda Item</th><th>Record</th><th>Notes</th></tr>
<tr><td>iv. Proposed adoption of updated prior authorization criteria.</td><td>Board Member Canty motioned to approve the criteria as presented with removal that a cardiologist prescribes the requested medication.

Board Member England seconded the motion.

A vote was held:

<table>
<tr><th></th><th>Yes</th><th>No</th><th>Abst.</th></tr>
<tr><td>Jennifer Wheeler, Pharm.D., Chair</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Netochi Adeolokun, Pharm.D., Vice Chair</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Mark Canty, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Crystal Castaneda, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Jessica Cate, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Dave England, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Jim Tran, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
</table></td><td></td></tr>
<tr><td>b. <u>For Possible Action</u>: Discussion and possible adoption of prior authorization criteria and/or quantity limits for Immunomodulator Drugs.</td><td></td><td></td></tr>
<tr><td>i. <u>Public comment</u> on proposed clinical prior authorization criteria.</td><td>Telephonic and web comment was called for, and the phone lines were opened.

No written comment was received.

No public comment was offered.</td><td></td></tr>
<tr><td>ii. Presentation of utilization and clinical information.</td><td>Dr. LeCheminant presented information regarding Skyrizi and discussed the new indication for Humira. Dr. LeCheminant reviewed the proposed Humira criteria presented in the binder and discussed utilization.</td><td></td></tr>
</table>

Agenda Item	Record	Notes
	Dr. Lim agreed with the proposed criteria and noted Humira had the highest use of the immunomodulator agents. Dr. Bitton agreed with the proposed criteria and discussed the volume of claims for Humira. Mr. Beranek agreed with the proposed criteria and stated that the majority of Humira claims were for the Humira pen.	
iii. Discussion by Board and review of utilization data.	Chairwoman Wheeler asked for comments from the Board Members. No comments were made.	
iv. Proposed adoption of updated prior authorization criteria.	Board Member Tran moved to approve the criteria as presented. Board Member Adeolokun seconded the motion. A vote was held: Jennifer Wheeler, Pharm.D., Chair ☒ Yes ☐ No ☐ Abst. Netochi Adeolokun, Pharm.D., Vice Chair ☒ ☐ ☐ Mark Canty, MD ☒ ☐ ☐ Crystal Castaneda, MD ☒ ☐ ☐ Jessica Cate, Pharm.D. ☒ ☐ ☐ Dave England, Pharm.D. ☒ ☐ ☐ Jim Tran, Pharm.D. ☒ ☐ ☐	
c. **For Possible Action**: Discussion and possible adoption of prior authorization criteria and/or quantity limits for Growth Hormones.		

Agenda Item	Record	Notes
i. Public comment on proposed clinical prior authorization criteria.	Telephonic and web comment was called for, and the phone lines were opened. No written comment was received. No public comment was offered.	
ii. Presentation of utilization and clinical information.	Dr. LeCheminant discussed various diagnoses and clinical studies supporting the efficacy of growth hormone agents. The criteria were presented with no proposed changes, and growth hormone agent utilization was reviewed. Dr. Lim agreed with the proposed criteria and highlighted the use of Norditropin. Dr. Bitton agreed with the proposed criteria and highlighted the use of Zomacton. Mr. Beranek agreed with the proposed criteria and discussed the use of growth hormone agents.	
iii. Discussion by Board and review of utilization data.	Chairwoman Wheeler asked for comments from the Board Members. No comments were made.	
iv. Proposed adoption of updated prior authorization criteria.	Board Member England moved to maintain the proposed criteria as presented. Board Member Adeolokun seconded the motion. A vote was held: Yes No Abst. Jennifer Wheeler, Pharm.D., Chair ☒ ☐ ☐	

Agenda Item	Record	Notes
	Netochi Adeolokun, Pharm.D., Vice Chair ☒ ☐ ☐ Mark Canty, MD ☒ ☐ ☐ Crystal Castaneda, MD ☒ ☐ ☐ Jessica Cate, Pharm.D. ☒ ☐ ☐ Dave England, Pharm.D. ☒ ☐ ☐ Jim Tran, Pharm.D. ☒ ☐ ☐	
d. **For Possible Action**: Discussion and possible adoption of prior authorization criteria and/or quantity limits for Gastrointestinal Prokinetic Agents.		
i. Public comment on proposed clinical prior authorization criteria.	Telephonic and web comment was called for, and the phone lines were opened. No written comment was received. No public comment was offered.	
ii. Presentation of utilization and clinical information.	Dr. LeCheminant discussed the new product, Gimoti, the mechanism of action, indication, administration, and clinical trial demonstrating efficacy. She noted the limitations of use for metoclopramide. Dr. LeCheminant reviewed the proposed criteria presented in the binder and discussed the utilization of the medications in the class. Dr. Lim agreed with the proposed criteria and reported no utilization for Gimoti. Dr. Bitton agreed with the proposed criteria and reported no utilization for Gimoti.	

Agenda Item	Record	Notes
	Mr. Beranek agreed with the proposed criteria and reported no utilization for Gimoti.	
iii. Discussion by Board and review of utilization data.	Chairwoman Wheeler asked for comments from the Board Members. No comments were made.	
iv. Proposed adoption of updated prior authorization criteria.	Board Member Castaneda moved to approve the proposed criteria as presented. Board Member Canty seconded the motion. A vote was held: Jennifer Wheeler, Pharm.D., Chair ☒ Yes ☐ No ☐ Abst. Netochi Adeolokun, Pharm.D., Vice Chair ☒ Yes ☐ No ☐ Abst. Mark Canty, MD ☒ Yes ☐ No ☐ Abst. Crystal Castaneda, MD ☒ Yes ☐ No ☐ Abst. Jessica Cate, Pharm.D. ☒ Yes ☐ No ☐ Abst. Dave England, Pharm.D. ☒ Yes ☐ No ☐ Abst. Jim Tran, Pharm.D. ☒ Yes ☐ No ☐ Abst.	
e. **For Possible Action**: Discussion and possible adoption of prior authorization criteria and/or quantity limits for Alzheimer's Agents.		
i. Public comment on proposed clinical prior authorization criteria.	Telephonic and web comment was called for, and the phone lines were opened. No written comment was received.	

Agenda Item	Record	Notes
	Comment was provided by Dr. Jeff Cummings, Professor of Brain Health at the University of Nevada and the former director of the UCLA Alzheimer's Disease Research Center. Dr. Cummings discussed the use of CDR and RBANS assessments as clinical trial tools and noted they are not commonly used in clinical practice. He recommended the MoCA, a widely used assessment tool, as an alternative. Comment was provided by Dr. Kaysen Bala, a Medical Value Liaison representing Biogen. Dr. Bala discussed the impact of Alzheimer's disease. He noted that Aduhelm treats the declining pathology of the disease. Dr. Bala described the use of CDR and RBANS assessments as clinical trial tools and the use of the MoCA as a well-established tool in clinical practice. He noted that PET imaging is considered investigational for Alzheimer's disease. Dr. Bala offered to answer any questions on Aduhelm clinical data.	
ii. Presentation of utilization and clinical information.	Dr. LeCheminant discussed the new product, Aduhelm, the mechanism of action, indication, administration, and clinical trial demonstrating efficacy. Dr. LeCheminant reviewed the proposed criteria presented in the binder and discussed the utilization of the medications in the class. Dr. Lim agreed with the proposed criteria and reported no utilization for Aduhelm. Dr. Bitton agreed with the proposed criteria and reported no utilization for Aduhelm. Mr. Beranek agreed with the proposed criteria and reported no utilization for Aduhelm.	
iii. Discussion by Board and review of utilization data.	Chairwoman Wheeler asked for comments from the Board Members.	

<table>
<tr><th>Agenda Item</th><th>Record</th><th>Notes</th></tr>
<tr><td></td><td>Board Member Castaneda noted the benefit of the MoCA and suggested adding the MoCA to the list of exams and require completion of two of the four exams listed. The Board discussed the different exams and how they are used to identify patients with mild cognitive impairment.</td><td></td></tr>
<tr><td>iv. Proposed adoption of updated prior authorization criteria.</td><td>Board Member Canty moved to approve the criteria as presented with the addition of the MoCA to the list of exams and to require two of the four exams to be completed.

Board Member Adeolokun seconded the motion.

A vote was held:

<table>
<tr><th></th><th>Yes</th><th>No</th><th>Abst.</th></tr>
<tr><td>Jennifer Wheeler, Pharm.D., Chair</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Netochi Adeolokun, Pharm.D., Vice Chair</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Mark Canty, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Crystal Castaneda, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Jessica Cate, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Dave England, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Jim Tran, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
</table></td><td></td></tr>
<tr><td>f. <u>For Possible Action</u>: Discussion and possible adoption of prior authorization criteria and/or quantity limits for CGRP Receptor Inhibitors.</td><td></td><td></td></tr>
<tr><td>i. <u>Public comment</u> on proposed clinical prior authorization criteria.</td><td>Telephonic and web comment was called for, and the phone lines were opened.

No written comment was received.</td><td></td></tr>
</table>

Agenda Item	Record	Notes
	Comment was provided by Dr. Charlie Lovan, a Medical Science Liaison representing AbbVie, stating she is available to answer questions regarding CGRP migraine products. Comment was provided by Mr. Ben Droese, with Amgen Medical Affairs, regarding Aimovig and its most common adverse reactions. He requested clarification on the Aimovig criteria to require a trial of two preferred products. Mr. Droese discussed a study that shows half of the migraine visits occur in the primary care setting and requested the removal of the prescriber specialty from the criteria.	
ii. Presentation of utilization and clinical information.	Dr. LeCheminant discussed the new indication for Nurtec of preventative treatment of migraine and clinical trial demonstrating efficacy. Dr. LeCheminant reviewed the proposed criteria presented in the binder and discussed the utilization of the medications in the class. Dr. Lim agreed with the proposed criteria and highlighted that some of the utilization of Ubrelvy has shifted to Nurtec. Dr. Bitton agreed with the proposed criteria and highlighted high utilization of Aimovig and Emgality and increasing utilization of Nurtec. Mr. Beranek agreed with the proposed criteria and highlighted increased utilization of Nurtec and Emgality.	
iii. Discussion by Board and review of utilization data.	Chairwoman Wheeler asked for comments from the Board Members. Board Member Castaneda commented on the benefit of removing the requirement for the prescriber to be a Pain Specialist or Neurologist and noted CGRP products are often prescribed in a	

<table>
<tr><th>Agenda Item</th><th>Record</th><th>Notes</th></tr>
<tr><td></td><td>primary care setting as there may be access issues for a specialist visit. Board Member, England is in favor of removing the prescriber specialty requirement.</td><td></td></tr>
<tr><td>iv. Proposed adoption of updated prior authorization criteria.</td><td>Board Member Castaneda moved to approve the criteria as presented with the removal of the requirement that the medication must be prescribed by a Neurologist or Pain Specialist.

Board Member Adeolokun seconded the motion.

A vote was held:

<table>
<tr><th></th><th>Yes</th><th>No</th><th>Abst.</th></tr>
<tr><td>Jennifer Wheeler, Pharm.D., Chair</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Netochi Adeolokun, Pharm.D., Vice Chair</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Mark Canty, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Crystal Castaneda, MD</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Jessica Cate, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Dave England, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
<tr><td>Jim Tran, Pharm.D.</td><td>☒</td><td>☐</td><td>☐</td></tr>
</table>

Chairwoman Wheeler requested the CGRP agents be reviewed at the next DUR meeting to ensure consistency within the criteria.</td><td></td></tr>
<tr><td>5. DUR Board Requested Reports</td><td></td><td></td></tr>
<tr><td>a. <u>For Possible Action</u>: Opioid utilization – top prescriber and members.</td><td></td><td></td></tr>
<tr><td>i. Information update from DHCFP Counsel</td><td>Ms. Homa Woodrum, Senior Deputy Attorney General, provided Board Requested information related to possible actions available to the Board relating to opioid utilization reports.</td><td></td></tr>
</table>

Agenda Item	Record	Notes
	Senior Deputy Attorney General Woodrum provided the option for the Board to move and vote to direct DHCFP to send a letter directly to the providers identified as prescribing high amounts of opioids with an option to follow up with a notice. If the prescribing trend continues, a request can be submitted to DHCFP to make a referral to the Surveillance, Utilization, and Review team. Board Member England expressed concern that previously, when prescriber letters have been sent, there is no follow-up. Senior Deputy Attorney General Woodrum explained the process of tracking which prescribers have been sent a letter and the option to escalate instances of providers that continue to prescribe high amounts of opioids to the Medicaid Fraud department.	
ii. Presentation of opioid criteria	Dr. LeCheminant reviewed the Chapter 1200 opioid criteria, and no changes were proposed.	
iii. Discussion by the Board and review of utilization data.	Dr. Lecheminant presented the opioid utilization identifying the addition of morphine equivalent dose (MED) per day information to the report. She summarized the opioid 12-month trend. Dr. Lecheminant discussed the patient diagnoses of the top utilizers. Dr. Lim presented opioid utilization trends and identified a steady MED level over time. He discussed the top providers and top utilizers and noted a lack of trend in the prescription count. Dr. Bitton presented opioid utilization trends. He noted a slight downward trend in opioid scripts and discussed the top prescribers, top members, and how the two lists correlate. Mr. Beranek presented opioid utilization trends highlighting a decrease in utilization. He noted little change in the top ten prescribers and discussed member diagnosis for the top ten utilizers.	

Agenda Item	Record	Notes
iv. Requests for further evaluation of proposed clinical criteria to be presented at a later date.	The Board made no requests.	
6. Standard DUR Reports		
a. Review of Prescribing/ Program Trends.		
i. Top 10 Therapeutic Classes for Q3 2020 and Q4 2020 (by Payment and by Claims).	Dr. LeCheminant presented the top classes with similar results over the quarter, with hemostatic agents on the top by spend amount and anticonvulsants in the top by claim count. Dr. Lim presented the top classes and highlighted viral vaccines as the top class by claim count. Dr. Bitton presented the top classes and identified viral vaccines as the top class by claim count. Mr. Beranek presented the top drug classes and identified viral vaccines as the top class by claim count.	
b. Concurrent Drug Utilization Review (ProDUR).		
i. Review of Q4 2020. ii. Review of Top Encounters by Problem Type.	Dr. LeCheminant highlighted the prospective DUR reports and the interventions. Dr. Lim discussed the prospective DUR and the interventions. Dr. Bitton pointed out the prospective DUR report and the interventions. Mr. Beranek called out some differences in the prospective DUR compared to other programs but nothing unexpected.	
c. Retrospective Drug Utilization Review (RetroDUR).		

Agenda Item	Record	Notes
i. Status of previous quarter. ii. Status of current quarter. iii. Review and discussion of responses.	Dr. LeCheminant discussed the retrospective DUR initiatives during the last quarter with long-term PPI use and montelukast utilizers less than 21 years without an Asthma diagnosis. Dr. Lim highlighted the retrospective DUR programs, including asthma and behavioral health programs. Dr. Bitton discussed retrospective DUR initiatives and results, highlighting the gap in care initiatives. Mr. Beranek discussed the retrospective DUR program highlighting outreach to members who are nonadherent on their antiepileptic medications.	
7. Closing Discussion		
a. Public Comment.	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.	Chairwoman Wheeler stated the next meeting is scheduled for January 27, 2022, and the location is yet to be determined.	
c. Adjournment.	The meeting adjourned at 4:02 p.m.	

Attachment A – Members of the Public in Attendance

Ashton, Elisa, Johnson & Johnson
Bala, Kaysen, Biogen
Belen, Valerie, Belz & Case
Belz, Jeanette, Belz & Case
Booth, Robert, AbbVie
Colabianchi, Jeana, Sunovion
Cummings, Jeffrey, CNS Innovations
De Rosa, Regina, WellPoint
Delgado, Jonathan, Novonordisk
Diebes, Tressa, Takeda
Droese, Ben, Amgen
Germain, Joe, Biogen
Glover, Jon, Pfizer
Gonzales, Becky, VIIV Healthcare
Grothe, Deron, Teva
Hawkins, Tina, Magellan
Hertzberg, Susan, Roche
Levin, Amy, WellPoint
Lovan, Charlie, AbbVie
Miller, Temyka, WellPoint
Nelson, Ann, Vertex
Nguyen, Bao, Janus
Ou, Karen, Gilead
Pearce, Robert, Teva
Powell, Natasha, WellPoint
Roa, Ryan, Merck
Robinson, Lovell, AbbVie
Santarone, Christopher, Bristol Myers Squibb
Smith, Olivia
Solomon, Adele, WellPoint
Sommers, Melissa, Novartis
Sullivan, Mike, Amgen
Tran, Jim, Uhsinc
Triola, Olga, Merck
Wright, Mathew, Artia Solutions
Yamashita, Kelvin
Zarob, Michael, Alkermes

Attendees with no last name available:
Alex
Jenny
Zanyae

Attachment B – Submitted Written Comment

Antipsychotics 1
Antipsychotics 2

Clinical Presentations

Prior Authorization Guideline

Guideline Name: CGRP Products

1. Criteria

Product Name: **Aimovig, Ajovy, Emgality, Nurtec, Qulipta**	
Diagnosis	Episodic Migraine
Approval Length	6 month(s)
Therapy Stage	Initial Authorization

Approval Criteria

1 - The recipient is 18 years of age or older

AND

2 - Diagnosis of episodic migraines

AND

3 – Documentation the recipient has at least 4 migraine days per month but not more than 14 headache days per month (for Nurtec requests, the recipient does not have more than 18 headache days per month).

AND

4 - The recipient has documented history of failure (after at least a two-month trial) or an intolerance/contraindication to at least one medication from TWO of the following categories:

- Elavil (amitriptyline) or Effexor (venlafaxine)
- Depakote/Depakote ER (divalproex) or Topamax (topiramate)
- One of the following beta blockers: atenolol, propranolol, nadolol, timolol or metoprolol

AND

5 - Medication will not be used in combination with any other CGRP inhibitor

Product Name: **Aimovig, Ajovy, Emgality, Nurtec, Qulipta**	
Diagnosis	Episodic Migraine
Approval Length	12 month(s)
Therapy Stage	Reauthorization

Approval Criteria

1 - The recipient must have documented positive clinical response to CGRP therapy, demonstrated by a reduction in headache frequency and/or intensity

AND

2 - The use of acute migraine medications (e.g., NSAIDs, triptans) has decreased since the start of CGRP therapy

Product Name: **Aimovig, Ajovy, Emgality**	
Diagnosis	Chronic Migraine
Approval Length	6 month(s)
Therapy Stage	Initial Authorization

Approval Criteria

1 - The recipient is 18 years of age or older

AND

2 - The recipient has a diagnosis of chronic migraines

AND

3 - The recipient has greater than or equal to 15 headache days per month, of which at least 8 must be migraine days for at least 3 months

AND

4 - The recipient has been considered for MOH and potentially offending medication(s) have been discontinued

AND

5 - The recipient has documented history of failure (after at least a two-month trial) or an intolerance/contraindication to at least one medication from TWO of the following categories:

- Elavil (amitriptyline) or Effexor (venlafaxine)
- Depakote/Depakote ER (divalproex) or Topamax (topiramate)
- One of the following beta blockers: atenolol, propranolol, nadolol, timolol or metoprolol

AND

6 - Medication will not be used in combination with any other CGRP inhibitor

Product Name: **Aimovig, Ajovy, Emgality**	
Diagnosis	Chronic Migraine
Approval Length	12 month(s)
Therapy Stage	Reauthorization

Approval Criteria

1 - The recipient must have documented positive clinical response to CGRP therapy, demonstrated by a reduction in headache frequency and/or intensity

AND

2 - The use of acute migraine medications (e.g., NSAIDs, triptans) has decreased since the start of CGRP therapy

AND

3 - The recipient continues to be monitored for MOH

Product Name: **Emgality**	
Diagnosis	Episodic Cluster Headaches
Approval Length	3 month(s)
Therapy Stage	Initial Authorization

Approval Criteria

1 - The recipient has a diagnosis of episodic cluster headache

AND

2 - The recipient has experienced at least two cluster periods lasting from seven days to 365 days, separated by pain-free periods lasting at least three months

AND

3 - The recipient is 18 years of age or older

AND

4 - Medication will not be used in combination with any other CGRP inhibitor

Product Name: **Emgality**	
Diagnosis	Episodic Cluster Headaches
Approval Length	12 month(s)
Therapy Stage	Reauthorization

Approval Criteria

1 - The recipient must have a documented positive response to therapy, demonstrated by a reduction in headache frequency and/or intensity

Product Name: **Nurtec, Ubrelvy**	
Diagnosis	Acute Migraine
Approval Length	6 month(s)
Therapy Stage	Initial Authorization

Approval Criteria

1 - Recipient must have a diagnosis of acute migraine with or without aura

AND

2 - Recipient is 18 years of age or older

AND

3 - The recipient has had at least one trial and failure of a triptan agent

Product Name: **Nurtec, Ubrelvy**	
Diagnosis	Acute Migraine
Approval Length	12 month(s)
Therapy Stage	Reauthorization

Approval Criteria

1 - The recipient must have a documented positive response to therapy

2. Background

Benefit/Coverage/Program Information

Quantity Limits

Drug	Strength	Treatment Type	Limit
Aimovig	70mg/mL, 140mg/mL	Preventative	1 syringe / 28 days
Ajovy	225mg/1.5mL	Preventative	3 syringe / 84days
Emgality	120mg/mL	Preventative - episodic and chronic	2 syringe loading dose then 1 syringe / 28 days
Emgality	100mg/mL	Preventative- Cluster	3 syringe / 28 days

Qulipta	10mg, 30mg, 60 mg	Preventative	30 tablets / 30 days
Nurtec	75mg	Preventative	16 tablets / 30 days
Nurtec	75mg	Acute	8 tablets / 30 days
Ubrelvy	50mg, 100mg	Acute	10 tablets / 30 days

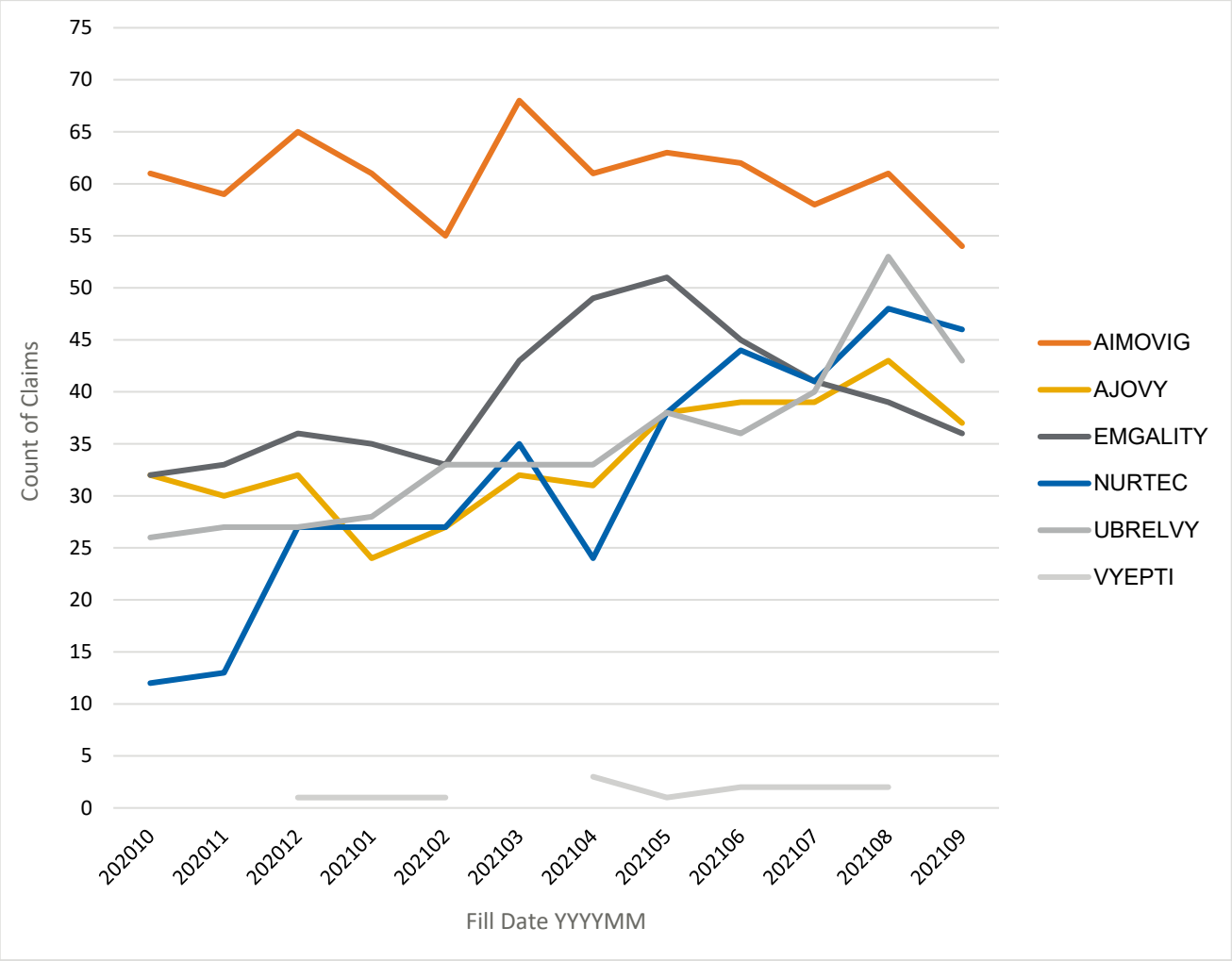
Nevada Medicaid

Utilization

Fee for Service

October 1, 2020 – September 30, 2021

Drug Name	Members	Claims	Total Day Supply	Total Quantity
AIMOVIG	98	728	23,052	842
AJOVY	74	404	14,131	708
EMGALITY	91	473	15,160	551
NURTEC	98	382	9,479	3,386
UBRELVY	96	417	10,118	4,848
VYEPTI	8	13	1,014	2,417



Therapeutic Class Overview
Calcitonin gene related peptide (CGRP) inhibitors

INTRODUCTION

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

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

observed with chronic use, which was likely related to the chemical structure of the compound. The manufacturer of olcegepant also ceased pursuing FDA approval; however, the manufacturer did not explicitly state the rationale. It has been widely speculated that olcegepant development ceased due to limitations associated with administration as an intravenous (IV)-only product (*Edvinsson et al 2017, Walker et al 2013*). No substantial issues with liver toxicity have been observed in trials with the currently marketed CGRP inhibitors.

- In April 2019, Teva announced that it would not pursue development of fremanezumab-vfrm for an episodic cluster headache indication due to results from the ENFORCE trial (*Teva Pharmaceuticals press release 2019*). Erenumab-aooe is not currently under clinical investigation for the indication of cluster headache; however, a trial has been initiated with eptinezumab-jjmr (*Clinicaltrials.gov 2021*).
- A CGRP inhibitor early in development is zavegepant, the first intranasally administered CGRP inhibitor in Phase 2/3 studies (*Biohaven Pharmaceutical 2021*). Atogepant, another oral CGRP inhibitor, was submitted for FDA approval in March 2021, with a decision anticipated for Q3 of 2021 *(AbbVie 2021)*.

- Medispan class: Migraine products – monoclonal antibodies; Calcitonin gene−related peptide (CGRP) receptor antagonists

Table 1. Medications Included Within Class Review

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

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

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

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

(*Prescribing information: Aimovig 2021, Ajovy 2021, Emgality 2019, Nurtec ODT 2021, Ubrelvy 2021, Vyepti 2020)*

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

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

CLINICAL EFFICACY SUMMARY

Prevention of episodic migraine

Eptinezumab-jjmr

- PROMISE-1 was a double-blind (DB), placebo-controlled (PC), multi-center (MC), Phase 3 trial in which adults with a history of episodic migraine were randomized to receive placebo (n = 222), eptinezumab-jjmr 100 mg (n = 221), or eptinezumab-jjmr 300 mg (n = 222) every 3 months for 12 months. The primary efficacy endpoint was the change in MMD from baseline to week 12. Eptinezumab-jjmr 100 mg and 300 mg significantly reduced MMDs across weeks 1 to 12 compared with placebo (placebo, −3.2; 100 mg, −3.9, p = 0.02; 300 mg, −4.3, p = 0.0001). The odds for a 50% reduction in MMD were approximately 1.7 to 2.2 times higher with eptinezumab-jjmr than placebo. Of note, the endpoints underwent a testing hierarchy and were not significant for 50% migraine responder rates in the 100 mg dose group (*Ashina et al 2020, Vyepti [dossier] 2020).*
  - The reduction in MMD was sustained through 1 year of follow-up for the eptinezumab-jjmr 300 mg group (-5.3 days), which was significant compared to placebo (-4.1 days) at weeks 37 to 48 (difference, -1.2; 95% CI, -1.95 to -0.46). The reduction in the 100 mg group was significantly greater compared to placebo at 25 to 36 weeks (-4.7 vs -4.0, respectively; difference, -0.72; 95% CI, -1.43 to -0.01), but not at 37 to 48 weeks (-4.5 vs -4.1; difference -0.38; 95% CI, -1.13 to 0.37) *(Smith et al 2020)*.

Erenumab-aooe

- The STRIVE trial was a 6-month, DB, PC, MC, Phase 3 trial in which 955 patients with episodic migraine were randomized to placebo (n = 319), erenumab-aooe 70 mg (n = 317), or erenumab-aooe 140 mg (n = 319) once monthly. The primary endpoint was the change in mean MMD from baseline to months 4 to 6, which favored treatment with erenumab−aooe 70 mg (mean change vs placebo, −1.4; 95% confidence interval [CI], −1.9 to −0.9; p < 0.001) and erenumab−aooe 140 mg (mean change vs placebo, −1.9; 95% CI, −2.3 to −1.4; p < 0.001). Erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 70 mg vs placebo, 16.7%; odds ratio [OR], 2.13; difference for 140 mg vs placebo, 23.4%; OR, 2.81). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 70 mg vs placebo, −0.9; difference for 140 mg vs placebo, −1.4) (*Goadsby et al 2017*). Data after 1 year of treatment found sustained efficacy in episodic migraine (*Goadsby et al 2020[a]*).
- The ARISE trial was a 12-week, DB, PC, MC, Phase 3 trial in which 577 patients with episodic migraine were randomized to placebo (n = 291) or erenumab-aooe 70 mg (n = 286) once monthly. The primary endpoint was the change in MMD from baseline to weeks 9 to 12, which favored treatment with erenumab−aooe 70 mg (mean change vs placebo, −1.0; 95% CI, −1.6 to −0.5; p < 0.001). Compared to placebo, erenumab−aooe significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference, 10.2%; OR, 1.59). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference, −0.6) (*Dodick et al 2018[a]*).
- The LIBERTY trial was a 12-week, DB, PC, MC, Phase 3b trial in which 246 patients with episodic migraine who failed 2 to 4 prior preventive migraine treatments were randomized to placebo (n = 125) or erenumab-aooe 140 mg (n = 121) once monthly. The primary endpoint was the proportion of patients with ≥ 50% reduction in MMD from baseline to the last 4 weeks of DB treatment (weeks 9 to 12), which erenumab−aooe significantly increased over placebo (difference, 16.6%; OR, 2.73; 95% CI, 1.43 to 5.19; p = 0.002). Compared to placebo, 5.9% more patients treated with erenumab−aooe 140 mg reported a 100% reduction in MMD, or migraine cessation. Erenumab-aooe 140 mg/month compared with placebo significantly reduced the MMD (difference, −1.61; 95% CI, −2.70 to −0.52; p = 0.004). Erenumab−aooe was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference, −1.73) (*Reuter et al 2018*).

Fremanezumab-vfrm

- The HALO-EM trial was a 12-week, DB, PC, MC, Phase 3 trial in which 875 patients with episodic migraine were randomized to placebo (n = 294), fremanezumab-vfrm 225 mg once monthly (n = 290), or fremanezumab-vfrm 675 mg once quarterly (n = 291). The primary endpoint was the change in mean MMD, which favored treatment with fremanezumab-vfrm 225 mg (mean change vs placebo, −1.5; 95% CI, −2.0 to −0.9; p < 0.001) and fremanezumab-vfrm 675 mg (mean change vs placebo, −1.3; 95% CI, −1.8 to −0.7; p < 0.001). Of note, HALO-EM was powered to detect a 1.6-day difference in the MMD between the fremanezumab-vfrm and placebo groups, but effect sizes resulted in a 1.5-day reduction for the fremanezumab-vfrm monthly dosing group and a 1.3-day reduction for the fremanezumab-vfrm

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

quarterly dosing group. Although the threshold was not reached, a minimal clinically important difference has not been established for this particular outcome. Compared to placebo, greater MMD reductions were also observed in patients who were prescribed fremanezumab-vfrm 225 mg (mean change vs placebo, −1.3) and 675 mg (mean change vs placebo, −1.1) as monotherapy. Fremanezumab-vfrm significantly increased the proportion of patients achieving ≥ 50% reduction in MMD (difference for 225 mg vs placebo, 19.8%; OR, 2.36; difference for 675 mg vs placebo, 16.5%; OR, 2.06). Additionally, fremanezumab-vfrm was associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 225 mg vs placebo, −1.4; difference for 675 mg vs placebo, −1.3) (*Dodick et al 2018[b]*). Data after 1 year of treatment found sustained efficacy in episodic migraine (*Goadsby et al 2020[b]*).

- FOCUS was a DB, PC, Phase 3b trial that evaluated 838 patients with episodic (39%) or chronic migraine (61%) who had previously not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, approximately 40% were classified as having episodic migraines and randomized to fremanezumab-vfrm 225 mg administered monthly with no loading dose (n = 110/283), fremanezumab-vfrm 675 mg administered quarterly (n = 107/276), or placebo (n = 112/279) for 12 weeks. Failure was defined as no clinically meaningful improvement after at least 3 months of therapy at a stable dose, as per the treating physician's judgment, discontinuation because of adverse events that made treatment intolerable, or treatment contraindicated or unsuitable for the preventive treatment of migraine for the patient. At baseline, the MMD was approximately 14.2 days and the MMHD (of at least moderate severity) was 12.6 days. For the overall population, the MMD reduction over 12 weeks was 0.6 (standard error [SE], 0.3) days for placebo, 4.1 (SE, 0.34) days for the monthly fremanezumab-vfrm group (least squares mean difference [LSMD] vs placebo, -3.5; 95% CI, -4.2 to -2.8 days; p < 0.0001), and 3.7 (SE, 0.3) for days for the quarterly fremanezumab-vfrm group (LSMD vs placebo, -3.1; 95% CI, -3.8 to -2.4 days; p < 0.0001). For episodic migraine and compared to placebo, the LSMD in MMD reduction over 12 weeks was 3.1 days for both dose groups (fremanezumab-vfrm monthly: LSMD, -3.1; 95% CI, -4.0 to -2.3 days; fremanezumab-vfrm quarterly: LSMD, -3.1; 95% CI, -3.9 to -2.2 days; p < 0.0001 for both). In the overall population, the proportions of patients with a ≥ 50% response over 12 weeks were 34% in both the quarterly and monthly fremanezumab-vfrm groups vs 9% with placebo (p < 0.0001). Only the monthly fremanezumab-vfrm arm achieved a ≥ 75% sustained responder rate that was statistically different from placebo (OR, 8.6; 95% CI, 2.0 to 37.9; p = 0.0045). Adverse events were similar for placebo and fremanezumab-vfrm. Serious adverse events were reported in 4 (1%) of 277 patients with placebo, 4 (1%) of 285 with monthly fremanezumab-vfrm, and 2 (< 1%) of 276 with quarterly fremanezumab-vfrm (*Ferrari et al 2019*).

Galcanezumab-gnlm

- The EVOLVE-1 and EVOLVE-2 trials were 6-month, DB, PC, MC, Phase 3 trials in 858 and 915 patients with episodic migraine, respectively. Patients were randomized to placebo (EVOLVE-1, n = 433; EVOLVE-2, n = 461), galcanezumab-gnlm 120 mg once monthly (EVOLVE-1, n = 213; EVOLVE-2, n = 231), or galcanezumab-gnlm 240 mg once monthly (EVOLVE-1, n = 212; EVOLVE-2, n = 223). Patients in the galcanezumab-gnlm 120 mg group received a loading dose of 240 mg at the first injection only. The EVOLVE-1 trial included a North American population and the EVOLVE-2 trial included a global population. The primary endpoint was the change in mean monthly migraine headache days (MMHD) (*Stauffer et al 2018, Skljarevski et al 2018*).
  - In EVOLVE-1, the primary endpoint outcome favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −1.9; 95% CI, −2.5 to −1.4; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.8; 95% CI, −2.3 to −1.2; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 23.7%; OR, 2.64; difference for 240 mg vs placebo, 22.3%; OR, 2.50). Compared to placebo, 9.4% more patients treated with galcanezumab-gnlm 120 mg and 9.4% more treated with galcanezumab-gnlm 240 mg reported a 100% reduction in MMHD, or migraine cessation. Galcanezumab-gnlm was also associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −1.8; difference for 240 mg vs placebo, −1.6) (*Stauffer et al 2018*).
  - In EVOLVE-2, the primary endpoint outcome favored treatment with galcanezumab-gnlm 120 mg (mean change vs placebo, −2.0; 95% CI, −2.6 to −1.5; p < 0.001) and galcanezumab-gnlm 240 mg (mean change vs placebo, −1.9; 95% CI, −2.4 to −1.4; p < 0.001). Galcanezumab-gnlm significantly increased the proportion of patients achieving ≥ 50% reduction in MMHD (difference for 120 mg vs placebo, 23.0%; OR, 2.54; difference for 240 mg vs placebo, 21.0%; OR, 2.34). Compared to placebo, 5.8% more patients treated with galcanezumab-gnlm 120 mg and 8.1% more treated with galcanezumab-gnlm 240 mg reported migraine cessation. Galcanezumab-gnlm was also

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 120 mg vs placebo, −1.8; difference for 240 mg vs placebo, −1.7) (*Skljarevski et al 2018*).
  - In an analysis of persistence for patients with episodic migraine, 41.5 and 41.1% of galcanezumab-gnlm-treated patients (120 mg and 240 mg, respectively) had a ≥ 50% response for ≥ 3 months, which was greater than placebo (21.4%; p < 0.001). Approximately 6% of galcanezumab-gnlm-treated patients maintained ≥ 75% response all 6 months vs 2% of placebo-treated patients. Few galcanezumab-gnlm-treated patients maintained 100% response for all 6 months (< 1.5%) (*Förderreuther et al 2018*).
- CONQUER was a DB, PC, Phase 3b trial that evaluated 462 patients with episodic (58%) or chronic migraine (42%) who had previously not responded to 2 to 4 classes of migraine preventive medications for 12 weeks. All galcanezumab-gnlm patients were administered a 240 mg loading dose, then 120 mg per month. Failure was defined as discontinuation owing to no response or inadequate response, or safety or tolerability event. At baseline, the MMHD was approximately 13.2 days with 9.3 in the episodic migraine group and 18.7 in the chronic migraine group. For the overall population, the MMHD reduction over 12 weeks was 1.0 (SE, 0.3) days for placebo, 4.1 (SE, 0.3) days for the monthly galcanezumab-gnlm group (LSMD, -3.1; 95% CI, -3.9 to -2.3 days; p < 0.0001). For episodic migraine and compared to placebo, the LSMD in MMHD reduction over 12 weeks was 2.6 days for the galcanezumab-gnlm monthly group (95% CI, -3.4 to -1.7 days; p < 0.0001). In the overall population, the proportions of patients with a ≥ 50% response over 12 weeks were 41.8% in the monthly galcanezumab-gnlm group vs 17.1% with placebo (p < 0.0001). Compared to placebo, the monthly galcanezumab-gnlm arm achieved a statistically significant improvement of ≥ 75% sustained responder (3.7 vs 18.4%; OR, 5.9; 95% CI, 2.4 to 14.6; p = 0.0001) and 100% sustained responder (0 vs 7.7%; p < 0.0001). Treatment-emergent adverse events were similar for placebo and galcanezumab-gnlm (53 vs 51%). Serious adverse events were reported in 2 patients (1%) of each of the groups (*Mulleners et al 2020*).
  - A post-hoc analysis evaluated the time to treatment onset, which showed a significant reduction in headache days with galcanezumab-gnlm beginning during the first month, which was significant compared to placebo (-4.0 vs -0.7, respectively; p ≤ 0.001). There was also a significantly greater reduction in weekly headache days with galcanezumab-gnlm beginning week 1 compared to placebo (-1.1 vs -0.2; p < 0.01) *(Schwedt et al 2021)*.

Rimegepant

- Rimegepant was studied in a MC, DB, PC, Phase 2/3 trial in adults with migraine for ≥ 1 year and with 4 to 18 moderate-to-severe migraine attacks per month. A total of 747 adults with ≥ 6 migraine days were randomized to rimegepant 75 mg (n = 370) orally every other day vs placebo (n = 371) for 12 weeks. Patients were allowed to continue 1 preventive medication excluding another CGRP inhibitor (ie, topiramate, gabapentin, beta-blockers, and tricyclic antidepressants), and rescue medication (ie, triptans, NSAIDs, paracetamol, aspirin, caffeine, baclofen, antiemetics, and muscle relaxants). At baseline, patients had a mean of 7.8 moderate-to-severe attacks per month, 40% with aura, and 23% had a history of chronic migraine. After 12 weeks of treatment, a reduction from observation period in MMD during weeks 9 to 12 was 4.3 vs 3.5 days for rimegepant vs placebo, respectively (p = 0.0099). A ≥ 50% reduction in moderate-to-severe MMDs during weeks 9 to 12 were observed in 49 vs 41% for rimegepant vs placebo, respectively (p = 0.044). A reduction in mean number of total migraine days per month during weeks 1 to 12 was 3.6 vs 2.7 days, respectively (p = 0.0017). Treatment related adverse events were reported in 11% in the rimegepant arm vs 9% in the placebo arm. All other incidences of adverse events were similar between groups. Most common adverse events included nausea, nasopharyngitis, urinary tract infection, and upper respiratory tract infection (*Croop et al 2021*).

Prevention of chronic migraine

Eptinezumab-jjmr

- The PROMISE-2 trial was a 12-week, DB, PC, MC, Phase 3 trial in which 1121 patients with chronic migraine were randomized to placebo (n = 366), eptinezumab-jjmr 100 mg (n = 356), or eptinezumab-jjmr 300 mg (n = 350) once every 12 weeks (or quarterly). The primary endpoint was the change in mean MMD. Treatment with eptinezumab 100 and 300 mg was associated with significant reductions in MMDs across weeks 1 to 12 compared with placebo (placebo −5.6; 100 mg −7.7, p < 0.0001; 300mg −8.2, p < 0.0001). The odds for a 50% reduction in MMD were approximately 2.1 to 2.4 times higher with eptinezumab-jjmr than placebo (*Lipton et al 2020[a]*). Updated data from PROMISE-2 demonstrated similar responses at 24 weeks as were observed at 12 weeks (*Silberstein et al 2020[a]*).
- The PREVAIL trial was an OL, single-arm, Phase 3 trial evaluating long-term outcomes for eptinezumab-jjmr for 2 years. A total of 128 adults with chronic migraine received eptinezumab-jjmr 300 mg every 12 weeks for up to 8 doses. The percentage of patients with severe disability measured using the Migraine Disability Assessment tool (MIDAS) decreased from 84.4% to 26.8% at 12 weeks and 20.8% at week 104 (*Kudrow et al 2021)*.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Erenumab-aooe

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

Fremanezumab-vfrm

- Fremanezumab-vfrm was studied in a 12-week, DB, PC, MC, Phase 3 trial, HALO-CM, in which 1130 patients with chronic migraine were randomized to placebo (n = 375), fremanezumab-vfrm 225 mg once monthly (n = 379), or fremanezumab-vfrm 675 mg once quarterly (n = 376). Patients in the fremanezumab-vfrm 225 mg group received a loading dose of 675 mg at the first injection only. The primary endpoint was the change in mean headache days (MHD), which favored treatment with fremanezumab-vfrm 225 mg (mean change vs placebo, −2.1; SE, ± 0.3; p < 0.001) and fremanezumab-vfrm 675 mg (mean change vs placebo, −1.8; SE, ± 0.3; p < 0.001). Fremanezumab-vfrm significantly increased the proportion of patients achieving ≥ 50% reduction in MHD (difference for 225 mg vs placebo, 22.7%; OR, 2.73; difference for 675 mg vs placebo, 19.5%; OR, 3.13). Additionally, fremanezumab-vfrm was associated with a significant decrease in the mean monthly acute migraine−specific medication treatment days (difference for 225 mg vs placebo, −2.3; difference for 675 mg vs placebo, −1.8) (*Silberstein et al 2017*). Data after 1 year of treatment found sustained efficacy in chronic migraine (*Goadsby et al 2020[b]*).
  - A subgroup analysis evaluated the proportion of patients reverting to episodic migraine, defined as < 15 headache days per month. A total of 44.5% of patients in the placebo group reverted to episodic migraine compared to 50.5% in the quarterly fremanezumab-vfrm group (p = 0.108) and 53.7% in the monthly dosing group (p = 0.012) *(Lipton et al 2020[b]).*
- FOCUS was previously described as including 838 patients overall who had not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, 61% were diagnosed with chronic migraine and were randomized to fremanezumab-vfrm 675 mg administered quarterly (n = 169/276), a fremanezumab-vfrm 675 mg loading dose followed by 225 mg administered monthly (n = 173/283), or placebo (n = 167/279). Among patients classified as having chronic migraine and compared to placebo, the LSMD in MMD reduction over 12 weeks was 3.8 days for the fremanezumab-vfrm monthly group and 3.2 days for the fremanezumab-vfrm quarterly group (fremanezumab-vfrm monthly: LSMD, -3.8; 95% CI, -4.8 to -2.8 days; fremanezumab-vfrm quarterly: LSMD, -3.2; 95% CI, -4.2 to -2.2 days; p < 0.0001 for both) (*Ferrari et al 2019*).

Galcanezumab-gnlm

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

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

of galcanezumab-gnlm-treated patients (120 mg and 240 mg, respectively) had a ≥ 50% response for ≥ 3 months, which was greater than placebo (6.3%; p < 0.001). Few patients maintained ≥ 75% response (< 3%) (*Förderreuther et al 2018*).

- CONQUER was previously described as including 462 patients overall who had not responded to 2 to 4 classes of migraine preventive medications. Of the patients enrolled, 42% were diagnosed with chronic migraine and were randomized to galcanezumab-gnlm 240 mg loading dose followed by 120 mg administered monthly (n = 95/193), or placebo (n = 98/193). Among patients classified as having chronic migraine and compared to placebo, the LSMD in MMHD reduction over 12 weeks was 3.7 days for the galcanezumab-gnlm monthly group (95% CI, -5.2 to -2.2 days; p < 0.0001) (*Mulleners et al 2020*).

Treatment of episodic cluster headache

Galcanezumab-gnlm

- Galcanezumab-gnlm was evaluated in an 8-week, DB trial, in which 106 patients with episodic cluster headache were randomized to placebo (n = 57) or galcanezumab-gnlm 300 mg once monthly (n = 49). A total of 90 (85%) patients completed the DB phase. Patients were allowed to use certain specified acute/abortive cluster headache treatments, including triptans, oxygen, acetaminophen (APAP), and NSAIDs during the study. At baseline, patients had a mean of 17.5 headache attacks/week, maximum of 8 attacks/day, minimum of 1 attack every other day, and at least 4 attacks during the prospective 7-day baseline period. For the primary endpoint, galcanezumab-gnlm significantly decreased the mean change from baseline in weekly cluster headache attack frequency during weeks 1 to 3 vs placebo (-8.7 vs -5.2 attacks; p = 0.036). Galcanezumab-gnlm was also associated with a significantly greater proportion of responders (≥ 50% reduction in weekly cluster headache attack frequency) at week 3 (71.4 vs 52.6%; p = 0.046). Adverse events did not differ between groups, except for a significant increase in the incidence of injection-site pain with galcanezumab-gnlm treated patients (8 vs 0%; p = 0.04) (*Clinicaltrials.gov [NCT02397473] 2021, Emgality prescribing information 2019, Goadsby et al 2019*).

Treatment of acute migraine (with or without aura)

Rimegepant ODT

- Rimegepant ODT was evaluated in a Phase 3, DB, MC, PC, randomized controlled trial (RCT) in 1466 patients (modified intention to treat, n = 1351) with migraine with or without aura. Patients were randomized to placebo (n = 682) or rimegepant ODT 75 mg (n = 669) and were not allowed a second dose of study treatment. Rescue medications allowed 2 hours post-dose included aspirin, ibuprofen, naproxen (or any other type of NSAID), APAP up to 1000 mg/day, antiemetics (eg, metoclopramide or promethazine), or baclofen. Approximately 14% of patients were taking preventive medications for migraine at baseline. The co-primary endpoints were pain freedom and most bothersome symptom (MBS) freedom at 2 hours post-dose. Among patients randomized, 92.2% were included in the efficacy analysis and 93.8% in the safety analysis (*Croop et al 2019, Nurtec ODT [dossier] 2020, Nurtec ODT prescribing information 2020*).
  - The percentage of patients achieving headache pain freedom and MBS freedom 2 hours after a single dose was statistically significantly greater in patients who received rimegepant ODT compared to those who received placebo.
    - *Pain-free at 2 hours*: 21.2% for rimegepant ODT 75 mg vs 10.9% for placebo (p < 0.0001)
    - *MBS-free at 2 hours*: 35.1% for rimegepant ODT 75 mg vs 26.8% for placebo (p = 0.0009)
  - Out of the 21 secondary endpoints tested hierarchically, significant results were achieved for the first 19 endpoints. Those endpoints that were considered not significant included freedom from nausea at 2 hours post-dose, and pain relapse from 2 to 48 hours.
  - The most common adverse events were nausea and urinary tract infection. No serious adverse events were reported.
- Three additional trials evaluating the efficacy and safety of rimegepant 75 mg in an oral tablet (non-ODT) formulation were considered supportive for approval.
  - A MC, DB, dose-ranging trial using an adaptive design was conducted to determine an effective and tolerable dose range of rimegepant for the acute treatment of migraine. A total of 885 adults with migraine with or without aura were randomized to 1 of 6 rimegepant dose groups (10, 25, 75, 150, 300, or 600 mg), sumatriptan 100 mg, or placebo. It was found that the proportion of patients who were pain-free 2 hours after receiving a single dose of rimegepant 75 mg oral tablet was significantly higher compared with placebo (31.4% [n = 27/86] vs 15.3% [n = 31/203]; p = 0.002). The most common adverse events were nausea, vomiting, and dizziness. No treatment-related serious AEs were reported (*Marcus et al 2014*).

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- A MC, DB, PC, Phase 3 trial (n = 1072 in efficacy analysis) evaluating rimegepant vs placebo for acute migraine treatment found that the proportion of patients who were pain-free 2 hours after receiving a single dose of rimegepant 75 mg oral tablet was significantly higher compared with placebo (19.6 vs 12.0%; absolute difference, 7.6%; 95% CI, 3.3 to 11.9; p < 0.001). In addition, the proportion of patients who were free from their MBS 2 hours post-dose was significantly higher with rimegepant 75 mg oral tablet compared with placebo (37.6 vs 25.2%; absolute difference, 12.4%; 95% CI, 6.9 to 17.9; p < 0.001). Nausea and urinary tract infection were the only AEs reported in > 1% of the patients in the rimegepant and placebo groups. A serious adverse event associated with rimegepant was back pain (n = 1) (*Lipton et al 2019[c]*, *Nurtec ODT [dossier] 2020*).
- A MC, DB, PC, Phase 3 trial (n = 1084 in efficacy analysis) evaluating rimegepant vs placebo for acute migraine treatment found that the proportion of patients who were pain-free 2 hours after receiving a single dose of rimegepant 75 mg oral tablet was significantly higher compared with placebo (19.2 vs 14.2%; p = 0.03). In addition, the proportion of patients who were free from their MBS 2 hours post-dose was significantly higher with rimegepant 75 mg oral tablet compared with placebo (36.6 vs 27.7%; p = 0.002). Nausea and dizziness were the most common adverse events reported in the rimegepant and placebo treatment groups, respectively. Serious adverse events were reported in 2 patients treated with rimegepant and 1 patient treated with placebo (*Lipton et al 2018 [poster], Nurtec ODT [dossier] 2020*).

- Data is emerging on the combination use of rimegepant with CGRP monoclonal antibodies. A sub-study nested within a MC, OL, long-term safety study evaluated outcomes of 13 patients on CGRP monoclonal antibodies (erenumab, n = 7; fremanezumab, n = 4; and galcanezumab, n = 2) who received rimegepant 75 mg as needed *(Berman et al 2020)*. An average of 7.8 rimegepant doses were administered over a 4-week period, and 5 patients experienced mild or moderate AEs and no patients experienced severe AEs *(Berman et al 2020; Mullin et al 2020)*. Of note, this data is only available in a very small number of patients.

Ubrogepant

- Ubrogepant was evaluated in 2 Phase 3, PC, DB trials (ACHIEVE I and II), in which 3358 patients (ACHIEVE I, n = 1672; ACHIEVE II, n =1686) were randomized to take 1 dose of placebo (n = 1122), ubrogepant 50 mg (n = 1118), or ubrogepant 100 mg (n = 557) (100 mg was evaluated in the ACHIEVE I trial only, and a 25 mg group was included in the ACHIEVE II trial only [n = 561]). Patients had 2 to 8 migraines/month with moderate to severe pain intensity in the past 3 months either with or without aura and had a history of migraine for ≥ 1 year. A second dose of study treatment (placebo or ubrogepant), or the patient's usual acute treatment for migraine, was allowed between 2 to 48 hours after the initial treatment for a non-responding or recurrent migraine headache. At baseline, 23% of patients were taking preventive medications for migraine, and approximately 23 to 27% were insufficient triptan responders. In ACHIEVE I, 79% were included in the efficacy analysis and 86% in the safety analysis, and in ACHIEVE II, 91.7% had a qualifying migraine event and 88% were included in the analysis (*Dodick et al 2019, Lipton et al 2019[a], Ubrelvy prescribing information 2021*).
  - Compared to placebo, significant improvements were demonstrated for the co-primary endpoints of pain freedom and the MBS freedom at 2 hours post-dose in the ubrogepant arms. MBS was a collection of selective, self-identified symptoms (ie, photophobia, phonophobia, or nausea). The following differences from placebo were demonstrated:
    - *Pain-free at 2 hours*: 7.4% (p = 0.002) and 7.5% (p = 0.007) for the ubrogepant 50 mg dose in ACHIEVE I and II trials, respectively, and 9.4% (p < 0.001) for ubrogepant 100 mg dose in ACHIEVE I trial.
    - *MBS-free at 2 hours*: 10.8% and 11.5% (p < 0.001 for both) for the ubrogepant 50 mg dose in ACHIEVE I and II trials, respectively, and 9.9% (p < 0.001) for ubrogepant 100 mg dose in ACHIEVE I trial.
  - The incidence of photo- and phonophobia was reduced following administration. Significantly more patients maintained pain freedom for 2 to 24 hours post-dose in the ubrogepant 100 mg arm (difference from placebo, 6.8%; p = 0.002) and the 50 mg arm for ACHIEVE II only (6.2%; p = 0.005).
  - In ACHIEVE I, the most common adverse events included nausea (1.5 to 4.7%), somnolence (0.6 to 2.5%), and dry mouth (0.6 to 2.1%). In ACHIEVE II, the most common adverse events within 48 hours were nausea (≤ 2.5% for all arms) and dizziness (≤ 2.1% for all arms). No serious adverse events or adverse events leading to discontinuation were reported 48 hours after the initial dose. In ACHIEVE II, the serious adverse events at 30 days included appendicitis, spontaneous abortion, pericardial effusion, and seizure.

Treatment of medication overuse headache

Eptinezumab-jjmr

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- A subgroup, exploratory analysis of the PROMISE-2 trial, which was previously described, evaluated eptinezumab-jjmr 100 mg (n = 139), 300 mg (n = 147), or placebo (n = 145) in patients with chronic migraine and medication overuse headache at baseline screening. Patients receiving eptinezumab-jjmr had a significantly greater reduction in MMDs compared to placebo over weeks 1 to 12 (placebo: change from baseline, -5.4; 100 mg: change from baseline, -8.4, difference from placebo, -3.0, 95% CI, -4.56 to -1.52, p < 0.0001 vs placebo; 300 mg: change from baseline, -8.6, difference from placebo, -3.2, 95% CI, -4.66 to -1.78, p < 0.0001) *(Diener et al 2021)*.

Erenumab-aooe

- A subgroup analysis was performed to evaluate patients with chronic migraine and medication overuse included in a double-blind, placebo-controlled study of 667 patients, previously described by *Tepper et al*. A total of 274 patients had medication overuse at baseline screening and were randomized to erenumab-aooe 70 mg (n=79) or 140 mg (n = 78) or placebo (n = 117). At month 3, there was a significant reduction in MMD in both erenumab-aooe dosing groups (-6.6) compared to placebo (-3.5; difference, -3.1; 95% CI, -4.8 to -1.4; p < 0.001). The percentage of patients with ≥ 50% response rate was significantly higher in the 70 mg group (36%; OR, 2.67; 95% CI, 1.36 to 5.22) and the 140 mg group (35%; OR, 2.51; 95% CI, 1.28 to 4.94) compared to placebo (18%) *(Tepper et al 2019)*.

Fremanezumab-vfrm

- The impact of fremanezumab-vfrm on medication overuse headaches in patients with chronic migraine was evaluated through a subgroup analysis of the HALO CM study, which was previously described. Of the 1130 patients enrolled in HALO CM, 587 had medication overuse at baseline and were randomized to fremanezumab-vfrm quarterly (n = 201), monthly (n = 198), or placebo (n = 188). Compared with placebo, the reduction in MMD was greater for patients receiving fremanezumab-vfrm quarterly (-2.5 vs -4.7; difference, -2.2; 95% CI, -3.1 to -1.2; p < 0.0001) and monthly (-2.5 vs -5.2; difference, -2.7; 95% CI, -3.7 to -1.8; p < 0.0001) *(Silberstein et al 2020[b])*.

Galcanezumab-gnlm

- A post-hoc analysis of 3 previously described Phase 3 studies in patients with episodic migraine (EVOLVE-1 and EVOLVE-2) or chronic migraine (REGAIN) evaluated the efficacy of galcanezumab-gnlm in the prevention of migraine in patients with and without medication overuse *(Dodick et al 2021)*.
  - In the subgroup analysis of patients with medication overuse headaches and episodic migraine, there was a significantly greater reduction in MMD with both galcanezumab-gnlm 120 mg (-6.3; difference from placebo, -3.6; 95% CI, -4.7 to -2.4; p < 0.001) and 240 mg (-5.8; difference from placebo, -3.1; 95% CI, -4.2 to -2.0; p < 0.001) compared to placebo (-2.7).
  - In the subgroup analysis of patients with medication overuse headaches and chronic migraine, there was a significantly greater reduction in MMD with both galcanezumab-gnlm 120 mg (-4.8; difference from placebo, -2.5; 95% CI, -3.6 to -1.5; p < 0.001) and 240 mg (-5.6; difference from placebo, -2.3; 95% CI, -3.3 to -1.2; p < 0.001) compared to placebo (-2.5).

CLINICAL GUIDELINES

Acute treatment of migraine

- The American Headache Society (AHS) published updated consensus statement guidelines for migraine in 2018. The AHS recommends the use of APAP, NSAIDs, non-opioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans or dihydroergotamine (DHE) are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics. These guidelines do not differentiate the triptans, but recommend that non-oral routes be used when severe nausea or vomiting is present. Overall, the AHS designated the following drugs as having efficacy (*AHS 2019*):
  - Established efficacy:
    - Triptans
    - Ergotamine derivatives
    - NSAIDs (aspirin, diclofenac, ibuprofen, naproxen)
    - Opioids (butorphanol, although use is not recommended)
    - Combination medications
  - Probably effective
    - Ergotamine or other forms of DHE
    - NSAIDs (ketoprofen, ketorolac intramuscular or IV, flurbiprofen)
    - Magnesium IV

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

    - Isometheptene compounds
    - Combination medications (codeine/APAP, tramadol/APAP)
    - Antiemetics (prochlorperazine, promethazine, droperidol, chlorpromazine, metoclopramide)
  - The AHS recommends that rimegepant and ubrogepant may have a role in patients who have contraindications to the use of triptans or who have failed to respond to or tolerate ≥ 2 oral triptans, as determined by either a validated acute treatment patient reported outcome questionnaire or healthcare provider attestation. Coverage should be provided until ≥ 2 attacks are treated to determine efficacy and tolerability.
    - Other agents have had more established efficacy and safety relative to the newly FDA-approved migraine agents.
- There are a number of older guidelines/treatment recommendations for the treatment of migraine but, similar to the 2018 guidelines, they do not state a preference for a particular triptan or therapy (*Evers et al 2009, Francis et al 2010, Marmura et al 2015, Silberstein 2000, Silberstein et al 2012 [guideline reaffirmed in 2015]*).
- In 2019, the American Academy of Neurology (AAN) and the AHS published a guideline on the acute treatment of migraine in children and adolescents. The guideline states that there is evidence to support the efficacy of ibuprofen, APAP (in children and adolescents), and triptans (mainly in adolescents) for migraine relief, although confidence in the evidence varies between agents (*Oskoui et al 2019[a]*).
  - Of note, the CGRP inhibitors have not been adequately studied in children or adolescents and are not currently FDA-approved for use in these populations.

Prevention of migraine

- According to the AAN/AHS evidence−based guideline update on the pharmacologic treatment for episodic migraine prevention in adults, the following medications are effective preventive treatment options (see Appendix A for a definition of classifications) (*Silberstein et al 2012*):
  - Level A (established efficacy and > 2 Class I trials):
    - Antiepileptic drugs: divalproex sodium, sodium valproate, and topiramate
    - Beta blockers: metoprolol, propranolol, and timolol
    - Triptans (for menstrual related migraine [MRM]): for short−term prophylaxis, frovatriptan
  - Level B (probably effective and 1 Class I or 2 Class II trials):
    - Antidepressants: amitriptyline and venlafaxine
    - Beta blockers: atenolol and nadolol
    - Triptans (for MRM): for short−term prophylaxis, naratriptan and zolmitriptan
  - Level C (possibly effective and 1 Class II trial):
    - Angiotensin−converting enzyme (ACE) inhibitors: lisinopril
    - Angiotensin II receptor blockers (ARBs): candesartan
    - Alpha agonists: clonidine and guanfacine
    - Antiepileptic drugs: carbamazepine
    - Beta blockers: nebivolol and pindolol
    - Antihistamines: cyproheptadine
- The AAN recommends onabotulinumtoxin A as an effective treatment option that should be offered for chronic migraine. However, onabotulinumtoxin A is considered ineffective for the treatment of episodic migraines and should not be offered. There is insufficient evidence to compare the effectiveness of botulinum neurotoxin A with that of oral prophylactic topiramate (*Simpson et al 2016 [guideline reaffirmed in 2019]*).
- In 2019, the AAN/AHS published a guideline on the preventive treatment of migraine in pediatric patients. The guideline states that the majority of preventive medications for pediatric migraine fail to demonstrate superiority to placebo. The guidelines make the following statements and recommendations for initial therapy (see Appendix B for a definition of classifications) (*Oskoui et al 2019[b]*):
  - It is possible that cognitive behavioral therapy (CBT) alone is effective in migraine prevention.
  - There is insufficient evidence to evaluate the effects of flunarizine, nimodipine, valproate, and onabotulinumtoxinA for use in migraine prevention in children and adolescents.
  - Acknowledging the limitations of currently available evidence, use of short-term treatment trials (a minimum of 2 months) may be warranted in those who could benefit from preventive treatment (Level B).
  - Consider amitriptyline combined with cognitive behavioral therapy (CBT) (inform of the potential adverse events, including risk of suicide) (Level B).

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Consider topiramate (Level B). Inform of side effects including decreased efficacy when combined with oral contraceptives and the teratogenic effect in patients of childbearing potential (Level A). In patients of childbearing potential, daily folic acid is recommended (Level A).
- Consider propranolol (Level B).
  - Of note, the CGRP inhibitors have not been adequately studied in children or adolescents and are not currently FDA-approved for use in these populations.

Cluster headache

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

SAFETY SUMMARY

- Ubrogepant is contraindicated with concomitant use of strong CYP3A4 inhibitors.
- Eptinezumab-jjmr, erenumab-aooe, fremanezumab-vfrm, galcanezumab-gnlm, and rimegepant are contraindicated in patients with serious hypersensitivity to the active ingredient or any of the excipients. Mild to moderate hypersensitivity reactions (eg, rash, dyspnea, pruritus, urticaria) were reported in trials. Cases of anaphylaxis and angioedema have been reported post-marketing. Delayed serious hypersensitivity has occurred with rimegepant. In cases of serious or severe reactions, treatment should be discontinued.
- Warnings and precautions associated with the CGRP inhibitors include hypersensitivity reactions, in some cases reactions were reported within hours to 1 month after administration. Erenumab-aooe has additional warnings and precautions associated with the following:
  - Constipation with serious complications: Constipation with serious complications has been reported post-marketing. Some cases have required hospitalization, including surgery. Constipation was a common adverse event reported in up to 3% of patients. Concurrent use of medication associated with decreased gastrointestinal motility may increase the risk for severe constipation.
  - Hypertension: Post-marketing reports of the development or worsening of hypertension have emerged. Some cases required pharmacological treatment to manage or, in other cases, hospitalization. Incidences of hypertension were most frequently reported within 7 days of treatment, and most cases were reported after the first dose.
- The CGRP inhibitors generally have a similar incidence of adverse events as placebo. Very few severe adverse events and treatment discontinuations due to adverse events were reported. Across studies, adverse events were generally mild and/or similar to placebo. The most common adverse events observed in studies of injectable CGRP inhibitors included injection site reactions (subcutaneous CGRP inhibitors), constipation (erenumab-aooe only), and

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

nasopharyngitis and hypersensitivity (eptinezumab-jjmr only). For the oral CGRP inhibitors, ubrogepant was associated with somnolence, and both ubrogepant and rimegepant were associated with nausea.

- There are no adequate data on the risks associated in patients who are pregnant or nursing, or in adolescent or pediatric populations.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Aimovig (erenumab−aooe)	Auto-injector (70 mg/mL or 140 mg/mL)	SC	*Prevention of migraine*: Once monthly (70 or 140 mg)	May be self−administered by patients in the abdomen, thigh, or back of upper arm. Latex−sensitive patients may have an allergic reaction to the needle shield within the white cap and the gray needle cap of the syringe. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, erenumab-aooe has a limited stability of 7 days.
Ajovy (fremanezumab−vfrm)	Auto-injector or prefilled syringe (225 mg/1.5 mL)	SC	*Prevention of migraine*: Once monthly (225 mg) or once every 3 months (675 mg)	May be self−administered by patients in the abdomen, thigh, or back of upper arm. The prefilled syringe cap is not made with natural rubber latex. Must be refrigerated and protected from light until time of use. If necessary, fremanezumab-vfrm may be stored at room temperature for a maximum of 7 days. After removal from the refrigerator, fremanezumab-vfrm must be used within 7 days or discarded.
Emgality (galcanezumab−gnlm)	Auto-injector (120 mg/mL) Prefilled syringe (100 mg/mL or 120 mg/mL)	SC	*Prevention of migraine*: 2 consecutive injections (120 mg each) as a loading dose, then once monthly (120 mg) *Episodic cluster headache*: 3 consecutive injections (100 mg each) at onset, and then once monthly until the end of the cluster period	May be self−administered by patients in the abdomen, thigh, back of upper arm or buttocks. The cap is not made with natural rubber latex. Must be refrigerated and protected from light until time of use. Once removed from the refrigerator, galcanezumab-gnlm has a limited stability of 7 days.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Nurtec ODT (rimegepant sulfate)	ODT (75 mg)	PO	*Acute migraine treatment:* As needed. Maximum dose: 75 mg in 24 hours. *Prevention of episodic migraine*: Every other day. Maximum dose: 75 mg in 24 hours.	The safety of using > 18 doses in a 30-day period has not been established. Avoid concomitant administration with strong or moderate inhibitors of CYP3A4 within 48 hours, moderate or strong inducers of CYP3A, or P-gp or BCRP inhibitors.
Ubrelvy (ubrogepant)	Oral tablets (50 and 100 mg)	PO	*Acute migraine treatment:* As needed. A second dose may be taken at least 2 hours after the initial dose. Maximum dose: 200 mg in 24 hours.	The safety of treating > 8 migraines in a 30 day period has not been established. Dose adjustments are warranted with certain concomitant drugs or in cases of metabolic impairment. Avoid use in patients with end stage renal disease (CrCL < 15 mL/min). Take with or without food
Vyepti (eptinezumab-jjmr)	Single-dose vial (100 mg/mL)	IV	*Prevention of migraine*: Once every 3 months (100 or 300 mg) The recommended dosage is 100 mg every 3 months; some patients may benefit from a dosage of 300 mg every 3 months.	Dilute with 0.9% sodium chloride injection. Following dilution, eptinezumab-jjmr must be infused within 8 hours. Infuse over approximately 30 minutes. Administered by a healthcare provider in a healthcare setting. Must be refrigerated and protected from light until time of use.

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

CONCLUSION

- Migraine is a common, recurrent, incapacitating disorder characterized by moderate to severe headaches and disabling features, including nausea, vomiting, neurologic symptoms, photophobia, and phonophobia. Migraines have a spectrum of frequency and severity that can significantly affect the quality of life of patients. Cluster headache is less prevalent than migraine and characterized by attacks of severe, unilateral pain with ipsilateral autonomic symptoms, which occur every other day to multiple times daily during a cluster period. Cluster headache is more likely to occur in men, whereas migraines are more likely to occur in women.
- Rimegepant and ubrogepant are oral CGRP inhibitors indicated for acute treatment of migraine with or without aura. Rimegepant is also indicated for the prevention of episodic migraine. The injectable CGRP inhibitors eptinezumab-jjmr, erenumab-aooe, fremanezumab-vfrm, and galcanezumab-gnlm are indicated for the prevention of migraine. Galcanezumab-gnlm has an additional indication for the treatment of episodic cluster headache. No CGRP inhibitor is

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

FDA-approved for use in patients aged < 18 years. Eptinezumab-jjmr is the only IV formulation and requires administration in a healthcare setting.

- Guidelines divide treatment recommendations according to age, prevention or treatment, and migraine type:
  - Current evidence−based prophylactic migraine treatment options and guidance are limited for chronic migraine, and oral prophylactic medications prescribed for episodic migraine are often used for the preventive treatment of chronic migraine. Prophylactic migraine treatment options include oral agents (mainly anti−seizure agents, antidepressants, and beta blockers), injectable agents (onabotulinumtoxin A for chronic subtypes only), or neuromodulation devices for migraine or headache attacks. Certain oral therapies may not be appropriate for individual patients due to intolerability or eventual lack of efficacy. There is no optimal prophylactic migraine therapy and head-to-head trials are lacking.
  - For the treatment of cluster headache, subcutaneous sumatriptan, zolmitriptan nasal spray, and oxygen have the most positive evidence for acute therapy according to the AHS guidelines. To date, only subcutaneous sumatriptan is FDA-approved for the acute treatment of cluster headache. Additionally, sumatriptan nasal spray, zolmitriptan oral formulations, and sphenopalatine ganglion stimulation are probably effective for acute treatment per guidelines. For prevention of cluster headaches, suboccipital steroid injections are most effective according to the guidelines; however, there is no preventive medication currently FDA-approved for cluster headache.
  - For acute treatment of migraine in adults, guidelines generally recommend the use of APAP, NSAIDs, non-opioid analgesics, or caffeinated analgesic combinations for mild or moderate attacks. The triptans or DHE are recommended for moderate or severe attacks as well as for mild attacks that respond poorly to other analgesics. Recent AHS guidelines state that rimegepant and ubrogepant may have a role in patients who have contraindications to the use of triptans or who have failed to respond to or tolerate ≥ 2 oral triptans.
- There are no head-to-head studies with the CGRP inhibitors, and no agent is clearly superior to others. Evidence for the CGRP inhibitors have demonstrated efficacy for the respective indications:
  - Like other preventive medications for migraine, the CGRP inhibitors are not likely to render patients migraine-free. Based on 3 to 6 month data, primary endpoint reductions are similar to many oral prophylactic therapies; however, comparisons are limited as endpoints have been inconsistently defined. There are limited analyses and trials examining efficacy in patients who failed ≥ 2 prior preventive therapies; however, available data suggest that these patients may achieve greater reductions in migraine/headache frequency. Further research is warranted.
    - Compared to placebo, the injectable CGRP inhibitors when prescribed for prophylactic migraine therapy consistently demonstrated modest but statistically significant reductions in primary endpoint measures (eg, MMD, MMH, or MMHD) ranged from 0.7 to 3.5 days after 3 to 6 months of treatment. The numbers needed to treat (NNTs) ranged from 3 to 10 in order to achieve a ≥ 50% reduction in MM(H)D. Subgroup analyses from Phase 3 CGRP inhibitor trials showed consistent benefit for prevention of migraine in patients with medication overuse headaches.
    - The only oral CGRP inhibitor indicated for prevention, although for only episodic migraine, had a significant reduction of 0.8 MMD after 3 months of treatment. The NNT was 13 in order to achieve a ≥ 50% reduction in moderate-to-severe MMDs.
  - For the treatment of cluster headaches, galcanezumab-gnlm demonstrated efficacy compared to placebo in an 8-week trial, which allowed for acute/abortive treatments during therapy. Galcanezumab-gnlm significantly decreased the mean change from baseline in weekly cluster headache attack frequency by 3.5 during weeks 1 to 3 vs placebo. Additionally, 18.8% more patients were classified as responders (≥ 50% reduction in weekly cluster headache attack frequency) with galcanezumab-gnlm at week 3 vs placebo (p = 0.046).
  - Ubrogepant and rimegepant are oral CGRP inhibitors FDA-approved for acute treatment of migraine with or without aura in adults. One differing characteristic is that ubrogepant allows for a second dose within 24 hours whereas rimegepant does not. Additionally, ubrogepant allows for 2 dosing options (50 or 100 mg), and rimegepant allows for one (75 mg).
    - Rimegepant ODT demonstrated efficacy compared to placebo for acute use. Patients were not allowed a second dose of study treatment (placebo or rimegepant). Rescue medications allowed 2 hours post-dose included aspirin, ibuprofen, naproxen (or any other type of NSAID), APAP up to 1000 mg/day, antiemetics (eg, metoclopramide or promethazine), or baclofen. Compared to placebo, significantly more patients treated with rimegepant were pain-free at 2 hours (difference vs placebo, 10.3%). For the co-primary endpoint of MBS, significantly more rimegepant-treated patients reported being MBS-free at 2 hours post-dose (difference vs placebo, 8.3%). Additional trials evaluating the efficacy and safety of rimegepant were considered supportive for approval.
    - Ubrogepant demonstrated efficacy compared to placebo for acute response to migraine treatment after 2 hours. A second dose of study treatment (placebo or ubrogepant), or the patient's usual acute treatment for migraine, was

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

allowed between 2 to 48 hours after the initial treatment for a non-responding or recurrent migraine headache. Compared to placebo, significantly more patients treated with ubrogepant were pain-free at 2 hours when administered the 50 mg (difference vs placebo, 7.4 to 7.5%) or 100 mg (difference vs placebo, 9.4%) dose. For the co-primary endpoint of MBS, significantly more ubrogepant-treated patients reported being MBS-free at 2 hours post dose for the 50 mg (difference vs placebo, 10.8 to 11.5%) and 100 mg (difference vs placebo, 9.9%) dose.

- Lack of information during pregnancy and breastfeeding is a consideration as many migraine patients are women of childbearing potential. The unknown risks of monoclonal antibodies and the effects on certain conditions are not fully characterized. Furthermore, rimegepant and ubrogepant have a number of drug interactions, and may not be appropriate with other medications. Important co-morbid populations were excluded from trials (eg, anxiety, depression, hypertension, and fibromyalgia), which also limits the generalizability to broader groups. There are no data in adolescents and children.
- The safety profiles of the subcutaneous CGRP inhibitors are generally mild with the most common adverse events observed being injection site reactions. Hypersensitivity and nasopharyngitis were the most commonly reported adverse events for the IV-administered agent, eptinezumab-jjmr. Mild to moderate hypersensitivity reactions, including rash, pruritus, drug hypersensitivity, and urticaria, were reported with all CGRP inhibitors. Post-marketing reports with erenumab-aooe have included hypertension and constipation with serious complications; some cases of constipation have required hospitalization and surgery. The oral CGRP inhibitors, ubrogepant and rimegepant, were associated with nausea; ubrogepant was additionally associated with somnolence.
- Overall for acute treatment, ubrogepant and rimegepant are alternatives to triptans and/or DHE in patients who are unable to tolerate or have an inadequate response or contraindication to established pharmacologic abortive migraine treatments. The injectable CGRP inhibitors represent another therapy option in the prevention of episodic or chronic migraine. Rimegepant is the only oral CGRP inhibitor that may be prescribed for the prevention of episodic migraines. Eptinezumab-jjmr and fremanezumab-vfrm are the only agents in the class that may be administered quarterly. Galcanezumab-gnlm is the only CGRP inhibitor indicated for the treatment of episodic cluster headaches. Dosage and administration vary by product and indication. Further long-term study is warranted.

APPENDICES

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

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

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

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

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

REFERENCES

- Aimovig [package insert], Thousand Oaks, CA: Amgen, Inc. and Novartis Pharmaceuticals Corp.; May 2021.
- AbbVie. U.S. FDA accepts AbbVie's new drug application for atogepant for the preventive treatment of migraine. AbbVie New Center. March 30, 2021. https://news.abbvie.com/news/press-releases/us-fda-accepts-abbvies-new-drug-application-for-atogepant-for-preventive-treatment-migraine.htm Accessed June 28, 2021.
- Ajovy [package insert], North Wales, PA: Teva Pharmaceuticals, Inc.; June 2021.
- American Migraine Foundation (AMF). Non−invasive neuromodulation devices. April 2, 2020. Web site. https://americanmigrainefoundation.org/resource-library/neuromodulation-for-migraine-treatment/. Accessed June 28, 2021.
- American Headache Society. The American Headache Society position statement on integrating new migraine treatments into clinical practice. *Headache*. 2019;59(1):1-18.
- Ashina M, Saper J, Cady R, et al. Eptinezumab in episodic migraine: A randomized, double-blind, placebo-controlled study (PROMISE-1). *Cephalalgia*. 2020;40(3):241-254.
- Berman G, Croop R, Kudrow D, et al. Safety of Rimegepant, an oral CGRP receptor antagonist, plus CGRP monoclonal antibodies for migraine. *Headache.* 2020; 60(8):1734-1742.
- Biohaven Pharmaceuticals. Zavegepant. 2021. https://www.biohavenpharma.com/science-pipeline/cgrp/bhv-3500. Accessed June 28, 2021.
- Burgos−Vega C, Moy J, Dussor G. Meningeal afferent signaling and the pathophysiology of migraine. *Prog Mol Biol Transl Sci*. 2015;131:537−64.
- Clinicaltrials.gov. US National Library of Medicine. 2021. Web site. https://www.clinicaltrials.gov/. Accessed June 28, 2021.
- Clinicaltrials.gov. A study of galcanezumab in participants with episodic cluster headache (NCT02397473). September 9, 2019. https://www.clinicaltrials.gov/ct2/show/NCT02397473?term=NCT02397473&rank=1. Accessed June 28, 2021.
- Croop R, Goadsby PJ, Stock DA, et al. Efficacy, safety, and tolerability of rimegepant orally disintegrating tablet for the acute treatment of migraine: a randomised, phase 3, double-blind, placebo-controlled trial. Lancet. 2019;394(10200):737-745.
- Croop R, Lipton RB, Kudrow D, et al. Oral rimegepant for preventive treatment of migraine: a phase 2/3, randomised, double-blind, placebo-controlled trial. *Lancet*. 2021;397(10268):51-60.
- Detke, H, Goadsby PJ, Wang S, et al. Galcanezumab in chronic migraine: The randomized, double-blind, placebo-controlled REGAIN study. *Neurology*. 2018;91(24):e2211-e2221.
- Diener H, Marmura MJ, Tepper SJ, et al. Efficacy, tolerability, and safety of eptinezumab in patients with a dual diagnosis of chronic migraine and medication-overuse headache: subgroup analysis of PROMISE-2. *Headache.* 2021;61(1):125-136.
- Dodick DW, Ashina M, Brandes JL, et al. ARISE: A phase 3 randomized trial of erenumab−aooe for episodic migraine. *Cephalalgia*. 2018[a]:38(6):1026-37.
- Dodick DW, Doty EG, Aurora SK, et al. Medication overuse in a subgroup analysis of phase 3 placebo-controlled studies of galcanezumab in the prevention of episodic and chronic migraine. *Cephalalgia.* 2021;41(3):340-352.
- Dodick DW, Silberstein SD, Bigal ME, et al. Effect of fremanezumab compared with placebo for prevention of episodic migraine: a randomized clinical trial (HALO EM). *JAMA*. 2018[b];319(19):1999-2008.
- Dodick DW, Lipton RB, Ailani J, et al. Ubrogepant for the treatment of migraine. *N Engl J Med*. 2019;381(23):2230-2241.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed June 28, 2021.
- Edvinsson L. The trigeminovascular pathway: role of CGRP and CGRP receptors in migraine. *Headache*. 2017;57 Suppl 2:47−55.
- Emgality [package insert], Indianapolis, IN: Eli Lilly and Company; December 2019.
- Evers S, Afra J, Frese A, et al. EFNS guideline on the drug treatment of migraine - revised report of an EFNS task force. *Eur J Neurol*. 2009;16(9):968-981.
- Ferrari MD, Diener HC, Ning X, et al. Fremanezumab versus placebo for migraine prevention in patients with documented failure to up to four migraine preventive medication classes (FOCUS): a randomised, double-blind, placebo-controlled, phase 3b trial. *Lancet*. 2019;394(10203):1030-1040.
- Förderreuther S, Zhang Q, Stauffer VL, et al. Preventive effects of galcanezumab in adult patients with episodic or chronic migraine are persistent: data from the phase 3, randomized, double-blind, placebo-controlled EVOLVE-1, EVOLVE-2, and REGAIN studies. *J Headache Pain*. 2018;19(1):121.
- Francis GJ, Becker WJ, Pringsheim TM. Acute and preventive pharmacologic treatment of cluster headache. *Neurology*. 2010;75:463-473.
- Global Burden of Disease (GBD) 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990−2015: a systematic analysis for the Global Burden of Disease Study 2015. *Lancet*. 2016;388:1545−602.
- Goadsby PJ, Reuter U, Hallström Y, et al. A controlled trial of erenumab−aooe for episodic migraine (STRIVE). *N Engl J Med*. 2017;377(22):2123−32.
- Goadsby PJ, Dodick DW, Leone M, et al. Trial of galcanezumab in prevention of episodic cluster headache. *N Engl J Med*. 2019;381(2):132-141.
- Goadsby P, Reuter U, Hallstrom Y, et al. One-year sustained efficacy of erenumab in episodic migraine: Results of the STRIVE study. *Neurology*. 2020[a] Aug 4;95(5):e469-e479.
- Goadsby P, Silberstein S, Yeung P, et al. Long-term safety, tolerability, and efficacy of fremanezumab in migraine: A randomized study. *Neurology*. 2020[b] Nov 3;95(18):e2487-e2499.
- Gronseth GS, Woodroffe LM, Getchius TS, et al; for the American Academy of Neurology. Clinical Practice Guideline Process Manual, 11th edition. 2011. Available at: http://tools.aan.com/globals/axon/assets/9023.pdf. Accessed June 28, 2021.
- Hoffman J and May A. Diagnosis, pathophysiology, and management of cluster headache. *Lancet Neurol*. 2018;17(1):75-83.
- International Headache Society (IHS). Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. 2018;38(1):1-211.
- Katsarava Z, Buse DC, Manack AN, et al. Defining the differences between episodic migraine and chronic migraine. *Curr Pain Headache Rep*. 2012;16(1):86-92.
- Kudrow D, Cady RK, Allan B, et al. Long-term safety and tolerability of eptinezumab in patients with chronic migraine: a 2-year, open-label, phase 3 trial. *BMC Neurol*. 2021;21:126.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Lipton RB, Cohen JM, Bibeau K, et al. Reversion from chronic migraine to episodic migraine in patients treated with fremanezumab: post hoc analysis from HALO CM study. *Headache*. 2020[b];60(10):2444-2453.
- Lipton RB, Conway, CM, Stock, EG, et al. Efficacy, safety, and tolerability of rimegepant 75 mg, an oral CGRP receptor antagonist, for the treatment of migraine: Results from a phase 3, double-blind, randomized, placebo-controlled trial, Study 301. [poster]. Presented at the 60th Annual Scientific Meeting of the American Headache Society; San Francisco, CA; 2018.
- Lipton RB, Croop R, Stock EG, et al. Rimegepant, an oral calcitonin gene-related peptide receptor antagonist, for migraine. *N Engl J Med*. 2019[c];381(2):142-149.
- Lipton RB, Dodick DW, Ailani J, et al. Effect of ubrogepant vs placebo on pain and the most bothersome associated symptom in the acute treatment of migraine: The ACHIEVE II randomized clinical trial. *JAMA*. 2019[a];322(19):1887-1898.
- Lipton RB, Goadsby PJ, Smith J, et al. Efficacy and safety of eptinezumab in patients with chronic migraine: PROMISE-2. *Neurology.* 2020[a];94(13):e1365-e1377.
- Lipton RB, Manack Adams A, Buse DC, et al. A comparison of the chronic migraine epidemiology and outcomes (CaMEO) study and American migraine prevalence and prevention (AMPP) study: demographics and headache−related disability. *Headache*. 2016;56:1280−9.
- Lipton RB, Tepper SJ, Reuter U, et al. Erenumab in chronic migraine: Patient-reported outcomes in a randomized double-blind study. *Neurology*. 2019[b];92(19):e2250-e2260.
- Ljubisavljevic S, Zidverc Trajkovic J. Cluster headache: pathophysiology, diagnosis and treatment. *J Neurol*. 2019;266(5):1059-1066.
- Manack AN, Buse DC, Lipton RB. Chronic migraine: epidemiology and disease burden. *Curr Pain Headache Rep*. 2011;15:70−8.
- Marcus R, Goadsby PJ, Dodick D, et al. BMS-927711 for the acute treatment of migraine: a double-blind, randomized, placebo controlled, dose-ranging trial. *Cephalalgia*. 2014;34(2):114-25.
- Marmura MJ, Silberstein SD, Schwedt TJ, et al. The acute treatment of migraine in adults: the American Headache Society evidence assessment of migraine pharmacotherapies. *Headache*. 2015;55(1):3-20.
- Mulleners W, Byung-Kun K, Lainex M, et al. Safety and efficacy of galcanezumab in patients for whom previous migraine preventive medication from two to four categories had failed (CONQUER): a multicentre, randomised, double-blind, placebo-controlled, phase 3b trial. *Lancet Neurol.* 2020 Oct;19(10):814-825.
- Mullin K, Kudrow D, Croop R, et al. Potential for treatment benefit of small molecule CGRP receptor antagonist plus monoclonal antibody in migraine therapy. *Neurology.* 2020;94(20):e2121-e2125.
- Nurtec ODT [dossier], New Haven, CT: Biohaven Pharmaceuticals; March 2020.
- Nurtec ODT [package insert], New Haven, CT: Biohaven Pharmaceuticals; May 2021.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed June 28, 2021.
- Oskoui M, Pringsheim T, Holler-Managan Y, et al. Practice guideline update summary: Acute treatment of migraine in children and adolescents: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2019[a];93(11):487-499.
- Oskoui M, Pringsheim T, Billinghurst L, et al. Practice guideline update summary: Pharmacologic treatment for pediatric migraine prevention: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology and the American Headache Society. *Headache*. 2019[b];59(8):1144-1157.
- Purple Book: Database of Licensed Biological Products. US Food and Drug Administration. Updated June 25, 2021. https://purplebooksearch.fda.gov/. Accessed June 28, 2021.
- Reuter U, Goadsby PJ, Lanteri-Minet M, et al. Efficacy and tolerability of erenumab in patients with episodic migraine in whom two-to-four previous preventive treatments were unsuccessful: a randomised, double-blind, placebo-controlled, phase 3b study. *Lancet*. 2018;392(10161):2280-7.
- Robbins MS, Starling AJ, Pringsheim TM, et al. Treatment of Cluster Headache: The American Headache Society Evidence-Based Guidelines. *Headache*. 2016;56(7):1093-106.
- Schwedt TJ, Kuruppu DK, Dong Y, Standley K, Yunes-Medina L, Pearlman E. Early onset of effect following galcanezumab treatment in patients with previous preventative medication failures. *J Headache Pain.* 2021;22(1):15.
- Silberstein SD. Practice parameter: Evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. 2000;55(6):754-762.
- Silberstein SD, Cohen JM, Seminerio MJ, et al. The impact of fremanezumab on medication overuse in patients with chronic migraine: subgroup analysis of the HALO CM study. *J Headache Pain.* 2020[b];21(1):114.
- Silberstein SD, Dodick DW, Bigal ME, et al. Fremanezumab for the preventive treatment of chronic migraine (HALO CM). *N Engl J Med*. 2017;377(22):2113-22.
- Silberstein SD, Holland S, Freitag F, et al. Evidence−based guideline update: pharmacologic treatment for episodic migraine prevention in adults: report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology*. 2012;78(17):1337−45. Reaffirmed July 18, 2015.
- Silberstein SD, Diamond M, Hindiyeh N, et al. Eptinezumab for the prevention of chronic migraine: efficacy and safety through 24 weeks of treatment in the phase 3 PROMISE-2 (Prevention of migraine via intravenous ALD403 safety and efficacy-2) study. *J Headache Pain*. 2020[a];21(1):120.
- Simpson DM, Hallett M, Ashman EJ, et al. Practice guideline update summary: Botulinum neurotoxin for the treatment of blepharospasm, cervical dystonia, adult spasticity, and headache: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2016;86(19):1818−26. Reaffirmed May 7, 2019.
- Skljarevski V, Matharu M, Millen BA, et al. Efficacy and safety of galcanezumab for the prevention of episodic migraine: Results of the EVOLVE-2 Phase 3 randomized controlled clinical trial. *Cephalalgia*. 2018;38(8):1442-54.
- Smith TR, Janelidze M, Chakhava G, et al. Eptinezumab for the prevention of episodic migraine: sustained effect through 1 year of treatment in the PROMISE-1 study. *Clin Ther.* 2020;42(12):2254-2265.e3.
- Starling AJ and Dodick DW. Best practices for patients with chronic migraine: burden, diagnosis, and management in primary care. *Mayo Clin Proc*. 2015;90(3):408−14.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Stauffer VL, Dodick DW, Zhang Q, et al. Evaluation of galcanezumab for the prevention of episodic migraine: The EVOLVE-1 randomized clinical trial. *JAMA Neurol*. 2018;75(9):1080-8.
- Sun H, Dodick DW, Silberstein S, et al. Safety and efficacy of AMG 334 for prevention of episodic migraine: a randomised, double-blind, placebo-controlled, phase 2 trial. *Lancet Neurol.* 2016;15(4):382-90.
- Tepper S, Ashina M, Reuter U, et al. Safety and efficacy of erenumab−aooe for preventive treatment of chronic migraine: a randomised, double−blind, placebo−controlled phase 2 trial. *Lancet Neurol*. 2017;16(6):425−34.
- Tepper SJ, Diener H, Ashina M, et al. Erenumab in chronic migraine with medication overuse: subgroup analysis of a randomized trial. *Neurology*. 2019;92(20):e2309-e2320.
- Teva Pharmaceutical press release. Teva bails on fremanezumab in cluster headache. April 23, 2019. https://seekingalpha.com/news/3452826-teva-bails-fremanezumab-cluster-headache. Accessed June 28, 2021.
- Ubrelvy [package insert], Madison, NJ: Allergan; March 2021.
- Vyepti [dossier], Bothell, WA: Lundbeck Pharmaceuticals; March 2020.
- Vyepti [package insert], Bothell, WA: Lundbeck Pharmaceuticals; February 2020.
- Walker CS and Hay DL. CGRP in the trigeminovascular system: a role for CGRP, adrenomedullin and amyline receptors? *Br J Pharmacol*. 2013; 170(7):1293-307.

Publication Date: June 30, 2021

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Prior Authorization Guideline

Guideline Note: Cystic Fibrosis Agents

1. Criteria

Product Name: **Kalydeco**	
Approval Length	12 month(s)
Therapy Stage	Initial Authorization

Approval Criteria

1 - The recipient is age appropriate according to the FDA-approved package labeling

AND

2 - The recipient has a diagnosis of cystic fibrosis

AND

3 - There is documentation that the recipient has had an FDA-approved cystic fibrosis mutation test confirming the presence of one of the gene mutations listed in the FDA-approved package insert

AND

4 - The medication is prescribed by or in consultation with a pulmonologist or a specialist affiliated with a cystic fibrosis care center

Product Name: **Orkambi**	
Approval Length	12 month(s)
Guideline Type	Initial Authorization

Approval Criteria

1 - The recipient is age appropriate according to the FDA-approved package labeling

AND

2 - The recipient has a diagnosis of cystic fibrosis

AND

3 - The recipient is homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene

AND

4 - The medication is prescribed by or in consultation with a pulmonologist or a specialist affiliated with a cystic fibrosis care center

Product Name: **Symdeko**	
Approval Length	12 month(s)
Therapy Stage	Initial Authorization

Approval Criteria

1 - The recipient is age appropriate according to the FDA-approved package labeling

AND

2 - The recipient has a documented diagnosis of cystic fibrosis

AND

3 - The medication must be prescribed by or in consultation with either a pulmonologist or a specialist associated with a cystic fibrosis care center

AND

4 - One of the following:

4.1 The recipient is homozygous for the F508del mutation as detected by an FDA cleared cystic fibrosis mutation test or CLIA approved facility

OR

4.2 The recipient has one of the FDA approved package insert listed mutations on at least one allele in the CF transmembrane conductance regulator (CFTR) gene as detected by FDA cleared cystic fibrosis mutation test or CLIA approved facility

Product Name: **Trikafta**	
Approval Length	12 month(s)
Therapy Stage	Initial Authorization

Approval Criteria

1 - The recipient is age appropriate according to the FDA-approved package labeling

AND

2 - The recipient has a documented diagnosis of cystic fibrosis

AND

3 - The recipient has at least one F508del mutation in the CFTR gene as detected by an FDA cleared CF mutation test, or a test performed at a CLIA approved facility

AND

4 - The medication is prescribed by or in consultation with either a Pulmonologist or a specialist affiliated with a cystic fibrosis care center

Product Name: **Kalydeco, Orkambi, Symdeko, Trikafta**	
Approval Length	12 month(s)
Therapy Stage	Reauthorization

Approval Criteria

1 - Documentation of a positive clinical response to therapy (i.e., improvement in lung function [forced expiratory volume in one second {FEV1}], decreased number of pulmonary exacerbations)

2. Background

Benefit/Coverage/Program Information

FDA Approved Age Indication

Drug	Dosage Form	Age Indication
Kalydeco	25mg, 50mg, 75mg granule packets; 150mg capsules	4 months or older
Orkambi	100mg/125mg granule packet	2 through 5 years weighing less than 14 kg
Orkambi	150mg/188mg granule packet	2 through 5 years weighing 14 kg or greater
Orkambi	100mg/125mg tablets	Age 6 through 11years
Orkambi	200mg/125mg tablets	12 years or older
Symdeko	50/75-75 mg tablets	6 years of age or older
Trikafta	50/25/37.5-75mg tablets	6 years of age or older

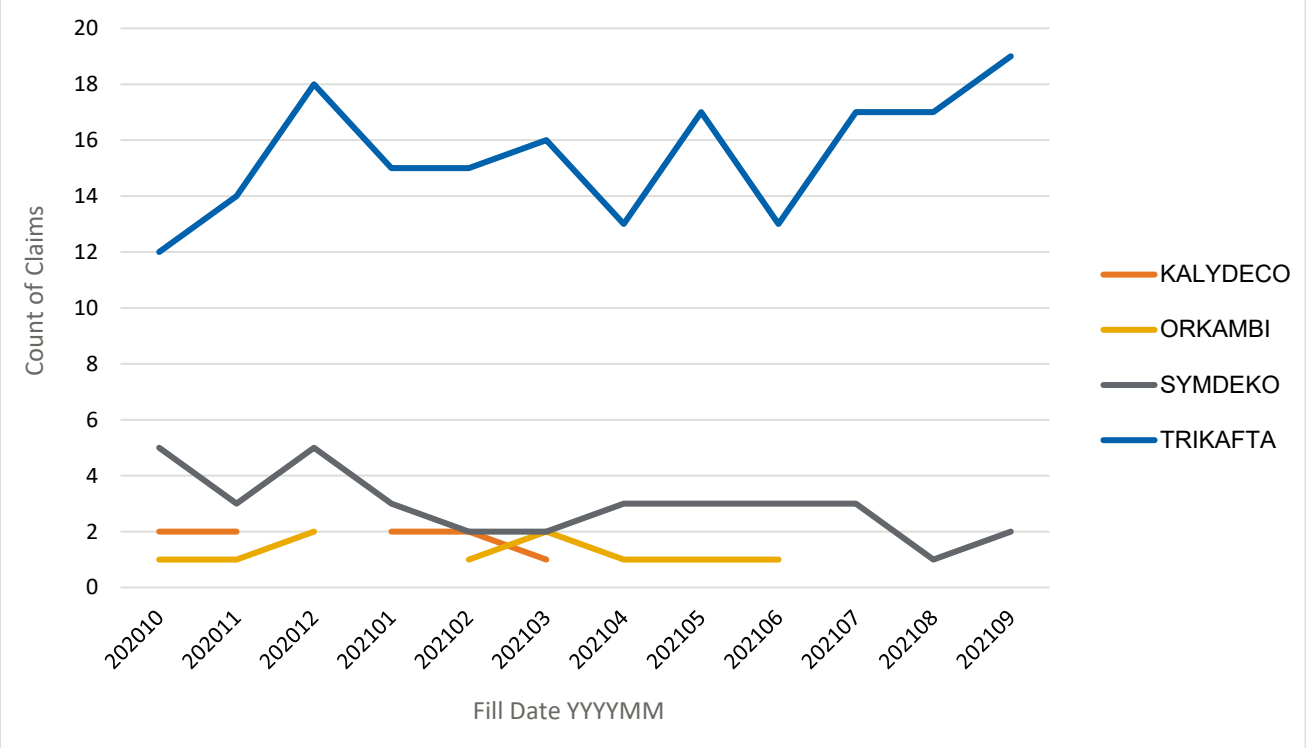
Nevada Medicaid

Utilization

Fee for Service

October 1, 2020 – September 30, 2021

Drug Name	Members	Claims	Total Day Supply	Total Quantity
KALYDECO	3	10	280	560
ORKAMBI	1	10	280	560
SYMDEKO	5	35	980	1,960
TRIKAFTA	25	186	5,264	15,624



Therapeutic Class Overview

Cystic fibrosis transmembrane conductance regulator (CFTR) modulators and dornase alfa

INTRODUCTION

- Cystic fibrosis (CF) is the most common fatal genetic disease, affecting approximately 30,000 patients in the United States (U.S.) (*National Institutes of Health 2013*). It is caused by mutations in the CF transmembrane conductance regulator (*CFTR*) gene, which encodes for the CFTR protein. This protein acts as an ion channel regulating salt and fluid homeostasis, and defects are associated with thickened secretions, obstruction, and damage to several organs (*Ong et al 2016*). Respiratory manifestations are a significant feature of the disease, and respiratory failure is the most common cause of death in patients who do not receive a lung transplant (*Elborn 2016*).
  - CF is an autosomal recessive disorder; 2 copies of an abnormal gene must be present for the disease to develop (*Elborn 2016*). Patients may have 2 copies of the same mutation (homozygous) or 2 different mutations (heterozygous) (*Ong et al 2016*). Approximately 2000 mutations have been identified in the *CFTR* gene, of which more than 300 have been confirmed to cause CF (*CFTR2 2019*, *Quon and Rowe 2016*). In general, these mutations either reduce the amount of CFTR protein that reaches the cell membrane surface or reduce the function of CFTR as a chloride channel (*Egan 2016*). The most common *CFTR* mutation leading to CF is the *F508del* mutation; approximately 50% of patients with CF are homozygous for this mutation, and 90% carry at least 1 copy (*Katkin 2019*).
- Treatment of CF has traditionally been limited to addressing disease manifestations in specific organs (*Quon and Rowe 2016*).
  - Inhaled antibiotics have commonly been used to treat persistent airway infection with *Pseudomonas aeruginosa*, which contributes to lung damage in patients with CF. A reduction of bacterial load in the lungs decreases inflammation and the deterioration of lung function (*Smith et al 2018*).
  - Inhaled dornase alfa, hypertonic saline, and mannitol have been used to enhance airway mucociliary clearance, and oral macrolide antibiotics and high-dose ibuprofen have been used to reduce inflammation (*Quon and Rowe 2016*).
    - Pulmozyme (dornase alfa), initially approved by the Food and Drug Administration (FDA) in 1993, is a recombinant DNase enzyme. In CF patients, retention of viscous purulent secretions in the airways contributes to reduced pulmonary function and to exacerbations of infection. Dornase alfa hydrolyzes deoxyribonucleic acid (DNA) in the sputum of CF patients, reducing sputum viscoelasticity. Guidelines recommend the use of dornase alfa for patients with CF aged ≥ 6 years with moderate-to-severe lung disease (to improve lung function and quality of life and to reduce exacerbations) and with asymptomatic or mild lung disease (to improve lung function and reduce exacerbations) (*Drugs@FDA 2020, Mogayzel et al 2013*).
- More recently, CFTR modulators have been made available that act on the basic defect(s) in CFTR function; these include Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor), Symdeko (tezacaftor/ivacaftor), and Trikafta (elexacaftor/tezacaftor/ivacaftor) (*Drugs@FDA 2020, Elborn 2016*). The CFTR modulators facilitate processing and trafficking of CFTR to the cell surface (CFTR correctors [tezacaftor, lumacaftor, and elexacaftor]) or facilitate increased chloride transport at the cell surface (CFTR potentiator [ivacaftor]). Eligibility for CFTR modulator therapy depends on the patient's age and CF-causing mutation(s).
  - In 2018, prior to the approval of Trikafta and some age expansions for the other CFTR modulators, it was estimated that only 55% of patients with a known genotype were eligible for CFTR modulator therapy (*Vertex CF portfolio guide 2018*). The approval of Trikafta may provide the opportunity for up to 90% of CF patients to be eligible for CFTR modulator therapy in the future (*Vertex 2019*).
  - The CFTR modulators are used in conjunction with traditional therapies in patients who are eligible.
- This review includes the 4 available CFTR modulators and dornase alfa.
- Medispan Class: CF Agents, CFTR Potentiators (Kalydeco); CF Agents, CF Agent-Combinations (Orkambi, Symdeko, and Trikafta); and CF Agents, Hydrolytic Enzymes (Pulmozyme)

Table 1. Medications Included Within Class Review

Drug	Generic Availability
CFTR Modulators	
Kalydeco (ivacaftor)	-
Orkambi (lumacaftor/ivacaftor)	-

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Drug	Generic Availability
Symdeko (tezacaftor/ivacaftor)	-
Trikafta (elexacaftor/tezacaftor/ivacaftor)	-
DNase enzyme	
Pulmozyme (dornase alfa)	-

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

INDICATIONS

Table 2. FDA Approved Indications

Indication	CFTR Modulators				DNase Enzyme
	Kalydeco (ivacaftor)	**Orkambi** (lumacaftor/ ivacaftor)	**Symdeko** (tezacaftor/ ivacaftor)	**Trikafta** (elexacaftor/ tezacaftor/ ivacaftor)	**Pulmozyme** (dornase alfa)
Treatment of CF in patients aged 6 months and older who have 1 mutation in the *CFTR* gene that is responsive to ivacaftor potentiation based on clinical and/or *in vitro* assay data*	✔				
Treatment of CF in patients aged 2 years and older who are homozygous for the *F508del* mutation in the *CFTR* gene		✔			
Treatment of patients with CF aged 6 years and older who are homozygous for the *F508del* mutation or who have at least 1 mutation in the *CFTR* gene that is responsive to tezacaftor/ ivacaftor based on *in vitro* data and/or clinical evidence†			✔		
Treatment of CF in patients aged 12 years and older who have at least 1 *F508del* mutation in the *CFTR* gene				✔	
For daily administration in conjunction with standard therapies for the management of CF patients to improve pulmonary function‡					✔

* The following 38 mutations are included: *E56K, P67L, R74W, D110E, D110H, R117C,* ***R117H***, ***G178R***, *E193K, L206W, R347H, R352Q, A455E,* ***S549N***, ***S549R***, ***G551D***, ***G551S***, *D579G, 711+3A→G, E831X, S945L, S977F, F1052V, K1060T, A1067T,* ***G1069R***, ***R1070Q***, *R1070W, F1074L, D1152H,* ***G1244E***, ***S1251N***, ***S1255P***, *D1270N,* ***G1349D***, *2789+5G→A, 3272-26A→G,* and *3849+10kbC→T.* Note: Bolded mutations are unique to the indication for Kalydeco and are not covered by another CFTR modulator.

† The following 27 mutations are included (patients must have 2 copies of the *F508del* mutation, or at least 1 copy of another listed medication, for Symdeko to be indicated): *E56K, P67L, R74W, D110E, D110H, R117C, E193K, L206W, R347H, R352Q, A455E, F508del, D579G, 711+3A→G, E831X, S945L, S977F, F1052V, K1060T, A1067T, R1070W, F1074L, D1152H, D1270N, 2789+5G→A, 3272-26A→G,* and *3849+10kbC→T.* Note: All of these mutations are also covered by either Kalydeco or Orkambi.

‡ In CF patients with a forced vital capacity (FVC) ≥ 40% of predicted, daily administration of dornase alfa has also been shown to reduce the risk of respiratory tract infections requiring parenteral antibiotics.

(*Prescribing information: Kalydeco 2019, Orkambi 2018, Pulmozyme 2018, Symdeko 2019, Trikafta 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.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

CLINICAL EFFICACY SUMMARY

CFTR Modulators

Note: The following is a brief overview of the clinical evidence supporting the efficacy of the CFTR modulators. Appendix A provides an overview of key clinical trials for CFTR modulators in a table format. Appendix B provides a description of study endpoints.

- The safety and efficacy of ivacaftor have been evaluated in a number of trials in patients with a variety of *CFTR* mutations. In addition to the clinical evidence available, ivacaftor has been FDA-approved for the treatment of some *CFTR* mutations based on *in vitro* assay data.
  - A 48-week, double-blind trial demonstrated improvement in percent predicted forced expiratory volume in 1 second ($ppFEV_1$) and exacerbations for ivacaftor vs placebo in 167 patients with CF aged ≥ 12 years with ≥ 1 *G551D* mutation (*Ramsey et al 2011*). A separate, placebo-controlled, 48-week double-blind trial in 52 patients aged 6 to 11 years with this mutation demonstrated improvement in $ppFEV_1$ (*Davies et al 2013*), and an open-label extension study of these 2 trials demonstrated sustained $ppFEV_1$ improvement over 96 weeks (*McKone et al 2014*).
  - A placebo-controlled crossover trial with two 8-week treatment periods demonstrated improved $ppFEV_1$ with ivacaftor in 39 patients with CF aged ≥ 6 years with a non-*G551D* gating mutation (*De Boeck et al 2014*).
  - A 24-week, double-blind, placebo-controlled trial evaluated the safety and efficacy of ivacaftor vs placebo in 69 patients aged ≥ 6 years with an *R117H* mutation (*Moss et al 2015*). In this trial, improvement in $ppFEV_1$ was demonstrated in adults but not in children aged 6 to 11 years; the authors suggested that the lack of effect may have been related to the high baseline $ppFEV_1$ in the pediatric patients enrolled.
  - A crossover study with two 8-week treatment arms enrolled a total of 246 patients aged ≥ 12 years with CF who were heterozygous for *F508del* and a residual function mutation (*Rowe et al 2017*). A comparison of the ivacaftor and placebo arms demonstrated an improvement in $ppFEV_1$ with ivacaftor. (See the tezacaftor/ivacaftor section below for information on comparisons of tezacaftor/ivacaftor to ivacaftor and placebo in this study.)
  - An open-label study in 34 patients aged 2 to 5 years with CF and ≥ 1 *CFTR* gating mutation evaluated weight-based dosing of ivacaftor in this age group (*Davies et al 2016*). Patients weighing < 14 kg received a dose of 50 mg and those ≥ 14 kg received a dose of 75 mg. Pharmacokinetic analyses demonstrated that exposure was similar to that reported with the approved dosing in adults. Improvements were also seen in weight and sweat chloride concentrations (a pharmacodynamic endpoint that reflects changes in CFTR function). No meaningful data on lung function were available, as the accuracy of spirometry results is limited in this age group.
  - The efficacy of ivacaftor in patients aged 6 to < 24 months was extrapolated from data in patients aged ≥ 6 years with support from pharmacokinetic analyses showing similar drug exposure levels to adults. Safety of ivacaftor in this age group was derived from a cohort of 11 patients aged 6 months to < 12 months and a cohort of 19 patients aged 12 months to < 24 months in a 24-week, open-label study, which demonstrated that the safety profile was similar in this age group to that observed in patients aged ≥ 24 months. The study also demonstrated improvements in sweat chloride and markers of pancreatic function in patients aged 12 months to < 24 months (*Kalydeco prescribing information 2018, Rosenfeld et al 2018*).
  - A systematic review and meta-analysis evaluated the use of ivacaftor vs placebo in patients with CF (*Skilton et al 2019*). The review included 5 trials evaluating ivacaftor in patients with the *F508del* mutation (1 trial, N = 140), the *G551D* mutation (3 trials, N = 238), or the *R117H* mutation (1 trial, N = 69). Primary outcomes included survival, quality of life as assessed by the CF questionnaire-revised (CFQ-R), and FEV_1. Overall, the authors found evidence supporting the efficacy of ivacaftor in patients with the *G551D* mutation, but not the *F508del* or *R117H* mutations. Key findings from the review were as follows:
    - No survival data or deaths were reported in any of the included trials.
    - In studies of patients with the *F508del* mutation, no improvement was demonstrated in CFQ-R or FEV_1.
    - In studies of patients with the *G551D* mutation, improvement was demonstrated in both CFQ-R and FEV_1, although improvements in CFQ-R were not statistically significant at all time points.
    - In studies of patients with the *R117H* mutation, improvement was demonstrated in CFQ-R (in adults but not children), and there was no improvement in FEV_1.
  - Support for ivacaftor's efficacy for additional mutations is available from *in vitro* assay data (*Kalydeco prescribing information 2018*). This assay was based on CFTR chloride transport in Fisher Rat Thyroid cells expressing mutant

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

CFTR. An increase in chloride transport of ≥ 10% was designated as the response threshold because it is predictive or reasonably expected to predict clinical benefit. Mutations meeting this threshold were considered responsive, and a patient must have at least 1 responsive mutation in order for ivacaftor to be indicated.

- A number of trials have evaluated the safety and efficacy of lumacaftor/ivacaftor for the treatment of patients with CF homozygous for the *F508del* mutation.
  - Two 24-week, double-blind, placebo-controlled trials evaluated the efficacy of lumacaftor/ivacaftor in a total of 1122 patients with CF aged ≥ 12 years who were homozygous for the *F508del* mutation (*Wainwright et al 2015*). Pooled data demonstrated an improvement in $ppFEV_1$ as well as exacerbations. Based on a 96-week open-label extension study, the $ppFEV_1$ remained above pre-treatment baseline in patients continuing lumacaftor/ivacaftor; however, the improvement was not statistically significant (*Konstan et al 2017*).
  - A 24-week, open-label study evaluated the use of lumacaftor/ivacaftor in 46 patients with CF aged ≥ 12 years who were homozygous for the *F508del* mutation and had severe lung disease ($ppFEV_1$ < 40) (*Taylor-Cousar et al 2018*). Dose modification to half the usual dose for 1 to 2 weeks at treatment initiation was permitted; 28 patients initiated treatment at full dose (400 mg/250 mg twice daily) and 18 patients initiated at half dose (200 mg/125 mg twice daily). The primary endpoints were safety and tolerability, which demonstrated that the most common adverse events (AEs) were respiratory in nature; patients initiating treatment at the reduced dose had less frequent respiratory events. Following an initial reduction, $ppFEV_1$ from week 4 to the end of the study was similar to baseline.
  - A 24-week, open-label study evaluated the use of lumacaftor/ivacaftor in 58 patients with CF aged 6 to 11 years who were homozygous for *F508del* (*Milla et al 2017*). At 24 weeks, there was a small improvement in $ppFEV_1$ that failed to reach statistical significance (p = 0.0671); the authors suggested that the lack of a significant effect might have been due to the small sample size and relatively mild lung disease in this population. A separate double-blind, placebo-controlled trial in 206 patients in this age group demonstrated a small but statistically significant effect on $ppFEV_1$ (*Ratjen et al 2017*).
  - An open-label, Phase 3 study evaluated the use of lumacaftor/ivacaftor in patients with CF aged 2 to 5 years who were homozygous for *F508del* (*McNamara et al 2019*). Patients weighing between 8 and 14 kg received a dose of 100 mg/125 mg and patients weighing ≥ 14 kg received a dose of 150 mg/188 mg, each given twice daily. A total of 12 patients were enrolled in part A of the study (assessing pharmacokinetics and safety over 15 days) and 60 were enrolled in part B (assessing pharmacokinetics, safety, pharmacodynamics, and efficacy over 24 weeks). The study demonstrated a reduction in mean sweat chloride concentrations, improvement in biomarkers of pancreatic function, and increased growth parameters. Safety and pharmacokinetics were consistent with previous studies of lumacaftor/ivacaftor.
- Two published Phase 3 trials have evaluated the safety and efficacy of tezacaftor/ivacaftor in patients with CF aged ≥ 12 years, and efficacy has been extrapolated to patients aged 6 to < 12 years. As with ivacaftor, tezacaftor/ivacaftor has additionally been FDA approved for the treatment of some *CFTR* mutations based on *in vitro* assay data.
  - A 24-week, double-blind trial compared tezacaftor/ivacaftor to placebo in 509 patients with CF aged ≥ 12 years who were homozygous for the *F508del* mutation (*Taylor-Cousar et al 2017*). The improvement in $ppFEV_1$ was greater with tezacaftor/ivacaftor vs placebo, and the rate of pulmonary exacerbations also favored tezacaftor/ivacaftor treatment.
  - A double-blind, crossover trial with two 8-week treatment periods evaluated tezacaftor/ivacaftor, ivacaftor monotherapy, and placebo in 246 patients with CF aged ≥ 12 years who were heterozygous for *F508del* and a second allele with a residual function mutation (*Rowe et al 2017*). Both tezacaftor/ivacaftor and ivacaftor monotherapy improved $ppFEV_1$ vs placebo, with tezacaftor/ivacaftor having a slightly larger effect than ivacaftor alone.
  - The efficacy of tezacaftor/ivacaftor in patients aged 6 to < 12 years was extrapolated from patients aged ≥ 12 years with support from population pharmacokinetic analyses showing similar tezacaftor and ivacaftor exposure levels in patients aged 6 to < 12 years to older patients. Safety of tezacaftor/ivacaftor in this population was derived from a 24-week, open-label trial in 70 patients aged 6 to < 12 years (*Symdeko prescribing information 2019*).
- Two published Phase 3 trials have evaluated the safety and efficacy of elexacaftor/tezacaftor/ivacaftor in patients with CF.
  - A 24-week, randomized, double-blind trial compared elexacaftor/tezacaftor/ivacaftor vs placebo in 403 patients ≥ 12 years of age with a single *F508del* mutation and a minimal function mutation (ie, a mutation that is nonresponsive to ivacaftor and tezacaftor/ivacaftor) (*Middleton et al 2019*). The primary endpoint, the absolute change from baseline in $ppFEV_1$ at week 4, was significantly greater in the elexacaftor/tezacaftor/ivacaftor group vs placebo, with a difference of 13.8 percentage points (95% confidence interval [CI], 12.1 to 15.4; p < 0.001). Differences also favored elexacaftor/tezacaftor/ivacaftor in the change from baseline in $ppFEV_1$ through week 24, number of pulmonary

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

exacerbations through week 24, and changes in CFQ-R respiratory domain score, body mass index (BMI), and sweat chloride concentration.
  - A 4-week, randomized, double-blind trial compared elexacaftor/tezacaftor/ivacaftor to tezacaftor/ivacaftor in 107 patients ≥ 12 years of age who were homozygous for the *F508del* mutation (*Heijerman et al 2019*). All patients received tezacaftor/ivacaftor in a 4-week run-in period that preceded the 4-week intervention period, and baseline measurements for the intervention period reflected measurements taken after the tezacaftor/ivacaftor run-in period. The primary endpoint, the absolute change from baseline in ppFEV$_1$ at week 4, was significantly greater in the elexacaftor/tezacaftor/ivacaftor group vs the tezacaftor/ivacaftor group, with a difference of 10.0 percentage points (95% CI, 7.4 to 12.6). Differences also favored elexacaftor/tezacaftor/ivacaftor in sweat chloride concentration and CFQ-R respiratory domain score.
- A systematic review and meta-analysis evaluated the use of CFTR correctors, alone or in combination with ivacaftor, vs placebo in patients with CF and class II mutations (predominantly patients homozygous for the *F508del* mutation) (*Southern et al 2018*). The authors found insufficient evidence that monotherapy with a CFTR corrector has any clinically important effects in patients homozygous for *F508del*. Lumacaftor/ivacaftor and tezacaftor/ivacaftor each resulted in similar, small improvements in clinical outcomes, including quality of life, respiratory function, and pulmonary exacerbations. With respect to tolerability, lumacaftor/ivacaftor was associated with an increase in early, transient shortness of breath and longer-term increases in blood pressure, neither of which was observed with tezacaftor/ivacaftor. The authors concluded that tezacaftor/ivacaftor has a better safety profile compared to lumacaftor/ivacaftor; however, the 2 combinations have not been directly compared.
- An additional systematic review and meta-analysis evaluated the use of CFTR modulators in patients with various genetic mutations (*Habib et al 2019*). A total of 14 trials (8 Phase 3 and 6 Phase 2) were included in the review; the elexacaftor/tezacaftor/ivacaftor triple therapy was not included.
  - The authors found that the largest improvement in ppFEV$_1$ vs placebo was demonstrated in patients with the *G551D* mutation treated with ivacaftor, with a weighted absolute mean difference of 10.8% (95% CI, 9.0 to 12.7). Patients with this mutation treated with ivacaftor also had the greatest reduction in pulmonary exacerbations.
  - Patients aged ≥ 12 years who were homozygous for the *F508del* mutation had smaller improvements vs placebo when treated with lumacaftor/ivacaftor or tezacaftor/ivacaftor. Improvements with each of these combination products were similar: 3.4% (95% CI, 2.4 to 4.4) with lumacaftor/ivacaftor and 4.0% (95% CI, 3.2 to 4.8) with tezacaftor/ivacaftor. Lumacaftor/ivacaftor and tezacaftor/ivacaftor also significantly reduced the risk of exacerbations vs placebo in patients with this genotype, but the risk reduction was less than that observed with ivacaftor in patients with the *G551D* mutation. Patients treated with lumacaftor/ivacaftor had more respiratory-related AEs leading to treatment discontinuation vs placebo.

Dornase alfa

- Pivotal trials have been conducted in CF patients with an FVC > 40% predicted and in patients with advanced lung disease (FVC < 40% predicted) (*Fuchs et al 1994, McCoy et al 1996*).
  - A 24-week, randomized, double-blind, placebo-controlled trial was conducted in 968 adults and children aged ≥ 5 years with clinically stable CF and FVC > 40% predicted (*Fuchs et al 1994*). Patients received dornase alfa 2.5 mcg once daily, dornase alfa 2.5 mcg twice daily, or placebo. A T-Updraft II Nebu-u-mist nebulizer with PulmoAide compressor was used for drug administration.
    - The administration of dornase alfa once or twice daily reduced the risk of an exacerbation requiring parenteral antibiotic treatment, although only the reduction with twice-daily dosing was statistically significant. Exacerbations requiring parenteral antibiotic therapy occurred in 27%, 22%, and 19% of patients in the placebo, once-daily, and twice-daily groups, respectively. The relative risk vs placebo was 0.78 (95% CI, 0.57 to 1.06; p = 0.11) in the once-daily dornase alfa group and 0.66 (95% CI, 0.48 to 0.91; p = 0.01) in the twice-daily group. When adjusted based on the estimated relative risk of exacerbation by patient age, the exacerbation reduction was statistically significant with both dose regimens (once daily: relative risk, 0.72; 95% CI, 0.52 to 0.98; p = 0.04; twice daily: relative risk, 0.63; 95% CI, 0.46 to 0.87; p < 0.01).
    - Dornase alfa also improved pulmonary function. FEV$_1$ improved an average of 5.8% and 5.6% with once- and twice-daily dosing, respectively, throughout the study, while placebo-treated patients did not improve (change of 0.0%) (p < 0.01 for both dose regimens vs placebo).
    - Dornase alfa also improved quality of life compared to placebo.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- A 12-week, randomized, double-blind, placebo-controlled trial was conducted in 320 patients (age range, 7 to 57 years) with clinically stable CF and FVC < 40% predicted (*McCoy et al 1996*). Patients received dornase alfa 2.5 mg once daily or placebo.
  - There were no statistically significant differences in the incidence of pulmonary exacerbations; the age-adjusted relative risk for patients treated with dornase alfa vs placebo was 0.925 (95% CI, 0.69 to 1.21; p = 0.52). However, the study may have been underpowered to detect a difference.
  - Dornase alfa significantly improved pulmonary function. The mean improvements in FEV_1 were 9.4% and 2.1% in the dornase alfa and placebo groups, respectively (p < 0.001), and the mean improvements in FVC were 12.4% and 7.3%, respectively (p < 0.01).
  - No differences were observed in dyspnea scores.
- A 2-year, randomized, double-blind, placebo-controlled trial was conducted in 474 children aged 6 to 10 years with CF and mild lung function abnormalities (FVC ≥ 85% predicted) (*Quan et al 2001*). Patients received dornase alfa 2.5 mg daily or placebo with a jet nebulizer and compressor.
  - After 2 years of therapy, patients treated with dornase alfa maintained their $ppFEV_1$ (mean change from baseline, 0.04% predicted), whereas patients treated with placebo had a decrease from baseline of 3.2% predicted (p = 0.006). Lung function benefit was also shown for the forced expiratory flow between 25% and 75% of vital capacity (difference, 7.9% predicted; p = 0.0008) and maximal expiratory flow rate at 50% of vital capacity (difference, 8.2% predicted; p = 0.0002); however, the treatment difference in FVC was not statistically significant (difference, 0.7% predicted; p = 0.51).
  - Use of dornase alfa also reduced pulmonary exacerbations. In the dornase alfa group, 40 patients (17%) had a total of 62 exacerbations, compared to 56 patients (24%) and 92 exacerbations in the placebo group (relative risk, 0.66; 95% CI, 0.44 to 1.00; p = 0.048).
- A randomized crossover study in 87 patients with CF aged ≥ 6 years compared administration of dornase alfa via a jet nebulizer to administration using the Pari eRapid electronic nebulizer (*Sawicki et al 2015*). The 2 devices led to comparable efficacy and safety, while the eRapid nebulizer was associated with shorter administration times and higher patient preference.
- A systematic review and meta-analysis evaluated the use of dornase alfa in patients with CF (*Yang and Montgomery 2018*). The review included randomized and quasi-randomized controlled trials comparing dornase alfa to placebo, standard therapy, or other medications that improve airway clearance. In all, 19 trials (N = 2565) were included, most of which compared dornase alfa to placebo. Trial duration ranged from 6 days to 3 years. Of the 19 trials included in the qualitative synthesis, 13 trials were included in the meta-analysis.
  - Compared to placebo or no dornase alfa treatment, dornase alfa was demonstrated to improve FEV_1 at various time points ranging from 1 month to 2 years. Results for efficacy at 1 month of treatment were pooled from 4 trials and demonstrated a mean improvement vs placebo of 9.51% (95% CI, 0.67 to 18.35). Results for later time points were based on a smaller number of trials and generally showed smaller improvements.
  - Pooled data for pulmonary exacerbations from 3 trials found a significant exacerbation reduction, with a risk ratio of 0.78 (95% CI, 0.62 to 0.96).
  - Effects on quality-of-life measurements such as symptoms, activity limitation, fatigue, and emotional well-being varied among trials, with some (but not all) showing significant benefits.
  - Based on 7 trials, mortality was not significantly different between dornase alfa and control groups (risk ratio, 1.7; 95% CI, 0.70 to 4.14). The majority of deaths were reported from trials in patients with severe lung disease.
  - Overall, voice alteration and rash were the only AEs associated with dornase alfa.
  - Evidence comparing dornase alfa to other medications was limited.

CLINICAL GUIDELINES

- **Cystic Fibrosis Foundation (CFF). Pulmonary guidelines: use of CFTR modulator therapy in patients with CF** (*Ren et al 2018*); endorsed by the American Thoracic Society
  - This guideline provides recommendations focused on 3 main questions:
    - 1: Should ivacaftor (vs no CFTR modulator treatment) be used for individuals with a CF diagnosis due to gating mutations other than *G551D* or *R117H* (ie, *G178R, S549N, S549R, G551S, G1244E, S1251N, S1255P*, or *G1349D*)?
    - 2: Should ivacaftor (vs no CFTR modulator treatment) be used for individuals with a CF diagnosis due to the *R117H* mutation?

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- 3: Should lumacaftor/ivacaftor combination (vs no CFTR modulator treatment) be used in individuals with 2 copies of the *F508del* mutation?

○ A total of 30 recommendations were provided, based on the questions above and patients' age and ppFEV$_1$. These recommendations are listed in Table 3.

○ The committee chose not to address clinical situations for which recommendations have already been published (see *Mogayzel et al 2013* and *Lahiri et al 2016)* or if the question was of low priority and unlikely to change practice.

Table 3. CFF recommendations for CFTR modulators in CF treatment (2018)

Patient Age (years)	ppFEV$_1$	Certainty	Recommendation
Question 1: Ivacaftor use in patients with gating mutation other than *G551D* or *R117H*			
2 to 5	Not applicable	Not applicable	Recommended*
6 to 11	< 40	Very low	Conditional for
6 to 11	40 to 90	Low	Conditional for
6 to 11	> 90	Low	Conditional for
12 to 17	< 40	Low	Conditional for
12 to 17	40 to 90	Moderate	Conditional for
12 to 17	> 90	Moderate	Conditional for
≥ 18	< 40	Low	Conditional for
≥ 18	40 to 90	Moderate	Conditional for
≥ 18	> 90	Moderate	Conditional for
Question 2: Ivacaftor use in patients with *R117H* mutation			
≤ 5	Not applicable	Very low	Conditional against
6 to 11	< 40	Very low	Conditional for
6 to 11	40 to 90	Very low	Conditional for
6 to 11	> 90	Low	Conditional against
12 to 17	< 40	Very low	Conditional for
12 to 17	40 to 90	Very low	Conditional for
12 to 17	> 90	Very low	Conditional against
≥ 18	< 40	Very low	Conditional for
≥ 18	40 to 90	Moderate	Conditional for
≥ 18	> 90	Low	Conditional for
Question 3: Lumacaftor/ivacaftor use in patients with 2 copies of *F508del*			
≤ 5	Not applicable	Not applicable	No recommendation
6 to 11	< 40	Very low	Conditional for
6 to 11	40 to 90	Very low	Conditional for
6 to 11	> 90	Very low	Conditional for
12 to 17	< 40	Moderate	Strong for
12 to 17	40 to 90	Moderate	Strong for
12 to 17	> 90	Low	Conditional for
≥ 18	< 40	Moderate	Strong for
≥ 18	40 to 90	Moderate	Strong for
≥ 18	> 90	Low	Conditional for

*Based on the Cystic Fibrosis Preschool Guidelines recommendations

- **CFF. CF pulmonary guidelines: chronic medications for maintenance of lung health** (*Mogayzel et al 2013*)
  - ○ This guideline provided several new recommendations when published in 2013, in addition to reaffirming several recommendations from a previous (2007) version of the guideline. It has not been updated since 2013 and thus does not include recommendations for combination CFTR modulators; recommendations also do not reflect the expanded indications for ivacaftor.
  - ○ For these guidelines, the severity of lung disease is defined by ppFEV$_1$ as follows: normal, > 90% predicted; mildly impaired, 70 to 89% predicted; moderately impaired, 40 to 69% predicted; and severely impaired, < 40% predicted.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- The level of evidence and strength of recommendations are based on the U.S. Preventive Services Task Force system.
- Recommendations specific to CFTR modulators and dornase alfa are shown in Table 4.

Table 4. CFF recommendations for CFTR modulators and dornase alfa in CF treatment (2013)

Treatment	Recommendation	Certainty of net benefit	Estimate of net benefit	Strength of Recommendation*
2007 recommendations, reaffirmed in 2013 without changes				
Dornase alfa – moderate-to-severe disease	For individuals with CF aged ≥ 6 years with moderate-to-severe lung disease, the CFF strongly recommends the chronic use of dornase alfa to improve lung function and quality of life, and reduce exacerbations.	High	Substantial	A
Dornase alfa – mild disease	For individuals with CF aged ≥ 6 years with asymptomatic or mild lung disease, the CFF recommends the chronic use of dornase alfa to improve lung function and reduce exacerbations.	High	Moderate	B
2013 new or modified recommendations				
Ivacaftor	For individuals with CF aged ≥ 6 years with at least 1 *G551D CFTR* mutation, the Pulmonary Clinical Practice Guidelines Committee strongly recommends the chronic use of ivacaftor to improve lung function and quality of life, and reduce exacerbations.	High	Substantial	A

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

- **CFF. Clinical practice guidelines from the CFF for preschoolers with CF** (*Lahiri et al 2016*)
  - This guideline focuses on the care of preschool children aged 2 to 5 years with CF. It includes recommendations in the areas of routine surveillance for pulmonary disease, therapeutics, and nutritional and gastrointestinal care. Table 5 highlights recommendations relevant to CFTR modulators and dornase alfa. The guideline does not include the more recent expanded indications for ivacaftor or recommendations for lumacaftor/ivacaftor.
  - The level of evidence and strength of recommendations are based on the U.S. Preventive Services Task Force.

Table 5. CFF recommendations for CFTR modulators and dornase alfa in preschoolers aged 2 to 5 with CF (2016)

Topic	Recommendation	Grade or Consensus		
		Certainty of net benefit	Estimate of net benefit	Strength of Recommendation*
Dornase alfa	The CFF recommends that dornase alfa be selectively offered to patients based on individual circumstances.	Moderate	Low	C
Ivacaftor	The Preschool Guidelines Committee recommends the routine use of ivacaftor in those with specific gating mutations (*G551D, G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N*, and *S549R*), and a consideration for those with a confirmed diagnosis of CF and a *R117H* mutation.	Consensus Recommendation		

***C**: The committee recommends that clinicians consider providing this therapy to selected patients depending on individual circumstances. However, for most individuals without signs or symptoms there is likely to be only a small benefit from this service.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- **Clinical Decision Support Resource: UptoDate Topic Review**
  CF: Treatment with CFTR modulators (*Simon 2019*)
  - The use of a CFTR modulator is recommended for most individuals with CF who are ≥ 12 years old and have responsive *CFTR* variants, and suggested for most younger patients with CF for whom sufficient evidence is available to allow FDA approval. Selection of a specific CFTR modulator depends on the patient's genotype and age.
  - Table 6 provides an overview of recommendations for the use of CFTR modulators. Gating and residual function mutations are listed in the boxes below the table.
    - These recommendations reflect the indications for each CFTR modulator as of October 2019 and consideration of each drug's efficacy, AEs, and potential for drug-drug interactions. Many of the recommendations were based upon comparisons of efficacy and safety data from clinical trials in which each treatment was studied independently rather than by direct comparison of multiple treatments within a single study. These recommendations are likely to change as new evidence becomes available.

Table 6. Recommendations for CFTR modulator therapy in patients with CF

Genotype	Age group	Kalydeco (ivacaftor)	Orkambi (lumacaftor/ ivacaftor)	Symdeko (tezacaftor/ ivacaftor)	Trikafta (elexacaftor/ tezacaftor/ ivacaftor)	None available
F508del homozygote	2 to 5 yrs		✔			
	6 to 11 yrs			✔		
	≥ 12 yrs				✔	
F508del heterozygote without a gating or residual function mutation	< 12 yrs					✔
	≥ 12 yrs				✔	
F508del heterozygote with gating mutation at other allele*	6 mos to 11 yrs	✔				
	≥ 12 yrs				✔	
F508del heterozygote with residual function mutation at other allele*	6 mos to 5 yrs	✔				
	6 to 11 yrs			✔		
	≥ 12 yrs				✔	
Gating mutation without *F508del*	≥ 6 mos	✔				
Residual function mutation without *F508del*	6 mos to 5 yrs	✔				
	≥ 6 yrs			✔		

Abbreviations: **mos** = months; **yrs** = years
*For patients heterozygous for *F508del* who also have gating or residual function variants, Trikafta is suggested if it is available and the patient is eligible (≥ 12 years) because the triple combination therapy is likely to be more effective than monotherapy or dual therapy.

Gating mutations approved by FDA for Kalydeco (but not Symdeko):
G1244E, G1349D, G178R, G551D, G551S, R117H, S1251N, S1255P, S549N, S549R, G1069R, R1070Q**
*Although *G1069R* and *R1070Q* are not considered prototypic gating variants, *in vitro* studies showed that ivacaftor increased their CFTR functional activity; these findings led to the FDA approval for ivacaftor.

Residual function mutations approved by FDA for Kalydeco and Symdeko:
A1067T, A455E, D110E, D110H, D1152H, D1270N, D579G, E193K, E56K, E831X, F1052V, F1074L, K1060T, L206W, P67L, R1070W, R117C, R347H, R352Q, R74W, S945L, S977F, 2789+5G → A, 3272-26A → G, 3849+10kbC → T, 711+3A → G

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

SAFETY SUMMARY

- **Kalydeco (ivacaftor):**
  - Contraindications: none
  - Warnings/precautions:
    - Elevated transaminases have been reported. It is recommended that alanine aminotransferase (ALT) and aspartate aminotransferase (AST) be assessed prior to initiating Kalydeco, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations, more frequent monitoring of liver function tests (LFTs) should be considered. Dosage interruptions may be necessary in patients with significant transaminase elevations.
    - Use of Kalydeco with strong cytochrome P450 (CYP) 3A inducers, such as rifampin, substantially decreases the exposure of ivacaftor and is not recommended. See the prescribing information for full details on drug interactions.
    - Non-congenital lens opacities/cataracts have been reported in pediatric patients. Although other risk factors were present in some cases, a possible risk attributable to ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating Kalydeco treatment.
  - The most common adverse reactions (≥ 8% in patients with CF who have a *G551D* mutation) were headache, oropharyngeal pain, upper respiratory tract infection, nasal congestion, abdominal pain, nasopharyngitis, diarrhea, rash, nausea, and dizziness.
- **Orkambi (lumacaftor/ivacaftor):**
  - Contraindications: none
  - Warnings/precautions:
    - Worsening of liver function, including hepatic encephalopathy, in patients with advanced liver disease has been reported. Orkambi should be used with caution in patients with advanced liver disease and only if the benefits are expected to outweigh the risks. If Orkambi is used in these patients, the patients should be closely monitored and the dose should be reduced.
    - Serious adverse reactions related to elevated transaminases have been reported; in some cases associated with concomitant elevations in total serum bilirubin. ALT, AST, and bilirubin should be assessed prior to initiating Orkambi, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of ALT, AST, or bilirubin elevations, more frequent monitoring should be considered. Dosage interruptions may be necessary in patients with significant transaminase or bilirubin elevations.
    - Respiratory events (eg, chest discomfort, dyspnea, and abnormal respiration) were observed more commonly in patients during initiation of Orkambi compared to those who received placebo. These events have led to drug discontinuation and can be serious, particularly in patients with advanced lung disease ($ppFEV_1 < 40$). Clinical experience in patients with $ppFEV_1 < 40$ is limited, and additional monitoring of these patients is recommended during initiation of therapy.
    - Increased blood pressure has been observed in some patients treated with Orkambi. Blood pressure should be monitored periodically.
    - Drug interactions:
      - Lumacaftor is a strong inducer of CYP3A. Administration of Orkambi may decrease systemic exposure of CYP3A substrates. Co-administration with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index is not recommended.
      - Orkambi may substantially decrease hormonal contraceptive exposure, reducing their effectiveness and increasing the incidence of menstruation-associated adverse reactions, eg, amenorrhea, dysmenorrhea, menorrhagia, and irregular menstruation (27% in women using hormonal contraceptives compared with 3% in women not using hormonal contraceptives). Hormonal contraceptives, including oral, injectable, transdermal, and implantable, should not be relied upon as an effective method of contraception when co-administered with Orkambi.
      - Ivacaftor is a substrate of CYP3A4 and CYP3A5 isoenzymes. Use of Orkambi with strong CYP3A inducers, such as rifampin, significantly reduces ivacaftor exposure and is not recommended.
      - See the prescribing information for full details on drug interactions.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Non-congenital lens opacities/cataracts have been reported in pediatric patients. Although other risk factors were present in some cases, a possible risk attributable to ivacaftor cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating Orkambi treatment.
- The most common adverse reactions (≥ 5% in patients with CF who are homozygous for the *F508del* mutation) were dyspnea, nasopharyngitis, nausea, diarrhea, upper respiratory tract infection, fatigue, abnormal respiration, increased blood creatine phosphokinase, rash, flatulence, rhinorrhea, and influenza.

- **Symdeko (tezacaftor/ivacaftor):**
  - Contraindications: none
  - Warnings/precautions:
    - Elevated transaminases have been observed in patients treated with Symdeko. Assessments of ALT and AST are recommended for all patients prior to initiating Symdeko, every 3 months during the first year of treatment, and annually thereafter. For patients with a history of transaminase elevations, more frequent monitoring should be considered. Dosage interruptions may be necessary in patients with significant transaminase elevations.
    - Use of Symdeko with strong CYP3A inducers significantly decreases exposure to ivacaftor and may decrease exposure to tezacaftor; co-administration is not recommended. See the prescribing information for full details on drug interactions.
    - Non-congenital lens opacities/cataracts have been reported in pediatric patients treated with Symdeko. Although other risk factors were present in some cases, a possible risk attributable to treatment with Symdeko cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with Symdeko.
  - The most common adverse reactions (≥ 3% of patients) were headache, nausea, sinus congestion, and dizziness.

- **Trikafta (elexacaftor/tezacaftor/ivacaftor):**
  - Contraindications: none
  - Warnings/precautions:
    - Elevated transaminases have been observed in patients treated with Trikafta. Bilirubin elevations have also been observed. Assessments of ALT, AST, and bilirubin are recommended for all patients prior to initiating Trikafta, every 3 months during the first year of treatment, and annually thereafter. More frequent monitoring should be considered in patients with a history of hepatobiliary disease or LFT elevations. Dosage interruptions may be necessary in patients with significant transaminase elevations.
    - Use of Symdeko with strong CYP3A inducers significantly decreases exposure to ivacaftor and would be expected decrease exposure to tezacaftor and elexacaftor; co-administration is not recommended.
    - Non-congenital lens opacities/cataracts have been reported in pediatric patients treated with ivacaftor-containing regimens. Although other risk factors were present in some cases, a possible risk attributable to treatment with Symdeko cannot be excluded. Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment with Trikafta.
  - The most common adverse reactions (≥ 5% of patients and more frequently than with placebo by ≥ 1%) were headache, upper respiratory tract infection, abdominal pain, diarrhea, rash, increased ALT, nasal congestion, increased blood creatine phosphokinase, increased AST, rhinorrhea, rhinitis, influenza, sinusitis, and increased blood bilirubin.

- **Pulmozyme (dornase alfa):**
  - Contraindications: patients with known hypersensitivity to dornase alfa, Chinese Hamster Ovary cell products, or any component of the product
  - Warnings/precautions: None
  - The most common adverse reactions (≥ 3% of patients) were voice alteration, pharyngitis, rash, laryngitis, chest pain, conjunctivitis, rhinitis, decrease in FVC of ≥ 10%, fever, and dyspnea.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

DOSING AND ADMINISTRATION

Table 7. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
CFTR Modulators				
Kalydeco (ivacaftor)	Tablets, oral granules	Oral	Twice daily	• Dose should be reduced in patients with moderate or severe hepatic impairment. • Dose should be reduced when co-administered with moderate or strong CYP3A inhibitors.
Orkambi (lumacaftor/ivacaftor)	Tablets, oral granules	Oral	Twice daily	• Dose should be reduced in patients with moderate or severe hepatic impairment. • Dose should be reduced for the first week of Orkambi treatment when co-administered with strong CYP3A inhibitors.
Symdeko (tezacaftor/ivacaftor)	Tablets	Oral	Twice daily	• The morning dose is 1 tezacaftor/ivacaftor combination tablet and the evening dose is 1 ivacaftor tablet. • Dose should be reduced in patients with moderate or severe hepatic impairment. • Dose should be reduced when co-administered with moderate or strong CYP3A inhibitors.
Trikafta (elexacaftor/tezacaftor/ivacaftor)	Tablets	Oral	Twice daily	• The morning dose is 2 elexacaftor/tezacaftor/ivacaftor combination tablets and the evening dose is 1 ivacaftor tablet. • Dose should be reduced if used in patients with moderate hepatic impairment (to be used only if benefits outweigh risks). Trikafta should not be used in patients with severe hepatic impairment. • Dose should be reduced when co-administered with moderate or strong CYP3A inhibitors.
DNase Enzyme				
Pulmozyme (dornase alfa)	Inhalation solution	Inhalation (with nebulizer)	Once daily; some patients may benefit from twice-daily administration	• Administered using a recommended jet nebulizer/compressor system or eRapid Nebulizer System.

See the current prescribing information for full details.

CONCLUSION

- The CFTR modulators, Kalydeco (ivacaftor), Orkambi (lumacaftor/ivacaftor) Symdeko (tezacaftor/ivacaftor), and Trikafta (elexacaftor/tezacaftor/ivacaftor), are used in the long-term management of CF in patients eligible for such treatment based on their age and specific *CFTR* mutations. These products act to facilitate processing and trafficking of CFTR to the cell surface or to increase chloride transport at the cell surface. These products have been demonstrated to improve lung function; some trials also demonstrated improvement in reducing pulmonary exacerbations and/or improving quality of life.
  - The approval of Trikafta expanded the population of patients eligible for highly effective CFTR modulator therapy. As a result of the Trikafta approval and expanded indications for existing agents, the majority of patients with CF have become eligible for CFTR modulator therapy.
  - Key warnings/precautions with the CFTR modulators include the risk of elevated transaminases, cataracts, and drug interactions. A key additional warning for Orkambi is the risk of respiratory events (eg, chest discomfort, dyspnea, and

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

abnormal respiration). Orkambi has also been associated with worsening of liver function in patients with advanced liver disease, and has more significant drug interactions than the other CFTR modulators.
  - The CFTR modulators are dosed orally twice daily.
- Pulmozyme (dornase alfa) is another key treatment used in the long-term management of CF. It works to reduce sputum viscoelasticity. Guidelines recommend its use in patients aged ≥ 6 years with moderate-to-severe lung disease (to improve lung function and quality of life and to reduce exacerbations) and with asymptomatic or mild lung disease (to improve lung function and reduce exacerbations).
  - Pulmozyme has no warnings/precautions listed in its prescribing information.
  - Pulmozyme is administered by inhalation with a nebulizer. Recommended dosing is once daily, although some patients may benefit from twice-daily administration.

APPENDICES

Appendix A: Additional Information on CFTR Modulators

Table 8. Overview of Key Clinical Trials for CFTR Modulators

Trial/Reference	Design/Population	Key Results	Comments/ Additional Data
Kalydeco (ivacaftor)			
STRIVE *Ramsey et al 2011*	Phase 3, 48-week, DB, PC trial in 167 patients aged ≥ 12 yrs with ≥ 1 *G551D* mutation	$ppFEV_1$: 24 weeks: 10.4 percentage points from baseline; difference from placebo, 10.6 percentage points (95% CI, 8.6 to 12.6; p < 0.0001)	Secondary endpoints: Improvements were observed in pulmonary exacerbations, CFQ-R score, and sweat chloride. Improvements were maintained through week 48.
ENVISION *Davies et al 2013*	Phase 3, 48-week, DB, PC trial in 52 patients aged 6 to 11 yrs with ≥ 1 *G551D* mutation	$ppFEV_1$: 24 weeks: 12.6 percentage points from baseline; difference from placebo, 12.5 percentage points (95% CI, 6.6 to 18.3; p < 0.0001)	Secondary endpoints: Improvements were observed in weight and sweat chloride. The improvement in CFQ-R (child version) did not reach statistical significance (TD, 6.0 points; p = 0.109); however, the parent/caregiver version did (TD, 5.9 points; p = 0.033). No statistically significant difference in exacerbations was demonstrated.
PERSIST *McKone et al 2014*	Phase 3, 96-week, OLE study of STRIVE and ENVISION; enrolled 192 patients aged ≥ 6 yrs with ≥ 1 *G551D* mutation; all received ivacaftor	Long-term safety (primary endpoint): Most AEs were mild or moderate and resolved during the reporting period; safety was consistent with the PC period of the trial $ppFEV_1$ (secondary endpoint): Improvements in FEV_1 were sustained through the 96-week extension period	Additional secondary endpoints: Improvements were sustained for weight gain, CFQ-R, and exacerbation rate.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

KONNECTION *De Boeck et al 2014*	Phase 3, DB, PC, XO trial (two 8-week treatment periods) in 39 patients aged ≥ 6 yrs with non-*G551D* gating mutation	$ppFEV_1$: 8 weeks: 7.5 percentage points from baseline; difference from placebo, 10.7 percentage points (95% CI, 7.3 to 14.1; p < 0.0001)	Secondary endpoints: Improvements were observed in weight, sweat chloride, and CFQ-R.
KONDUCT *Moss et al 2015*	Phase 3, 24-week, DB, PC trial in 69 patients aged ≥ 6 yrs with *R117H* mutation	$ppFEV_1$: 24 weeks: 2.6 percentage points from baseline; difference from placebo, 2.1 percentage points (95% CI, -1.13 to 5.35; p = 0.20); in a pre-specified subgroup analysis, $ppFEV_1$ significantly improved with ivacaftor in patients aged ≥ 18 yrs, with a TD vs placebo of 5.0 percentage points (95% CI, 1.15 to 8.78), but not in patients aged 6 to 11 yrs, with a TD vs placebo of -6.3 percentage points (95% CI, -11.96 to -0.71; p = 0.03)	Secondary endpoints: Improvements were observed in sweat chloride and CFQ-R. The lack of effect for $ppFEV_1$ in the pediatric and overall populations may be related in part to the fact that pediatric patients had a high baseline $ppFEV_1$. Most patients (N = 65) entered a washout period followed by an OLE period; at a 12-week analysis, patients in both the placebo-to-ivacaftor and ivacaftor-to-ivacaftor groups showed a significant $ppFEV_1$ improvement from post-washout baseline (5.0 [p = 0.0005] and 6.0 [p = 0.0006] percentage points, respectively).
EXPAND *Rowe et al 2017* *(ivacaftor and placebo arms)*	Phase 3, DB, PC, XO trial (two 8-week treatment periods) in 246 patients aged ≥ 12 yrs heterozygous for *F508del* and a residual function mutation (of these, 157 and 162 patients were treated with ivacaftor and placebo, respectively)	$ppFEV_1$: Average of 4 and 8 week assessments: difference from placebo, 4.7 percentage points (95% CI, 3.7 to 5.8; p < 0.001)	Secondary endpoint: Improvements were observed for ivacaftor vs placebo for CFQ-R. Benefits were also observed for other secondary endpoints, but statistical significance cannot be claimed due to the statistical design.
KIWI *Davies et al 2016*	Phase 3, 24-week, OL study in 34 patients aged 2 to 5 yrs with ≥ 1 *CFTR* gating mutation; patients received a dose of 50 mg (weight 8 to 14 kg) or 75 mg (weight ≥ 14 kg), each given twice daily	Pharmacokinetics: Exposure was similar to that reported with the approved dosing in adults Safety: Safety was similar to use in adults, although there was an increased incidence of LFT elevations; most AEs were mild or moderate; common AEs included cough and vomiting	Secondary endpoints: Improvements were demonstrated for weight and sweat chloride. No meaningful data on lung function were available (spirometry results are limited in this age group).

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

ARRIVAL *Rosenfeld et al 2018*	Phase 3, 24-week, OL study in 19 patients aged 12 to < 24 months with a *CFTR* gating mutation on ≥ 1 allele (study part B); patients received a dose of 50 mg (weight 7 to 14 kg) or 75 mg (weight ≥ 14 to < 25 kg), each given twice daily	Pharmacokinetics: Exposure of ivacaftor was similar to that in older children in adults The safety profile was consistent with experience in older children; most AEs were mild or moderate and considered unlikely to be (nor not) related to ivacaftor; 27.8% of patients had elevated ALT and/or AST > 3 x ULN	Secondary endpoint: Improvements were demonstrated in sweat chloride. Biomarkers of pancreatic function improved (increased fecal elastase-1, decreased serum immunoreactive trypsinogen). Mean serum lipase and amylase were elevated at baseline and decreased rapidly with ivacaftor. Growth status was generally well maintained.
Orkambi (lumacaftor/ivacaftor)			
TRAFFIC and **TRANSPORT** *Wainwright et al 2015*	Two Phase 3, 24-week, DB, PC trials in 1122 patients aged ≥ 12 yrs homozygous for *F508del*	$ppFEV_1$: 24 weeks, pooled data: 2.5 percentage points from baseline; difference from placebo, 2.8 percentage points (95% CI, 1.8 to 3.8; p < 0.001)	Secondary endpoints: In the pooled analysis, there were improvements in weight and exacerbations. The difference in CFQ-R did not reach statistical significance, with an improvement of 2.2 (95% CI, 0.0 to 4.5; p = 0.05).
PROGRESS *Konstan et al 2017*	Phase 3, 96-week, OLE study of TRAFFIC and TRANSPORT; enrolled 1030 patients aged ≥ 12 yrs homozygous for *F508del*; all received lumacaftor/ivacaftor	Long-term safety (primary endpoint): Most AEs were mild or moderate; rates of AEs were similar or reduced to rates during the PC period of the trial; an increase in blood pressure was noted $ppFEV_1$ (secondary endpoint): Mean $ppFEV_1$ remained above pre-treatment baseline in patients continuing lumacaftor/ivacaftor, but the improvement was not statistically significant	Additional secondary endpoints: The pulmonary exacerbation rate remained low. Improvements in BMI and CFQ-R continued throughout the study. Analysis of lung function change over time showed a slower rate of decline compared to matched registry patients.
Taylor-Cousar et al 2018	Phase 3b, 24-week, OL study in 46 patients aged ≥12 yrs homozygous for *F508del* who had advanced lung disease ($ppFEV_1$ < 40); 28 received lumacaftor/ ivacaftor at the usual dose (400 mg/250 mg twice daily) and 18 patients initiated at half-dose (200 mg/125 mg twice daily) for	Safety/tolerability: The most common AEs were respiratory in nature (infective pulmonary exacerbation, abnormal respiration, cough, dyspnea); patients initiating on half-dose had less frequent respiratory events (56% vs 71%) and events were of shorter duration (median 4 vs 9	Secondary endpoints: There was an initial decrease in $ppFEV_1$ that returned to baseline at week 4 and remained near baseline throughout the remainder of the study. Improvements vs baseline were seen in sweat chloride and BMI. Reductions in intravenous antibiotics and all-cause hospitalization were shown between the study period and the 24-week period prior to the study. Improvements in CFQ-R were not

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

	1 to 2 weeks before increasing to full-dose	days); 5 patients (11%) had ALT or AST elevation > 3 x ULN	statistically significant.
Milla et al 2017	Phase 3, 24-week, OL study in 58 patients aged 6 to 11 yrs homozygous for *F508del*	$ppFEV_1$: 24 weeks: 2.5 percentage points from baseline (95% CI, -0.2 to 5.2; p = 0.0671)	Secondary endpoints: Improvements from baseline were seen in sweat chloride, weight, and CFQ-R. The small sample size and relatively mild lung disease in this population may explain the lack of significant effect on $ppFEV_1$. The safety profile was similar to that seen in larger trials in older patients.
Ratjen et al 2017	Phase 3, 24-week, DB, PC trial in 206 patients aged 6 to 11 yrs homozygous for *F508del*	Mean change in lung clearance index ($LCI_{2.5}$; see Appendix B) from baseline to average of all visits up to and including week 24 (primary endpoint): -1.0 with lumacaftor/ivacaftor vs 0.1 with placebo; TD, -1.1 (95% CI, -1.4 to -0.8; p < 0.0001) $ppFEV_1$: Average of all visits up to and including week 24: 1.1 percentage points from baseline; difference from placebo, 2.4 percentage points (95% CI, 0.4 to 4.4; p = 0.0182)	Additional secondary endpoints: Improvements were observed in sweat chloride. Changes in BMI and CFQ-R were not statistically significant.
McNamara et al 2019	Phase 3, 24-week, OL study in 60 patients aged 2 to 5 yrs homozygous for *F508del* (study part B); patients received a dose of 100 mg/125 mg (weight 8 to 14 kg) or 150 mg/188 mg (weight ≥ 14 kg), each given twice daily	Pharmacokinetics: Exposures of both lumacaftor and ivacaftor were within the targeted range for older patients and similar to concentrations previously reported The safety profile was consistent with experience in adults; 10% of patients had respiratory AEs (dyspnea, abnormal respiration, wheezing); 15% had increased ALT and/or AST > 3 x ULN	Secondary endpoints: Improvements were demonstrated for weight and sweat chloride. Biomarkers of pancreatic function improved (increased fecal elastase-1, decreased serum immunoreactive trypsinogen). Limited data on lung function were available (spirometry results are limited in this age group). $LCI_{2.5}$ demonstrated a numerical, nonsignificant improvement (exploratory/optional endpoint).

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Symdeko (tezacaftor/ivacaftor)			
EVOLVE *Taylor-Cousar et al 2017)*	Phase 3, 24-week, DB, PC trial in 509 patients aged ≥ 12 yrs homozygous for *F508del*	$ppFEV_1$: 24 weeks: 3.4 percentage points from baseline; difference from placebo, 4.0 percentage points (95% CI, 3.1 to 4.8; p < 0.001)	Secondary endpoints: Patients treated with tezacaftor/ivacaftor had a reduced number of pulmonary exacerbations. Numerical improvements were seen in BMI, CFR-Q, and sweat chloride. The change in BMI was not statistically significant, and the changes in CFQ-R and sweat chloride were not assessed for statistical significance due to the testing hierarchy. The rate of respiratory AEs was not higher in the tezacaftor/ivacaftor group than the placebo group; this compares favorably to studies with lumacaftor/ivacaftor.
EXPAND *Rowe et al 2017*	Phase 3, DB, PC, XO trial (two 8-week treatment periods) in 246 patients aged ≥ 12 yrs heterozygous for *F508del* and a residual function mutation	$ppFEV_1$: 8 weeks: difference for tezacaftor/ivacaftor vs placebo, 6.8 percentage points (95% CI, 5.7 to 7.8; p < 0.0001); difference for tezacaftor/ivacaftor vs ivacaftor, 2.1 percentage points (95% CI, 1.2 to 2.9; p < 0.0001)	Secondary endpoints: Improvement was seen in CFQ-R for tezacaftor/ivacaftor vs placebo; the difference in CFQ-R between tezacaftor/ivacaftor and ivacaftor was not statistically significant. A numerical improvement was observed in sweat chloride, but significance was not assessed due to the statistical hierarchy.
Trikafta (elexacaftor/tezacaftor/ivacaftor)			
VX17-445-102 *Middleton et al 2019*	Phase 3, 24-week, DB, PC trial in 403 patients aged ≥ 12 years heterozygous for *F508del* and a minimal function mutation	$ppFEV_1$: 4 weeks: difference for elexacaftor/tezacaftor/ ivacaftor vs placebo, 13.8 percentage points (95% CI, 12.1 to 15.4; p < 0.001) 24 weeks: difference for elexacaftor/tezacaftor/ ivacaftor vs placebo, 14.3 percentage points (95% CI, 12.7 to 15.8; p < 0.001)	Secondary endpoints: Improvements were observed in pulmonary exacerbations, CFQ-R score, sweat chloride, and BMI.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

VX17-445-103 *Heijerman et al 2019*	Phase 3, 4-week, DB, AC trial in 107 patients aged ≥ 12 years homozygous for *F508del*	ppFEV$_1$: 4 weeks: difference for elexacaftor/tezacaftor/ivacaftor vs tezacaftor/ivacaftor: 10.0 percentage points (95% CI, 7.4 to 12.6; p < 0.0001)	Secondary endpoints: Improvements were seen in CFQ-R score and sweat chloride. Exacerbations were not defined as an efficacy endpoint, but were reported as an AE less frequently in the elexacaftor/tezacaftor/ivacaftor group than in the tezacaftor/ivacaftor group. BMI was not defined as an efficacy endpoint but increased more in the elexacaftor/tezacaftor/ivacaftor group (nominal p < 0.0001).

Note: CFQ-R scores refer to the respiratory domain.
Abbreviations: **AC** = active-controlled, **AE** = adverse event, **ALT** = alanine aminotransferase, **AST** = aspartate aminotransferase, **BMI** = body mass index, **CFQ-R** = cystic fibrosis questionnaire-revised, **CI** = confidence interval, **DB** = double-blind, **LCI** = lung clearance index, **LFT** = liver function test, **OL** = open-label, **OLE** = open-label extension, **PC** = placebo-controlled, **ppFEV$_1$** = percent predicted forced expiratory volume in 1 second, **TD** = treatment difference, **ULN** = upper limit of normal, **XO** = crossover, **yrs** = years

Appendix B: Study endpoint descriptions

- **CF Questionnaire (CFQ); CF Questionnaire-Revised (CFQ-R)** (*American Thoracic Society 2002, Quittner et al 2009*)
  - This is a disease-specific quality-of-life instrument designed to measure impact of CF on overall health, daily life, perceived well-being, and symptoms.
  - The CFQ-R has 9 quality-of-life domains (physical, role/school, vitality, emotion, social, body image, eating, treatment burden, and health perceptions) and 3 symptom scales (weight, respiratory, and digestion).
  - Scaling of items uses 4-point Likert scales (eg, always/often/sometimes/never).
  - Each health-related quality-of-life domain is scored. Standardized scores range from 0 to 100, with higher scores indicating better quality of life.
  - The minimal clinically important difference in CFQ-R respiratory scores has been estimated to be approximately 8.5 points in patients experiencing a CF exacerbation and 4.0 points in stable CF patients.
- **Lung Clearance Index (LCI$_{2.5}$)** (*Ratjen et al 2017*)
  - This is a measure of the number of lung volume turnovers required to reach 2.5% of tracer gas concentration.
  - Elevated LCI$_{2.5}$ values reflect increasing unevenness of gas mixing within the lung caused by early lung disease secondary to mucus plugging and airway wall changes.
  - LCI$_{2.5}$ may be more sensitive than FEV$_1$ for the presence of early structural lung abnormalities, particularly in the pediatric population.
- **Sweat chloride test** (*Durmowicz et al 2013, Farrell et al 2017*)
  - This test measures the amount of chloride in a patient's sweat. It is considered the gold standard for diagnosis of CF.
  - A sweat test concentration of ≥ 60 mmol/L indicates a diagnosis of CF, and a concentration of < 30 mmol/L indicates that CF is unlikely. Patients with results in the intermediate range (30 to 59 mmol/L) and certain clinical characteristics (positive newborn screen, symptoms of CF, or a positive family history) may have CF and further testing should be considered.
  - Based on the diagnostic relationship between sweat chloride and CF, change in sweat chloride has been used as a measure of CFTR function and as a pharmacodynamic endpoint in clinical trials. A reduction in sweat chloride has been demonstrated in clinical trials of CFTR modulators. However, a correlation between changes in sweat chloride and improvements in FEV$_1$ has not been consistently demonstrated, and there is no specific improvement in sweat chloride concentration that can predict FEV$_1$ improvement. This may be related to the multiple physiologic, environmental, and genetic factors that modulate CF severity.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

REFERENCES

- American Thoracic Society; Quality of Life Resource. Cystic fibrosis questionnaire (CGQ); Cystic Fibrosis Questionnaire Revised (CFQ-R). http://qol.thoracic.org/sections/instruments/ae/pages/cfq-cfq-r.html. April 2002. Accessed January 6, 2020.
- CFTR2: Clinical and functional translation of CFTR; in collaboration with the Cystic Fibrosis Foundation and Johns Hopkins University. https://www.cftr2.org/mutations_history. March 2019. Accessed January 8, 2020.
- Davies JC, Cunningham S, Harris WT, et al. Safety, pharmacokinetics, and pharmacodynamics of ivacaftor in patients aged 2-5 years with cystic fibrosis and a *CFTR* gating mutation (KIWI): an open-label, single-arm study. *Lancet Respir Med*. 2016;4:107-115.
- Davies JC, Wainwright CE, Canny GJ, et al. Efficacy and safety of ivacaftor in patients aged 6 to 11 years with cystic fibrosis with a *G551D* mutation. *Am J Respir Crit Care Med*. 2013;187(11):1219-1225.
- De Boeck K, Munck A, Walker S, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-*G551D* gating mutation. *J Cyst Fibros*. 2014;13(6):674-680.
- Durmowicz AG, Witzmann KA, Rosenbraugh CJ, Chowdhury BA. Change in sweat chloride as a clinical end point in cystic fibrosis clinical trials: the ivacaftor experience. *Chest*. 2013;143(1):14-18.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed January 6, 2020.
- Egan ME. Genetics of cystic fibrosis: clinical implications. *Clin Chest Med*. 2016;37:9-16.
- Elborn JS. Cystic fibrosis. *Lancet*. 2016;388:2519-2531.
- Farrell PM, White TB, Ren CL, et al. Diagnosis of cystic fibrosis: consensus guidelines from the cystic fibrosis foundation. *J Pediatr*. 2017;181S:S4-15.
- Fuchs HJ, Borowitz DS, Christiansen DH, et al; for the Pulmozyme Study Group. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. *N Engl J Med*. 1994;331:637-643.
- Habib AR, Kajbafzadeh M, Desai S, Yang CL, Skolnik K, Quon BS. A systematic review of the clinical efficacy and safety of CFTR modulators in cystic fibrosis. *Sci Rep*. 2019;9(1):7234.
- Heijerman HGM, McKone EF, Downey DG, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the *F508del* mutation: a double-blind, randomised, phase 3 trial. *Lancet*. 2019;394(10212):1940-1948.
- Kalydeco [package insert], Boston, MA: Vertex Pharmaceuticals, Inc.; April 2019.
- Katkin JP. Cystic fibrosis: genetics and pathogenesis. UpToDate Web site. https://www.uptodate.com. Updated December 4, 2019. Accessed January 6, 2020.
- Konstan MW, McKone EF, Moss RB, et al. Assessment of safety and efficacy of long-term treatment with combination lumacaftor and ivacaftor therapy in patients with cystic fibrosis homozygous for the F508del-CFTR mutation (PROGRESS): a phase 3, extension study. *Lancet Respir Med*. 2017;5:107-118.
- Lahiri T, Hempstead SE, Brady C, et al. Clinical practice guidelines from the Cystic Fibrosis Foundation for preschoolers with cystic fibrosis. *Pediatrics*. 2016;137(4):e20151784. doi: 10.1542/peds.2015-1784.
- McCoy K, Hamilton S, Johnson C; for the Pulmozyme Study Group. Effects of 12-week administration of dornase alfa in patients with advanced cystic fibrosis lung disease. *Chest*. 1996;110:889-895.
- McKone EF, Borowitz D, Drevinek P, et al. Long-term safety and efficacy of ivacaftor in patients with cystic fibrosis who have the Gly551Asp-*CFTR* mutation: a phase 3, open-label extension study (PERSIST). *Lancet Respir Med*. 2014;2:902-910.
- McNamara JJ, McColley SA, Marigowda G, et al. Safety, pharmacokinetics, and pharmacodynamics of lumacaftor and ivacaftor combination therapy in children aged 2-5 years with cystic fibrosis homozygous for *F508del-CFTR*: an open-label phase 3 study. *Lancet Respir Med*. 2019;7(4):325-335.
- Middleton PG, Mall MA, Dřevinek P, et al, for the VX17-445-102 Study Group. Elexacaftor-tezacaftor-ivacaftor for cystic fibrosis with a single Phe508del allele. *N Engl J Med*. 2019;381(19):1809-1819.
- Milla CE, Ratjen F, Marigowda G, et al. Lumacaftor/ivacaftor in patients aged 6-11 years with cystic fibrosis and homozygous for *F508del*-CFTR. *Am J Respir Crit Care Med*. 2017;195(7):912-920.
- Mogayzel PJ, Naureckas ET, Robinson KA, et al; Pulmonary Clinical Practice Guidelines Committee. Cystic fibrosis pulmonary guidelines: chronic medications for maintenance of lung health. *Am J Respir Crit Care Med*. 2013;187(7):680-689.
- Moss RB, Flume PA, Elborn JS, et al. Efficacy and safety of ivacaftor in patients with cystic fibrosis who have an *Arg117His-CFTR* mutation: a double-blind, randomised controlled trial. *Lancet Respir Med*. 2015;3(7):524-533.
- National Institutes of Health; National Human Genome Research Institute. Learning about cystic fibrosis. https://www.genome.gov/10001213/. Updated December 27, 2013. Accessed January 6, 2020.
- Ong T, Ramsey BW. New therapeutic approaches to modulate and correct cystic fibrosis transmembrane conductance regulator. *Pediatr Clin N Am*. 2016;63:751-764.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed January 6, 2020.
- Orkambi [package insert], Boston, MA: Vertex Pharmaceuticals, Inc.; August 2018.
- Pulmozyme [package insert], South San Francisco, CA: Genentech, Inc.; January 2018.
- Quan JM, Tiddens HA, Sy JP, et al. A two-year randomized, placebo-controlled trial of dornase alfa in young patients with cystic fibrosis and mild lung function abnormalities. *J Pediatr*. 2001;139(6):813-820.
- Quittner AL, Modi AC, Wainwright C, et al. Determination of the minimal clinically important difference scores for the cystic fibrosis questionnaire-revised respiratory symptom scale in two populations of patients with cystic fibrosis and chronic *Psuedomonas aeruginosa* airway infection. *Chest*. 2009;135:1610-1618.
- Quon BS, Rowe SM. New and emerging targeted therapies for cystic fibrosis. *BMJ*. 2016;352:i859. doi: 10.1136/bmj.i859.
- Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the *G551D* mutation. *N Engl J Med*. 2011;365(18):1663-1672.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Ratjen F, Hug C, Marigowda G, et al. Efficacy and safety of lumacaftor and ivacaftor in patients aged 6-11 years with cystic fibrosis homozygous for *F508del-CFTR*: a randomised, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2017;5(7):557-567.
- Ren CL, Morgan RL, Oermann C, et al. Cystic Fibrosis Foundation pulmonary guidelines: use of cystic fibrosis transmembrane conductance regulator modulator therapy in patients with cystic fibrosis. *Ann Am Thorac Soc*. 2018;15(3):271-280.
- Rosenfeld M, Wainwright CE, Higgins M, et al. Ivacaftor treatment of cystic fibrosis in children aged 12 to < 24 months and with a CFTR gating mutation (ARRIVAL): a phase 3 single-arm study. *Lancet Respir Med*. 2018;6(7):545-553.
- Rowe SM, Daines C, Ringshausen FC, et al. Tezacaftor-ivacaftor in residual-function heterozygotes with cystic fibrosis. *N Engl J Med*. 2017;377(21):2024-2035.
- Sawicki GS, Chou W, Raimundo K, et al. Randomized trial of efficacy and safety of dornase alfa delivered by eRapid nebulizer in cystic fibrosis patients. *J Cyst Fibros*. 2015;14(6):777-783.
- Simon RH. Cystic fibrosis: treatment with CFTR modulators. UpToDate Web site. https://www.uptodate.com. Updated November 18, 2019. Accessed January 6, 2020.
- Skilton M, Krishan A, Patel S, Sinha IP, Southern KW. Potentiators (specific therapies for class III and IV mutations) for cystic fibrosis. *Cochrane Database Syst Rev*. 2019;1:CD009841. doi: 10.1002/14651858.CD009841.pub3.
- Smith S, Rowbotham NJ, Regan KH. Inhaled anti-pseudomonal antibiotics for long-term therapy in cystic fibrosis. *Cochrane Database Syst Rev*. 2018;3:CD001021. doi: 10.1002/14651858.CD001021.pub3.
- Southern KW, Patel S, Sinha IP, Nevitt SJ. Correctors (specific therapies for class II CFTR mutations) for cystic fibrosis. *Cochrane Database Syst Rev*. 2018;8:CD010966. doi:10.1002/14651858.CD010966.pub2.
- Symdeko [package insert], Boston, MA: Vertex Pharmaceuticals, Inc.; December 2019.
- Taylor-Cousar JL, Jain M, Barto TL, et al. Lumacaftor/ivacaftor in patients with cystic fibrosis and advanced lung disease homozygous for *F508del-CFTR*. *J Cyst Fibros*. 2018;17(2):228-235.
- Taylor-Cousar JL, Munck A, McKone EF, et al. Tezacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del. *N Engl J Med*. 2017;377(21):2013-2023.
- Trikafta [package insert], Boston, MA: Vertex Pharmaceuticals, Inc.; October 2019.
- Vertex Pharmaceuticals Inc. Vertex Cystic Fibrosis Portfolio: a quick guide to approved Vertex cystic fibrosis products and associated eligible populations. 2018.
- Vertex Pharmaceuticals Inc. FDA approves Trikafta (elexacaftor/tezacaftor/ivacaftor and ivacaftor) to treat the underlying cause of cystic fibrosis in people ages 12 and older who have at least one F508del mutation. https://investors.vrtx.com/news-releases/news-release-details/adding-multimedia-fda-approves-trikafta. October 21, 2019. Accessed January 8, 2020.
- Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor-ivacaftor in patients with cystic fibrosis homozygous for Phe508del *CFTR*. *N Engl J Med*. 2015;373:220-231.
- Yang C, Montgomery M. Dornase alfa for cystic fibrosis. *Cochrane Database Syst Rev*. 2018;9:CD001127. doi: 10.1002/14651858.CD001127.pub4.

Publication Date: January 16, 2020

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Prior Authorization Guideline

Guideline Name Topical Immunomodulators

1. Criteria

Product Name: **Elidel, pimecrolimus**	
Approval Length	1 year(s)
Guideline Type	Prior Authorization
Approval Criteria **1** - The patient has a documented diagnosis of mild to moderate Atopic Dermatitis **AND** **2** - Patient is 2 years of age or older **AND** **3** - The medication will not be used chronically **AND** **4** - Patient does not have a diagnosis of Netherton's syndrome (not recommended with this diagnosis due to the potential for systemic absorption) **AND** **5** - Patient is not immunocompromised	

Product Name: **Protopic 0.03%, tacrolimus 0.03%**	
Approval Length	1 year(s)
Guideline Type	Prior Authorization
Approval Criteria **1** - The patient has a documented diagnosis of moderate to severe Atopic Dermatitis **AND** **2** - Patient is 2 years of age or older	

AND

3 - The medication will not be used chronically

AND

4 - Patient is not immunocompromised

Product Name: **Protopic 0.1%, tacrolimus 0.1%**	
Approval Length	1 year(s)
Guideline Type	Prior Authorization

Approval Criteria

1 - The patient has a documented diagnosis of moderate to severe Atopic Dermatitis

AND

2 - Patient is 16 years of age or older

AND

3 - The medication will not be used chronically

AND

4 - Patient is not immunocompromised

Product Name: **Eucrisa**	
Approval Length	1 year(s)
Guideline Type	Prior Authorization

Approval Criteria

1 - The patient has a documented diagnosis of mild to moderate Atopic Dermatitis

AND

2 - Patient is 3 months of age or older

AND

3 - The medication will not be used chronically

AND

4 - Patient is not immunocompromised

Product Name: **Opzelura**	
Approval Length	1 year(s)
Guideline Type	Prior Authorization

Approval Criteria

1 - The patient has a documented diagnosis of mild to moderate Atopic Dermatitis

AND

2 - Patient is 12 years of age or older

AND

3 - The medication will not be used chronically

AND

4 - Patient is not immunocompromised

AND

5- One of the following:

- Disease is not adequately controlled with topical prescription therapies
- Topical prescription therapies are not advised for the patient

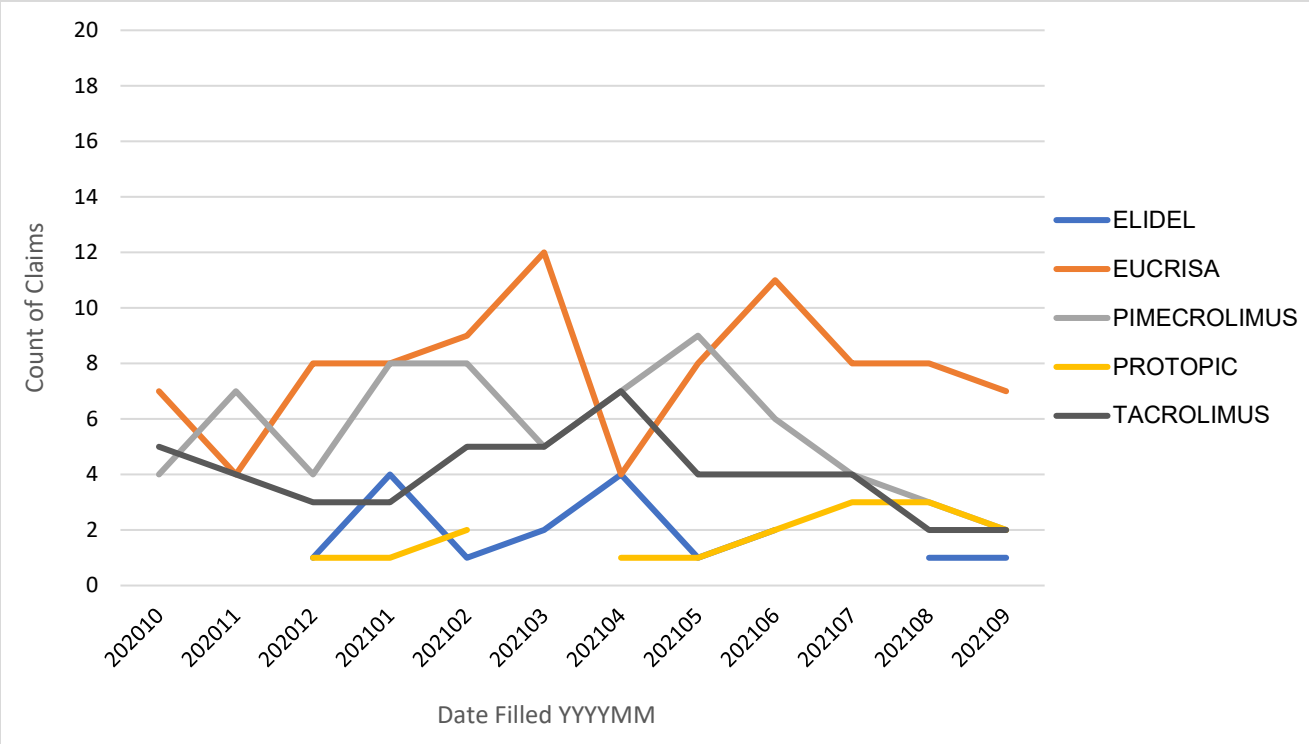
Nevada Medicaid

Utilization

Fee for Service

October 1, 2020 – September 30, 2021

Drug Name	Members	Claims	Total Day Supply	Total Quantity
ELIDEL		19	461	630
EUCRISA		94	2,830	6,120
PIMECROLIMUS		67	1,732	3,130
PROTOPIC		20	483	630
TACROLIMUS		48	1,351	2,710



Therapeutic Class Overview
Atopic dermatitis agents

INTRODUCTION

- Atopic dermatitis, also referred to as atopic eczema, is a chronic, highly pruritic, and relapsing inflammatory skin condition. As a chronic inflammatory skin condition characterized by dry skin, erythema, oozing, crusting, and severe pruritus exacerbated by various environmental stimuli, it is associated with increased immunoglobulin E (IgE) levels and a history of atopy (asthma, allergic rhinitis, or eczema). The prevalence of atopic dermatitis is estimated to be between 15% to 30% in children and 2 to 10% in adults; approximately 18 million children and adults have atopic dermatitis in the United States (US). Atopic dermatitis is one of the most common skin disorders in children with more than 90% of cases starting before the age of 5 years. It can manifest at different sites depending on the age at onset. The prevalence appears to be increasing especially in Western societies *(Berke et al 2012, Eichenfield et al 2014a, Food and Drug Administration [FDA] presentation 2015, Sidbury et al 2014*, *Weston and Howe 2021)*.
- The pathogenesis of atopic dermatitis can be explained by impaired epidermal barrier function due to structural and functional abnormalities in the skin as well as a cutaneous inflammatory response to environmental factors. Pruritus is one of the most common symptoms of atopic dermatitis, and it is an essential feature which provokes a vicious "itch-scratch" cycle that compromises the epidermal barrier, resulting in water loss, xerosis, microbial colonization, and secondary infection. The clinical manifestations of atopic dermatitis vary according to age and disease activity; however, almost all patients with atopic dermatitis report dry skin. The infantile and childhood stages are characterized by pruritic, red, crusted lesions and generally involve the face, neck, and extensor skin surfaces. The adult stage of atopic dermatitis is more lichenified and localized to the flexural folds of the extremities *(Castro 2008, Eichenfield et al 2014a*, *Weston and Howe 2021)*.
- Diagnosis is based on a constellation of clinical symptoms. There is no optimal long-term maintenance treatment of the disease and there is no cure. The general approach for the treatment of atopic dermatitis involves elimination of exacerbating factors, restoring the skin's abnormal barrier function, hydrating the skin, and controlling active disease with topical and/or systemic agents *(Eichenfield et al 2014b, Schneider et al 2013, Tollefson et al 2014)*.
- Patients with atopic dermatitis should avoid exacerbating factors including excessive bathing, low humidity environments, emotional stress, xerosis, and exposure to detergents. Thick creams with low water content or ointments which have zero water content protect against xerosis and should be utilized. Antihistamines are utilized as an adjunct in patients with atopic dermatitis to control pruritus and eye irritation. Sedating antihistamines (eg, diphenhydramine, hydroxyzine) appear to be more effective than non-sedating ones (eg, fexofenadine, loratadine). However, evidence supporting their use is weak due to lack of controlled trials *(Eichenfield et al 2014b)*.
- Topical emollients and topical corticosteroids are first-line treatments for atopic dermatitis. Second- and subsequent-line topical treatment options include topical calcineurin inhibitors and a topical Janus kinase (JAK) inhibitor. The use of systemic therapies is reserved for patients with moderate to severe disease and can include phototherapy, oral cyclosporine or other systemic immunosuppressants, and a biologic interleukin inhibitor, Dupixent (dupilumab) *(Eichenfield et al 2014b, Schneider et al 2013, Tollefson et al 2014, Weston and Howe 2021)*.
  - Low- to high-potency topical corticosteroids are utilized 1 or more times daily for the treatment of acute flares, as well as intermittently to prevent relapses. There are tolerability and safety concerns regarding the use of topical corticosteroids including skin atrophy, striae, and telangiectasia, which may limit long-term use of these agents. These adverse reactions occur more frequently when topical corticosteroids are used on sensitive areas of thin skin including skin folds and the face or neck *(Eichenfield et al 2014b, Krakowski et al 2008, Schneider et al 2013)*.
  - Eucrisa (crisaborole) is a non-steroidal, topical treatment for mild to moderate atopic dermatitis that works by way of phosphodiesterase (PDE)-4 inhibition. Inflammation is associated with elevated PDE-4 enzyme activity and overactive PDE-4 has been shown to contribute to the signs and symptoms of atopic dermatitis. Eucrisa enhances cellular control of inflammation by inhibiting PDE-4 and its ability to degrade intracellular cyclic adenosine monophosphate (cAMP), thereby suppressing the release of cytokines *(Paller et al 2016, Zane et al 2016)*.
  - Opzelura (ruxolitinib) is a JAK inhibitor, non-steroidal, topical treatment for mild to moderate atopic dermatitis; however, use is limited to those patients who are not adequately controlled with other topical prescription therapies, or when those therapies are not advisable. Ruxolitinib is available as an oral tablet and a topical cream; only the cream is indicated for atopic dermatitis. As a kinase inhibitor, ruxolitinib inhibits inflammation-causing JAK1 and JAK2

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

enzymes, responsible for signaling several cytokines and growth factors. It is not completely known how inhibiting JAK enzymes is responsible for the efficacy in atopic dermatitis (*Clinical Pharmacology 2021*).

- Topical immunosuppressive agents for atopic dermatitis include Elidel (pimecrolimus) and Protopic (tacrolimus). Elidel and Protopic inhibit calcineurin, a calcium-dependent phosphatase, by binding with high affinity to immunophilin-12 (FKBP-12), which is theorized to be the primary mode of inflammation reduction in atopic dermatitis. Protopic and Elidel provide immunosuppression via inhibition of T-cell activation *(Clinical Pharmacology 2021)*.
- Dupixent (dupilumab) is a human monoclonal antibody that inhibits signaling of interleukin (IL)-4 and IL-13. This results in a reduction of the release of inflammatory mediators including cytokines, chemokines, nitric oxide, and IgE. These actions are useful for controlling symptoms of moderate to severe atopic dermatitis *(Clinical Pharmacology 2021)*.

- The scope of this review includes agents FDA-approved for the treatment of atopic dermatitis. General anti-inflammatory agents such as the corticosteroids are not included. Only information pertaining to the indication of atopic dermatitis is included within this document.
- Medispan Class: Immunosuppressive Agents – Topical; Phosphodiesterase 4 (PDE4) Inhibitors – Topical; Macrolide Immunosuppressants – Topical; Atopic dermatitis – Monoclonal Antibodies; Atopic dermatitis – Janus Kinase (JAK) Inhibitors

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Systemic agents	
Dupixent (dupilumab)	-
Topical agents	
Elidel (pimecrolimus)	✔
Protopic (tacrolimus)	✔
Eucrisa (crisaborole)	-
Opzelura (ruxolitinib)	-

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

INDICATIONS

Table 2. FDA-approved indications for topical agents

Indication	Elidel (pimecrolimus)	Protopic (tacrolimus)	Eucrisa (crisaborole)	Opzelura (ruxolitinib)
Second-line therapy for the short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised adults and children aged ≥ 2 years, who have failed to respond adequately to other topical prescription treatments, or when those treatments are not advisable.	✔			
Second-line therapy for the short-term and non-continuous chronic treatment of moderate to severe atopic dermatitis in non-immunocompromised adults and children who have failed to respond adequately to other topical prescription treatments for atopic dermatitis, or when those treatments are not advisable.		✔ *		
Topical treatment of mild to moderate atopic dermatitis in patients aged ≥ 3 months.			✔	
Topical short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in				✔ †

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Indication	Elidel (pimecrolimus)	Protopic (tacrolimus)	Eucrisa (crisaborole)	Opzelura (ruxolitinib)
non-immunocompromised patients aged ≥ 12 years whose disease is not adequately controlled with topical prescription therapies or when those therapies are not advisable				

*Both 0.03% and 0.1% ointment for adults and only 0.03% ointment for children 2 to 15 years of age.
†Limitation of use: Use of Opzelura in combination with therapeutic biologics, other JAK inhibitors, or potent immunosuppressants such as azathioprine or cyclosporine is not recommended.

(*Prescribing information: Elidel 2020, Eucrisa 2020, Opzelura 2021, Protopic 2019*)

Table 3. FDA-approved indications for systemic agents

Indication	Dupixent (dupilumab)
Treatment of patients ≥ 6 years of age with moderate-to-severe atopic dermatitis not adequately controlled with topical prescription therapies or when those therapies are not advisable	✔ *

*Dupixent can be used with or without topical corticosteroids.

(*Prescribing information: Dupixent 2021*)

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

CLINICAL EFFICACY SUMMARY

Elidel and Protopic

- The FDA approval of pimecrolimus cream was based on 3 randomized, double-blind (DB), vehicle-controlled, Phase 3 studies in patients 3 months to 17 years of age with mild to moderate atopic dermatitis (n = 589). Two of these 3 trials support the use of pimecrolimus cream in patients 2 years of age and older with mild to moderate atopic dermatitis. Two other identical, 6-week, vehicle-controlled, Phase 3 trials were conducted in pediatric patients 2 to 17 years of age (n = 403). These studies showed significant clinical response based on physician's global evaluation for pimecrolimus-treated patients compared to patients in the vehicle group. These studies are outlined in the manufacturer product labeling.
- The FDA approval of tacrolimus ointment was based on 3 randomized, DB, vehicle-controlled, Phase 3 studies in patients with moderate to severe atopic dermatitis. One of the studies was conducted in pediatric patients (n = 351) ages 2 to 15 years, and the other 2 studies were conducted in adult patients (n = 632). The primary efficacy endpoint was met by all 3 studies with a significantly greater percentage of patients achieving at least 90% improvement based on the physician's global evaluation of clinical response in the tacrolimus group compared to the vehicle group ($p < 0.001$). There was some evidence that tacrolimus 0.1% ointment may provide more efficacy than the 0.03% ointment in adult patients who had severe disease at baseline. There was no difference in efficacy between the tacrolimus strengths in the pediatric study. These studies are outlined in the manufacturer product labeling.
- Pimecrolimus and tacrolimus have been directly compared in clinical trials. One trial compared pimecrolimus 1% to tacrolimus 0.03% in patients 2 to 17 years of age (n = 141) and found no difference in the incidence of application site reactions between the topical immunomodulators in the 6-week study *(Kempers et al 2004)*. However, itching was reported at a significantly higher rate in the tacrolimus group. In 2 other clinical trials, tacrolimus 0.1% was compared to pimecrolimus in adult patients over 6 weeks. Patients treated with tacrolimus had a significantly greater improvement in the Eczema Area Severity Index (EASI) score compared to those treated with pimecrolimus. The success in therapy based on the Investigator Global Atopic Dermatitis Assessment, improvement in percent body surface area (BSA) affected, and improvement in signs and symptoms of atopic dermatitis in face and neck were all statistically significant for the tacrolimus group in both studies. There were no differences in adverse effects (AEs) between the groups *(Abramovits et al 2008, Fleischer et al 2007)*.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- A total of 3 randomized controlled trials (RCTs) showed that both adults and children in the tacrolimus-treated group had a significantly greater improvement in EASI score at week 6 as compared to the pimecrolimus group. The most common AEs in all studies were local application site reactions including burning and stinging *(Paller et al 2005)*.
- A meta-analysis (MA) of 25 RCTs (n = 6897) showed that tacrolimus 0.1% was equally efficacious as potent topical corticosteroids and more efficacious than mild topical corticosteroids for the treatment of atopic dermatitis. Additionally, pimecrolimus was found to be less effective than potent topical corticosteroids *(Ashcroft et al 2005)*. Individual clinical trials have reported conflicting results *(Bieber et al 2007, Doss et al 2009, Doss et al 2010)*.
- A MA and systematic review (SR) assessed the effectiveness of topical immunomodulators compared to topical corticosteroids and/or placebo (n = 7378). In terms of overall comparison, pimecrolimus was found to be more effective than vehicle at 3 and 6 weeks. However, a long-term study that was included in this review did not find any difference between these 2 groups at 6 and 12 months. Also, betamethasone valerate, a potent topical corticosteroid, was found to be significantly more effective in adults (3 weeks) than pimecrolimus in the treatment of moderate to severe atopic dermatitis. Although this MA showed that pimecrolimus seems to be less effective than topical corticosteroids, Pimecrolimus would be efficacious in areas where topical corticosteroids may not be recommended such as the face and sensitive areas including skin folds. Pooled analysis of tacrolimus trials demonstrated that tacrolimus was more effective than vehicle. When compared to mild potency topical corticosteroids like hydrocortisone acetate, tacrolimus was more efficacious. However, when compared to moderate potency topical corticosteroids, tacrolimus 0.03% was significantly less effective than topical corticosteroids, and tacrolimus 0.1% was equal in effectiveness to the topical corticosteroids. Overall, tacrolimus was found to be more effective than mild topical corticosteroids and equally effective as moderately potent topical corticosteroids *(El-Batawy et al 2009)*.
- A SR of 20 RCTs (n = 6288) showed that tacrolimus was more efficacious than placebo or mild topical corticosteroids for the treatment of atopic dermatitis. Additionally, pimecrolimus was more efficacious than placebo and equally efficacious as mild topical corticosteroids for the treatment of atopic dermatitis. In this review, 3 trials comparing pimecrolimus to tacrolimus were identified. While 2 of the trials did find tacrolimus to be significantly more efficacious, no significant difference was found in the third trial *(Chen et al 2010)*.
- The following studies outlines data regarding the potential risk for malignancies with topical calcineurin inhibitor use:
  - A 5-year, OL, multicenter (MC) study evaluated the use of pimecrolimus in 2418 infants compared to topical corticosteroids. The primary endpoint was safety; the secondary endpoint was long-term efficacy defined as a score of 0 to 5 on the IGA. Topical corticosteroids included low-potency such as hydrocortisone 1% or medium-potency such as hydrocortisone butyrate 0.1%. For safety, no differences between the groups were observed for growth rate or bacterial or viral infections. More pimecrolimus-treated patients reported bronchitis ($p = 0.02$), infected eczema ($p < 0.001$), impetigo ($p = 0.045$), and nasopharyngitis ($p = 0.04$). Serious infections and infestations were similar between the groups. Two malignancies occurred in the corticosteroid-treated group, and one benign tumor was reported in the pimecrolimus-treated group. Over the 5-year period, 88.7% and 92.3% of the pimecrolimus- and corticosteroid-treatment groups, respectively, reported overall IGA treatment success. Significant attrition occurred with only 69.4% and 72.1% of pimecrolimus- and corticosteroid-treated patients completing the study *(Sigurgeirsson et al 2015)*.
  - A retrospective cohort evaluated initial cancer diagnosis in patients with a diagnosis of atopic dermatitis or eczema and found that while exposure to pimecrolimus or tacrolimus was not associated with an increase in overall cancer rates, exposure to these agents was associated with an increased risk of T-cell lymphoma ($p < 0.001$ and $p = 0.01$, respectively). However, after the exclusion of 4 cases due to physician suspected T-cell lymphoma prior to exposure, the risks were only significant for patients exposed to tacrolimus and not pimecrolimus ($p < 0.001$, $p = 0.086$, respectively) *(Hui et al 2009)*.
  - A recent MA of observational studies (N = 11 studies, including 8 cohort studies in which 408,366 patients were treated with topical calcineurin inhibitors) published up to October 2020, evaluated the association between topical calcineurin inhibitor use and risk of malignant neoplasms vs controls (non-active comparator or topical corticosteroids). There was no association between topical calcineurin inhibitor use and cancer overall vs non-active comparators (RR, 1.03; 95% CI, 0.92 to 1.16). However, the lymphoma risk was elevated with topical calcineurin inhibitors compared to both the non-active comparators (RR, 1.86; 95% CI, 1.39 to 2.49) and the topical corticosteroids (RR, 1.35; 95% CI, 1.13 to 1.61). No significant association was found between topical calcineurin inhibitor use and increased skin cancer (melanoma and keratinocyte carcinoma) (*Lam et al 2021*).

Eucrisa

- The safety and efficacy of crisaborole were demonstrated in 2 identically designed, randomized, Phase 3, DB, vehicle-controlled trials in a total of 1522 patients with mild to moderate atopic dermatitis and ≥ 5% treatable BSA. The primary

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

endpoint of success was defined as the proportion of subjects at Day 29 who were clear or almost clear with a ≥ 2-grade improvement from baseline by the Investigator's Static Global Assessment (ISGA) scale. More patients receiving crisaborole vs vehicle achieved the primary endpoint of ISGA success (Study AD-301: 32.8 vs 25.4%, p = 0.038; Study AD-302: 31.4 vs 18.0%, p < 0.001), with a greater percentage achieving clear/almost clear overall (51.7 vs 40.6%, p = 0.005; 48.5 vs 29.7%, p < 0.001). In addition, crisaborole-treated patients achieved greater ISGA score improvements and improvement in pruritus earlier (both p < 0.001) *(Eucrisa dossier 2018, Paller et al 2016)*.
    - An open-label (OL) extension trial of AD-301 and AD-302 evaluated the safety of crisaborole in 517 patients with mild to moderate atopic dermatitis for 48 weeks. Patients underwent an average of 6 treatment periods and used an average of 133 grams of ointment/month. Most treatment-emergent AEs (TEAEs) were mild (51.2%) or moderate (44.6%) and were considered unrelated to treatment with crisaborole (93.1%). The most commonly observed AEs (≥ 1% of patients) included atopic dermatitis flares (3.1%), application site pain (2.3%), and application site infection (1.2%). Most patients (77.8%) did not require rescue medications. Children and adolescents made up 48% of those patients that initiated rescue therapies (*Eichenfield et al 2017*).
- The CrisADe CARE 1 trial (n = 137) was a Phase 4, OL trial which demonstrated that crisaborole was tolerated and effective in children aged 3 to 24 months with mild to moderate atopic dermatitis. Crisaborole systemic exposures in infants were comparable with those of patients aged ≥ 2 years. TEAEs were reported for 88 (64.2%) patients (98.9% were mild/moderate). The most frequently reported TEAEs were application site pain (3.6%), application site discomfort (2.9%), and erythema (2.9%). ISGA clear/almost clear scores with ≥ 2-grade improvement at day 29 were achieved by 30.2% of patients. From baseline to day 29, mean percentage change in EASI score was -57.5%, and mean change in Patient-Oriented Eczema Measure (POEM) total score was -8.5 (*Schlessinger et al 2020*).
- One SR and network MA (NMA) of 9 RCTs evaluated crisaborole vs other topical treatments for mild to moderate atopic dermatitis. Patients were more likely to achieve ISGA 0 to 1 with crisaborole than with pimecrolimus 1% cream (hazard ratio [HR], 1.62; 95% credible interval [CrI], 1.04 to 2.48; probability treatment was better vs comparator = 98.3%). There was weak evidence of a difference between crisaborole and tacrolimus 0.03% (HR, 1.35; 95% CrI, 0.95 to 1.84; probability treatment was better vs comparator = 95.7%) and no evidence of a difference vs tacrolimus 0.1% (HR, 1.18; 95% CrI, 0.64 to 1.96; probability treatment was better vs comparator = 71.6%). The NMA for safety was not feasible due to data limitations (*Fahrbach et al 2020*).

Opzelura

- The safety and efficacy of Opzelura were demonstrated in 2 identically designed, randomized, Phase 3, DB, vehicle-controlled trials (TRuE-AD1 and TRuE-AD2) in a total of 1249 patients aged ≥ 12 years with atopic dermatitis and 3 to 20% affected BSA and a baseline Investigator's Global Assessment (IGA) score of 2 or 3. The primary endpoint was defined as the proportion of patients at week 8 with an IGA score of 0 (clear) or 1 (almost clear) with a ≥ 2-grade improvement from baseline. Patients were randomized (2:2:1) to ruxolitinib 0.75% cream twice daily (n = 500), ruxolitinib 1.5% cream twice daily (n = 499; FDA-approved dose), or vehicle cream twice daily (n = 250) for 8 weeks. A total of 11.5% of patients in TRuE-AD1 and 9.2% of patients in TRuE-AD2 did not complete the 8-week trials. In TRuE-AD1 and TRuE-AD2, more ruxolitinib-treated patients achieved IGA treatment success with ruxolitinib 0.75% (50.0 vs 39.0%, respectively) and ruxolitinib 1.5% (53.8 vs 51.3%, respectively), vs the vehicle (15.1 vs 7.6%, respectively; p < 0.0001) at week 8. In addition, both ruxolitinib strengths demonstrated significant reductions in itch (as measured by daily itch numerical rating scale scores) and an increase in patients achieving a 75% improvement in EASI (EASI-75) compared to the vehicle. A larger proportion of vehicle-treated patients reported TEAE(s) vs patients treated with the ruxolitinib 1.5% cream (33.2 vs 26.5%, respectively). A total of 15 patients discontinued from both studies due to TEAEs (n = 8 [3.2%] with vehicle and 7 with ruxolitinib [0.6% in the ruxolitinib 1.5% cream group) (*Papp et al 2021*).
    - The long-term safety of ruxolitinib cream was presented at the Revolutionizing Atopic Dermatitis Symposium in June 2021, with data yet to be published. Although available data are limited, ruxolitinib cream appeared to be well tolerated through 1 year of treatment, with no AEs suggestive of a relationship to systemic exposure (*Blauvelt et al 2021*).
    - The TRuE-AD3 trial, an 8-week efficacy trial followed by a 44-week long-term safety trial, is currently evaluating approximately 250 children with atopic dermatitis aged 2 to 11 years (*Clinicaltrials.gov [NCT04921969] 2021*).
- One, dose-ranging, DB/OL, Phase 2 trial evaluated the effectiveness of ruxolitinib vs triamcinolone. The DB phase evaluated ruxolitinib (doses ranging from 0.15 to 1.5% once to twice daily) cream (n = 50 administered ruxolitinib 1.5% twice daily cream) vs triamcinolone 0.1% cream twice daily (n = 51) vs a vehicle cream twice daily (n = 52) in 307 adults with atopic dermatitis, an IGA score of 2 or 3 (mild-to-moderate disease), and 3 to 20% affected BSA at baseline. Treatment continued for 8 weeks, except the triamcinolone group which was treated for only 4 weeks. Therapeutic

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

benefit was demonstrated with ruxolitinib as early as week 4, regardless of dose. The ruxolitinib 1.5% twice daily cream demonstrated the greatest improvement in IGA responses vs the vehicle at week 4 (38.0 vs 7.7%, respectively; p < 0.001) and week 8 (48.0 vs 9.6%, respectively; p < 0.001). Ruxolitinib 1.5% twice daily cream was not statistically different from the triamcinolone 0.1% twice daily cream for IGA responses at week 4 (38.0 vs 25.5%, respectively). Of note, no comparisons between ruxolitinib and triamcinolone could be made at week 8, because triamcinolone treatment was stopped at week 4 (*Kim et al 2020*).

Dupixent

- The efficacy and safety of dupilumab compared to placebo in adults with moderate-to-severe atopic dermatitis was evaluated in two Phase 3 trials, SOLO 1 (n = 671) and SOLO 2 (n = 708). Adults who did not have an adequate response to topical treatments were included. Patients were randomized to either placebo, dupilumab 300 mg subcutaneously (SC) weekly or every other week for 16 weeks. The proportion of patients with an IGA score of 0 or 1 (indicating clear or almost clear skin) and a reduction of 2 points or more in the score from baseline at week 16 was the primary outcome. In both studies between 36% and 38% of patients who received either regimen of dupilumab achieved the primary outcome compared to 8% to 10% of patients who received placebo (p < 0.001 for all comparisons). Significantly more patients who received dupilumab achieved EASI-75 compared to those who received placebo (p < 0.001). Pruritus and quality of life measures were also significantly improved with dupilumab. The most common AEs with dupilumab compared to placebo were conjunctivitis and injection-site reactions (*Simpson et al 2016*).
- The long-term efficacy and safety of dupilumab were compared to placebo in 740 patients with moderate to severe atopic dermatitis not adequately controlled with topical corticosteroids in the LIBERTY AD CHRONOS study. Patients received either dupilumab 300 mg once weekly, once every 2 weeks, or placebo for 52 weeks. The co-primary endpoints were the proportion of patients achieving an IGA score of 0 or 1 and ≥ 2-point improvement from baseline and EASI-75 at week 16. At week 16, 39% of patients in both dupilumab groups achieved an IGA score of 0 or 1 compared to 12% of patients who received placebo. EASI-75 was achieved in 64% and 69% of the dupilumab groups vs 23% in the placebo group (p < 0.0001). Similar efficacy results were reported at week 52. At 1 year, the most common AEs associated with dupilumab were injection-site reactions and conjunctivitis. Localized herpes simplex infections were more common with dupilumab while herpes zoster and eczema herpeticum were more common in the placebo group (*Blauvelt et al 2017*).
- A variety of studies with dupilumab have been conducted in pediatric patients:
  - The efficacy of dupilumab compared to placebo was evaluated in 251 patients 12 to 17 years of age with moderate-to-severe atopic dermatitis in a DB, MC, RCT. Patients < 60 kg received dupilumab 400 mg initially then 200 mg every 2 weeks and patients ≥ 60 kg received 600 mg initially then 300 mg every 2 weeks for 16 weeks. Compared with placebo, dupilumab resulted in significantly higher proportions of patients achieving EASI-75 at week 16 (41.5% vs 8.2%; p < 0.001) and IGA score of 0 or 1 with 2 or more points improvement at week 16 (24.4% vs 2.4%; p < 0.001) (*Dupixent prescribing information 2021, Simpson et al 2020*).
  - The efficacy of dupilumab plus topical corticosteroids was compared to topical corticosteroids alone in 367 patients 6 to 11 years of age with moderate-to-severe atopic dermatitis in a 16-week DB, MC, RCT. Patients < 30 kg received dupilumab 200 mg initially then 100 mg every 2 weeks and patients ≥ 30 kg received 400 mg initially then 200 mg every 2 weeks. Patients in a third group were dosed regardless of weight at 600 mg initially and 300 mg every 4 weeks thereafter. The primary endpoint was the proportion of patients with an IGA score of 0 (clear) or 1 (almost clear) at Week 16. In patients who received dupilumab 300 mg every 4 weeks plus topical corticosteroids, 30% achieved the primary outcome vs 13% with topical corticosteroids alone. In patients who received dupilumab 200 mg every 2 weeks, 39% achieved the primary outcome vs 10% with topical corticosteroids alone (*Dupixent prescribing information 2021, Paller et al 2020*).
  - One OL extension in 33 children aged 6 to 11 years with severe atopic dermatitis evaluated dupilumab 2 mg/kg or 4 mg/kg for a duration of 16 weeks. TEAEs were mostly mild to moderate in nature, and none led to treatment discontinuation. The most commonly reported TEAEs for the 2 mg/kg and 4 mg/kg doses were nasopharyngitis (47 and 56%, respectively) and atopic dermatitis exacerbation (29 and 13%, respectively). Single-dose dupilumab improved atopic dermatitis, with further improvements with continued treatment through week 52 in children with severe disease (*Cork et al 2021*).
  - It was recently announced that treatment with dupilumab, via the LIBERTY AD PRESCHOOL trial, demonstrated significant reductions in the signs and symptoms of moderate-to-severe atopic dermatitis in children aged 6 months to 5 years of age. Data has yet to be presented or FDA-approved (*Sanofi press release 2021*).

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- An NMA of 74 studies (n = 8177), with 11 trials comparing dupilumab vs placebo, examined the comparative effectiveness of systemic immunosuppressive treatments for moderate to severe atopic dermatitis. Dupilumab was associated with an increased proportion of patients achieving EASI-75 at ≤ 16 weeks (risk ratio [RR], 3.04; 95% CI, 2.53 to 3.65; 8 trials; n = 3150) and at > 16 weeks (RR, 2.59; 95% CI, 1.87 to 3.60; 2 trials; n = 1162). An EASI-75 was achieved by 18 to 20% of placebo-treated patients. An increased proportion of dupilumab-treated patients had an IGA score of 0 to 1 point at ≤ 16 weeks (RR, 3.58; 95% CI, 3.00 to 4.26; 10 trials; n = 3634). Dupilumab was more effective than placebo in achieving improvement in POEM score (mean difference, 7.30; 95% CI, 6.61 to 8.00) at short-term follow-up. Dupilumab had a decreased risk of serious AEs at ≤ 16 weeks (RR, 0.35; 95% CI, 0.19 to 0.64; 9 trials; n = 2628), but no significant difference in serious AEs at > 16 weeks (3 trials; n = 1541). Overall, the authors suggested that dupilumab ranks first for effectiveness compared with other biological treatments for atopic dermatitis (*Sawangjit et al 2020*). Another MA of 50 RCTs (n = 6681) examined systemic agents for atopic dermatitis. Results indicated that for EASI-75, the efficacy of off-label baricitinib (risk difference [RD], 0.16; 95% CI, 0.10 to 0.23) and FDA-approved dupilumab (RD, 0.37; 95% CI, 0.32 to 0.42; I^2 = 19%) demonstrated superiority vs placebo for < 16 weeks (*Siegels et al 2020*). Other biologics are in development for the treatment of atopic dermatitis, but are investigational at this time.

CLINICAL GUIDELINES

- According to the American Academy of Dermatology, interventions that provide effective control of atopic dermatitis for a majority of patients include non-pharmacologic interventions with emollients, topical treatment with corticosteroids and calcineurin inhibitors, and avoidance of environmental triggers. Phototherapy is the next option for children and adults with moderate to severe atopic dermatitis not controlled with the first-line interventions. A third-line treatment recommended for patients who fail phototherapy is treatment with systemic immunomodulators, such as cyclosporine and methotrexate. The guidelines did not provide a recommendation on use of topical crisaborole, topical ruxolitinib, or injectable dupilumab due to limited data available at the time of publication (*Sidbury et al 2014*).

Topical agents

- Treatment guidelines generally agree that a stepwise approach to treatment is needed. Nonpharmacological therapies (ie, lukewarm baths, skin moisturizers, etc.) are followed by topical corticosteroids and/or topical calcineurin inhibitors. Low- to high-potency topical corticosteroids are the standard of care, and strength is selected based on severity, duration of treatment, location of exacerbation, and age of the patient. Pimecrolimus and tacrolimus are topical calcineurin inhibitors that are recommended as second-line therapy in patients who fail or cannot tolerate corticosteroids. Crisaborole and ruxolitinib have not yet been added to the guidelines *(Eichenfield et al 2014a, Eichenfield et al 2014b, Schneider et al 2013, Sidbury et al 2014, Tollefson et al 2014)*.
  - The use of a topical calcineurin inhibitor is recommended for flares associated with specific clinical situations. Specific recommended uses for topical calcineurin inhibitors include any of the following: recalcitrance to steroids, sensitive areas (face, anogenital, skin folds), steroid-induced atrophy, and long-term uninterrupted topical steroid use (*Eichenfield et al 2014a).*
  - For patients with recurrent flares of disease, proactive maintenance treatment with topical steroid (1 to 2 times/week) or topical calcineurin inhibitor (2 to 3 times/week) at sites that typically flare are recommended to help prevent relapses, and are more effective than emollients alone. Combination topical steroid plus topical calcineurin inhibitor, concomitantly or sequentially, may be considered as a steroid-sparing regimen (*Eichenfield et al 2014a)*.
- In May 2021, the National Institute for Health and Care Excellence (NICE) announced it was unable to make a recommendation for the use of crisaborole in treating children aged ≥ 2 years for mild to moderate atopic dermatitis, because Pfizer withdrew its evidence submission. Pfizer stated they did not want to submit for evidence appraisal, because the technology would not be launched in the United Kingdom (*NICE 2021*).

Systemic agents

- A 2018 European consensus guideline from a variety of organizations on treatment of atopic dermatitis includes dupilumab as a treatment option for patients with moderate-to-severe disease in whom an adequate response is not achieved with topical treatments and for whom other systemic treatments are not available. Concomitant use of emollients is recommended and combination with topical agents may be needed. No specific information on pediatric treatment was provided due to lack of data (*Wollenberg et al 2018*).
- The International Eczema Council 2017 provides similar guidance as the American Academy of Dermatology as well as additional steps to be taken before initiation of systemic treatment. These include consideration of an alternative

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

diagnosis, ensuring patient compliance with topical treatment, a trial of intensive topical therapy, treatment of infection, identification and avoidance of all potential triggers, and use of phototherapy if possible. The guidance does not comment on use of biologic agents due to limited data (*Simpson et al 2017*). The International Eczema Council also published a position statement on conjunctivitis in atopic dermatitis with and without dupilumab therapy based on an opinion survey and roundtable discussion of its members. Based on expert opinion, a consensus was reached that patients should be informed about possible conjunctivitis with dupilumab prior to treatment, and treatment should be continued after referral to an ophthalmologist should new-onset conjunctivitis occur *(Thyssen et al 2019).*

SAFETY SUMMARY

Elidel and Protopic

- There are some concerns regarding the long-term safety of these agents. On January 19, 2006, the FDA approved updated labeling for the agents. This updated labeling was a result of cancer-related AEs with the use of these medications. The labeling includes a boxed warning about a possible risk of cancer and a medication guide for patients to ensure that they are aware of this concern. A definitive causal link between the topical immunosuppressants and the incidence of malignancy has not been established *(FDA press release 2006)*.
  - A number of analyses have evaluated the risk of malignancy in patients administered topical calcineurin inhibitors. Long-term exposure to pimecrolimus or tacrolimus may not be associated with an increase in overall cancer rates; however, exposure to these agents may be associated with an increased risk of lymphoma. Further data may be warranted to validate this potential issue (*Hui et al 2009, Lam et al 2021, Sigurgeirsson et al 2015).*
- Boxed warning: Although a causal relationship has not been established, rare cases of malignancy (eg, skin and lymphoma) have been reported in patients treated with topical calcineurin inhibitors.
  - Avoid continuous long-term use in any age group, and limit application to areas of involvement with atopic dermatitis.
  - Both agents are not indicated for use in children less than 2 years of age. Only Protopic 0.03% ointment is indicated for use in children 2 to 15 years of age; Protopic 0.1% and Elidel are indicated for children 2 years and older and adults.
- Key warnings and precautions:
  - Do not use on malignant or pre-malignant skin conditions.
  - Resolve bacterial or viral infections at the treatment site.
  - While using avoid exposure to sunlight.
  - Do not use in immunocompromised patients.
- AEs: Application site irritation and reactions such as skin burning, itching, redness, and rash. Hypersensitivity reactions can also occur.

Eucrisa

- Contraindications: Known hypersensitivity to Eucrisa or any component of the formulation
- Key warnings and precautions:
  - Hypersensitivity reactions, including contact urticaria, have occurred in patients treated with Eucrisa. Hypersensitivity should be suspected in the event of severe pruritus, swelling, and erythema at the application site or at a distant site. If signs and symptoms of hypersensitivity occur, Eucrisa should be discontinued immediately, and appropriate therapy initiated.
- AEs:
  - In pivotal studies AD-301 and AD-302, the AE reported by ≥ 1% of Eucrisa-treated patients (45/1012 [4%] vs 6/499 [1%] of vehicle-treated patients) was application site pain, referring to skin sensations such as burning or stinging. Less common (< 1%) AEs in patients treated with Eucrisa included contact urticaria.
  - No safety signals were identified from vital signs or laboratory assessments in the pivotal studies or in the 48-week, long-term safety extension study *(Eucrisa dossier 2018, Paller et al 2016)*.

Opzelura

- Boxed warnings include serious infections, mortality, malignancy, major adverse cardiovascular events (MACE), and thrombosis. Further details are described below.
- Key warnings and precautions:
  - Serious infections, including fatal, have been reported with the oral JAK inhibitors (including tuberculosis, bacterial, mycobacterial, invasive fungal, viral or opportunistic infections). Serious lower respiratory tract infections have been

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

reported with topical Opzelura. Avoid Opzelura in cases of active, serious infections, including localized infections. Herpes viral reactivations have been reported with Opzelura; discontinue treatment until the episode resolves. Do not use Opzelura in patients with active hepatitis B or C.
  - Thrombocytopenia, anemia, and neutropenia have been reported with Opzelura. Should signs and/or symptoms of these occur, discontinue treatment.
  - The following events have been observed with JAK inhibitors prescribed for inflammatory conditions:
    - Mortality, including a higher rate of all-cause mortality and sudden cardiovascular (CV) death.
    - Malignancy and lymphoproliferative disorders, with an increased risk observed in patients who are past or current smokers.
    - MACE defined as CV death, non-fatal myocardial infarction, and non-fatal stroke has been observed at a higher rate.
    - Thrombosis including deep venous thrombosis, pulmonary embolism, and arterial thrombosis, have been observed at a higher rate; some cases resulted in death. Opzelura should be used with caution in patients at an increased risk of thrombosis.
  - Lipid elevations (eg, total cholesterol, low-density lipoprotein cholesterol, triglycerides) have been reported with oral ruxolitinib.
- AEs: The most common AEs (incidence ≥ 1%) were nasopharyngitis (13%), diarrhea, bronchitis, ear infection, eosinophil count increased, urticaria, folliculitis, tonsillitis, and rhinorrhea (1% for each).

Dupixent
- Contraindications: Known hypersensitivity to Dupixent or any component of the formulation
- Key warnings and precautions:
  - Hypersensitivity reactions (eg, anaphylaxis, erythema nodosum, serum sickness, urticaria, and rash) have occurred after administration of Dupixent. Dupixent should be discontinued in the event of a hypersensitivity reaction.
  - Conjunctivitis and keratitis occurred more often with Dupixent than placebo in atopic dermatitis clinical trials (conjunctivitis was the most frequently reported eye disorder). New or worsening eye symptoms should be reported to a healthcare provider.
  - Pre-existing helminth infections should be treated before therapy with Dupixent. If a patient becomes infected while receiving Dupixent and does not respond to anti-helminth treatment, Dupixent should be discontinued until the parasitic infection resolves.
- AEs: The most common adverse reactions in patients with atopic dermatitis included injection-site reactions, conjunctivitis, blepharitis, oral herpes, keratitis, eye pruritus, other herpes simplex virus infection, and dry eye.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Systemic agents				
Dupixent (dupilumab)	Single-dose pre-filled syringe, single-dose pre-filled pen	SC	Adults: Initial, Two injections; Maintenance, One injection every other week Pediatric: Initial, Two injections; Maintenance for 15 to 29 kg, One injection every 4 weeks; Maintenance for ≥ 30 kg, One injection every other week	Safety and efficacy in pediatric patients < 6 years of age have not been established.* May be administered by a healthcare professional or self-administered via pre-filled syringe or pen. The pre-filled pen is only for use in adults and adolescents aged ≥ 12 years. Concomitant topical corticosteroids may be used. Concomitant topical calcineurin inhibitors (Elidel or Protopic) may be used, but reserved

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				for problem areas only (eg, face, neck, intertriginous or genital areas).
Topical agents				
Elidel (pimecrolimus)	Cream (1%)	Topical	Two times daily (applied as a thin layer)	Do not use in children less than 2 years of age. Do not use with occlusive dressings since occlusion may promote systemic exposure. Safety has not been evaluated. If signs and symptoms persist beyond 6 weeks, patients should be re-examined by their health care provider to confirm the diagnosis. Continuous long-term use should be avoided, and application should be limited to areas of involvement.
Protopic (tacrolimus)	Ointment (0.03% and 0.1%)	Topical	Two times daily (applied as a thin layer)	Do not use in children less than 2 years of age. Do not use with occlusive dressings since occlusion may promote systemic exposure. Safety has not been evaluated. If signs and symptoms persist beyond 6 weeks, patients should be re-examined by their health care provider to confirm the diagnosis. Continuous long-term use should be avoided, and application should be limited to areas of involvement.
Eucrisa (crisaborole)	Ointment (2%)	Topical	Two times daily (applied as a thin layer)	Safety and effectiveness in pediatric patients below the age of 3 months have not been established.
Opzelura (ruxolitinib)	Cream (1.5%)	Topical	Two times daily (applied as a thin layer)	Do not use in children less than 12 years of age. Do not use > 60 grams per week. Apply only up to 20% of BSA. If signs and symptoms persist beyond 8 weeks, patients should be re-examined by their health care provider to confirm the diagnosis. Continuous long-term use should be avoided, and application should be limited to areas of involvement.

See the current prescribing information for full details
*Safety and effectiveness of Dupixent has been established in patients aged ≥ 12 years of age for asthma and ≥ 18 years of age for chronic rhinosinusitis with nasal polyposis.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

CONCLUSION

- Topical treatments for atopic dermatitis include the topical calcineurin inhibitors, Elidel (pimecrolimus) and Protopic (tacrolimus); a topical JAK inhibitor, Opzelura (ruxolitinib); and topical PDE-4 inhibitor, Eucrisa (crisaborole). Therapy is often a stepwise approach to improve symptoms and achieve long-term disease control based on disease severity.
  - The use of a topical calcineurin inhibitor is recommended for flares associated with specific clinical situations. Specific recommended uses for topical calcineurin inhibitors include any of the following: recalcitrance to steroids, sensitive areas (face, anogenital, skin folds), steroid-induced atrophy, and long-term uninterrupted topical steroid use (*Eichenfield et al 2014a).*
  - For patients with recurrent flares of disease, proactive maintenance treatment with topical steroid (1 to 2 times/week) or topical calcineurin inhibitor (2 to 3 times/week) at sites that typically flare are recommended to help prevent relapses, and are more effective than emollients alone. Combination topical steroid plus topical calcineurin inhibitor, concomitantly or sequentially, may be considered as a steroid-sparing regimen (*Eichenfield et al 2014a)*. Eucrisa and Opzelura have not been added to guidelines at the time of review.
  - For patients with severe atopic dermatitis refractory to other treatments, systemic therapy with either dupilumab or off-label treatments such as cyclosporine or azathioprine is recommended. These therapies may be administered concomitantly with topical treatments (*Wollenberg et al 2018*). Dupixent has not been added to US guidelines at the time of review.
- The topical atopic dermatitis agents may be prescribed in combination with systemic agents to improve disease control. Elidel and Protopic are indicated as second-line therapies for the short-term and non-continuous chronic treatment of atopic dermatitis (Elidel: mild to moderate atopic dermatitis; Protopic: moderate to severe atopic dermatitis) in non-immunocompromised adults and children (Elidel: ≥ 2 years of age; Protopic: 0.03% and 0.1% in adults, 0.03% in patients 2 to 15 years of age). Eucrisa has proven effectiveness in mild to moderate atopic dermatitis in patients aged ≥ 3 months. Opzelura (ruxolitinib) has proven effectiveness in short-term and non-continuous chronic treatment of mild to moderate atopic dermatitis in non-immunocompromised patients aged ≥ 12 years; however, use is limited to those patients who are not adequately controlled with other topical prescription therapies, or when those therapies are not advisable.
  - Eucrisa demonstrated short-term efficacy over vehicle ointment in 2 identically designed, 28-day, Phase 3, DB, randomized trials; more patients receiving Eucrisa vs vehicle achieved the primary endpoint of ISGA success, with a greater percentage of Eucrisa-treated patients achieving clear/almost clear overall. Over 28 days, application site pain was the most commonly reported AE. Data gleaned from the 48-week, long-term study revealed no significant safety signals (*Fahrbach et al 2020)*. Similar efficacy was demonstrated in children aged 3 to 24 months (*Schlessinger et al, 2020*).
  - Opzelura demonstrated efficacy and safety over a vehicle cream in 2 identically designed, 8-week, Phase 3, DB, randomized trials (TRuE-AD1 and TRuE-AD2); more patients receiving Opzelura vs vehicle achieved the primary endpoint of IGA success, with a greater percentage of Opzelura-treated patients achieving clear/almost clear skin. A larger proportion of vehicle-treated patients reported TEAE(s) vs patients treated with the ruxolitinib 1.5% cream. The most common AE was nasopharyngitis (*Papp et al 2021*). The long-term safety of ruxolitinib cream was presented at the Revolutionizing Atopic Dermatitis Symposium in June 2021, with data yet to be published (*Blauvelt et al 2021*).
    - The labeling for Opzelura does include the significant safety concerns including Boxed warnings for the JAK inhibitor class (eg, risks for serious infection, mortality, malignancy, MACE, and thrombosis). Serious lower respiratory tract infections, thrombocytopenia, anemia, and neutropenia have been reported with topical Opzelura. Further data are needed to confirm whether events described in the other JAK inhibitor class warnings may occur with Opzelura.
  - Several head-to-head studies comparing the efficacy of the calcineurin inhibitors have been conducted. Three studies directly comparing Elidel and Protopic evaluated the change from baseline in EASI score at week 6 of treatment. Results favored treatment with Protopic, and AEs between the groups were similar *(Paller et al 2005)*. A MA evaluating Elidel, Protopic, topical corticosteroids, and vehicle preparations demonstrated a significantly greater change in EASI score in patients using Protopic compared to patients using Elidel in addition to better Investigator Global Atopic Dermatitis Assessment in patients with moderate to severe disease *(Ashcroft et al 2005)*. Protopic was found to be more effective than mild topical corticosteroids and equally effective as moderately potent topical corticosteroids *(El-Batawy et al 2009)*.
    - Concerns regarding the long-term safety of the topical calcineurin inhibitors have been addressed in the guidelines and position papers outlined in this review. In 2005, the FDA released a Public Health Advisory to communicate the

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

potential risk of cancer of these products to healthcare providers and patients. The FDA has advised that Elidel and Protopic be used only as labeled and asked providers and patients to consider these agents only as second-line therapies *(FDA press release 2006)*. A recent MA evaluated observational studies published up to October 2020 and the authors concluded there may be an association between topical calcineurin inhibitor use and the risk of lymphoma vs topical corticosteroids or non-active comparators (*Lam et al 2021*).

- Dupixent is the only FDA-approved systemic therapy for the treatment of moderate-to-severe atopic dermatitis in patients ≥ 6 years of age when not adequately controlled with topical prescription therapies or when those therapies are not advisable. Dupixent is an IL-4/IL-13 antagonist which may be administered by a healthcare professional or self-administered SC. It may be used with or without topical corticosteroids. The use of Dupixent in atopic dermatitis should be determined by its approved indication and clinician judgment.
  - Comparative effectiveness reviews examined systemic treatments for moderate to severe atopic dermatitis. Dupixent was associated with an increased proportion of patients achieving EASI-75 at short- and long-term follow up. Dupixent also had a decreased risk of serious AEs at short-term follow up, but no significant difference after long-term follow up. Overall, one author suggested that Dupixent ranks first for effectiveness compared with other biological treatments for atopic dermatitis; however, biologic therapies other than Dupixent are investigational at this time (*Sawangjit et al 2020; Siegels et al 2020*).
  - Possible AEs or safety concerns associated with Dupixent include injection-site reactions, serious allergic reactions, and ophthalmic issues, such as conjunctivitis or keratitis.
- Current guidelines for the treatment of atopic dermatitis recommend the use of topical treatments upfront in therapy and systemic agents when not adequately controlled with topical prescription therapies or when those topical therapies are not advisable *(Eichenfield et al 2014a, Eichenfield et al 2014b, Schneider et al 2013, Sidbury et al 2014, Tollefson et al 2014)*.

REFERENCES

- Abramovits W, Fleischer Jr AB, Jaracz E, et al. Adult patients with moderate atopic dermatitis: Tacrolimus ointment versus pimecrolimus cream. *J Drugs Dermatol.* 2008;12(7):1153-8.
- Ashcroft D, Dimmock P, Garside R, et al. Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: a meta-analysis of randomized controlled trials. *BMJ*. 2005;330(7490):516-24.
- Berke R, Singh A, Guralnick M. Atopic dermatitis: an overview. *Am Fam Physician*. 2012;86(1):35-42.
- Bieber T, Vick K, Fölster-Holst R, et al. Efficacy and safety of methylprednisolone aceponate ointment 0.1% compared to tacrolimus 0.03% in children and adolescents with an acute flare of severe atopic dermatitis. *Allergy*. 2007;62(2):184-9.
- Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet*. 2017;389 (10086):2287-2303.
- Blauvelt A, Eichenfield LF, Kullgowski ME, et al. Long-term safety and disease control with ruxolitinib cream among patients with atopic dermatitis based on previous medication history: Pooled results from two Phase 3 studies. [abstract 515]. Presented June 13, 2021 at the Revolutionizing Atopic Dermatitis Symposium. Virtual. https://revolutionizingad.com/education-resources/june-2021-abstracts/515. Accessed September 26, 2021.
- Castro AP. Calcineurin inhibitors in the treatment of allergic dermatitis. *J Pediatr (Rio J)*. 2006;82(5):166-72.
- Chen SL, Yan J, Wang FS. Two topical calcineurin inhibitors for the treatment of atopic dermatitis in pediatric patients: a meta-analysis of randomized clinical trials. *J Dermatolog Treat*. 2010;21:144-56.
- Clinical Pharmacology [database online]. Tampa, FL: Gold Standard, Inc.; 2021. Available at: http://www.clinicalpharmacology.com. Accessed September 25, 2021.
- Clinicaltrials.gov. A study to assess the efficacy and safety of ruxolitinib cream in children with atopic dermatitis (TRuE-AD3). NCT04921969. Last updated September 22, 2021. https://clinicaltrials.gov/ct2/show/NCT04921969. Accessed September 26, 2021.
- Cork MJ, Thaci D, Eichenfield LF, et al. Dupilumab provides favourable long-term safety and efficacy in children aged ≥ 6 to < 12 years with uncontrolled severe atopic dermatitis: results from an open-label phase IIa study and subsequent phase III open-label extension study. *Br J Dermatol*. 2021;184(5):857-870.
- Doss N, Kamoun M-R, Dubertret L, et al. Efficacy of tacrolimus 0.03% ointment as second-line treatment for children with moderate to severe atopic dermatitis: evidence from a randomized, double-blind non-inferiority trial vs fluticasone 0.005% ointment. *Pediatr Allergy Immunol.* 2010;21:321-329.
- Doss N, Reitamo S, Dubertret L, et al. Superiority of tacrolimus 0.1% ointment compared with fluticasone 0.005% in adults with moderate to severe atopic dermatitis of the face: results from a randomized, double-blind trial. *Br J Dermatol.* 2009;161:427-34.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed September 25, 2021.
- Dupixent [package insert], Bridgewater, NJ: Sanofi-Aventis US, LLC and Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; June 2021.
- Eichenfield LF, Call RS, Forsha DW, et al. Long-term safety of crisaborole ointment 2% in children and adults with mild to moderate atopic dermatitis. *J Am Acad Dermatol*. 2017;77(4):641-649.e5.
- Eichenfield LF, Tom WL, Chamlin SL, et al. Guidelines of care for the management of atopic dermatitis: section 1. Diagnosis and assessment of atopic dermatitis. *J Am Acad Dermatol.* 2014a;70(2):338-51.
- Eichenfield LF, Tom WL, Berger TG, et al. Guidelines of care for the management of atopic dermatitis: section 2. Management and treatment of atopic dermatitis with topical therapies. *J Am Acad Dermatol*. 2014b;71:116-32.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- El-Batawy MM, Bosseila MA, Mashaly HM, et al. Topical calcineurin inhibitors in atopic dermatitis: a systematic review and meta-analysis. *J Dermatol Science*. 2009;54(2):76-87.
- Elidel [package insert], Bridgewater, NJ: Valeant Pharmaceuticals North America, LLC; September 2020.
- Eucrisa [package insert], New York, NY: Pfizer, Inc.; April 2020.
- Eucrisa [product dossier], New York, NY: Pfizer, Inc.; December 2018.
- Fahrbach K, Tarpey J, Washington EB, et al. Crisaborole ointment, 2%, for treatment of patients with mild-to-moderate atopic dermatitis: systematic literature review and network meta-analysis. *Dermatol Ther (Heidelb)*. 2020;10(4):681-694.
- FDA presentation. Dermatologic and Ophthalmic Drugs Advisory Committee Meeting: Atopic Dermatitis. March 2015 https://web.archive.org/web/20170304160918/http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/DermatologicandOphthalmicDrugsAdvisoryCommittee/UCM439354.pdf. Accessed September 25, 2021.
- FDA press release. FDA approves updated labeling with boxed warning and medication guide for two eczema drugs, Elidel and Protopic. January 19, 2006. Available at: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/pimecrolimus-marketed-elidel-cream-information. Accessed September 25, 2021.
- Fleischer Jr AB, Abramovits W, Breneman D, et al. Tacrolimus ointment is more effective than pimecrolimus cream in adult patients with moderate to very severe atopic dermatitis. *J Dermatolog Treat*. 2007;18:151-7.
- Hui RL, Lide W, Chan J, et al. Association between exposure to topical tacrolimus or pimecrolimus and cancers. *Ann Pharmacother*. 2009;43:1956-63.
- Kempers S, Boguniewicz M, Carter E, et al. A randomized investigator-blinded study comparing pimecrolimus cream 1% with tacrolimus ointment 0.03% in the treatment of pediatric patients with moderate atopic dermatitis. *J Am Acad Dermatol*. 2004;51(4):515-25.
- Kim BS, Howell MD, Sun K, et al. Treatment of atopic dermatitis with ruxolitinib cream (JAK1/JAK2 inhibitor) or triamcinolone cream. *J Allergy Clin Immunol*. 2020;145(2):572-582.
- Krakowski AC, Eichenfield LF, Dohil MA. Management of atopic dermatitis in the pediatric population. *Pediatrics*. 2008;122(4):812-24.
- Lam M, Zhu JW, Tadrous M, et al. Association between topical calcineurin inhibitor use and risk of cancer, including lymphoma, keratinocyte carcinoma, and melanoma: A systematic review and meta-analysis. *JAMA Dermatol*. 2021;157(5):549-558.
- National Institute for Health and Care Excellence (NICE). Crisaborole for treating mild to moderate atopic dermatitis in people 2 years and older (terminated appraisal). May 19, 2021. https://www.nice.org.uk/guidance/ta701/resources/crisaborole-for-treating-mild-to-moderate-atopic-dermatitis-in-people-2-years-and-older-terminated-appraisal-pdf-82611068067781. Accessed September 26, 2021.
- Opzelura [package insert], Wilmington, DE: Incyte Corporation, Inc.; September 2021.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed September 25, 2021.
- Paller AS, Lebwohl M, Fleischer AB Jr, et al. Tacrolimus ointment is more effective than pimecrolimus cream with a similar safety profile in the treatment of atopic dermatitis: results from 3 randomized, comparative studies. *J Am Acad Dermatol*. 2005;52(5):810-22.
- Paller AS, Tom WL, Lebwohl MG, et al. Efficacy and safety of crisaborole ointment, a novel, nonsteroidal phosphodiesterase 4 (PDE4) inhibitor for the topical treatment of atopic dermatitis (AD) in children and adults. *J Am Acad Dermatol*. 2016;75(3):494-503.e4.
- Paller AS, Siegfried EC, Thaçi D, et al. Efficacy and safety of dupilumab with concomitant topical corticosteroids in children 6 to 11 years old with severe atopic dermatitis: A randomized, double-blinded, placebo-controlled phase 3 trial. *J Am Acad Dermatol*. 2020;83(5):1282-1293.
- Papp K, Szepietowski JC, Kircik L, et al. Efficacy and safety of ruxolitinib cream for the treatment of atopic dermatitis: Results from 2 phase 3, randomized, double-blind studies. *J Am Acad Dermatol*. 2021;85(4):863-872.
- Protopic [package insert], Seven Giralda Farms, Madison, NJ: LEO Pharma Inc.; February 2019.
- Sanofi press release. Dupixent (dupilumab) pivotal trial meets all primary and secondary endpoints becoming first biologic medicine to significantly reduce signs and symptoms of moderate-to-severe atopic dermatitis in children as young as 6 months. August 30, 2021. https://www.sanofi.com/en/media-room/press-releases/2021/2021-08-30-07-00-00-2288011. Accessed September 28, 2021.
- Sawangjit R, Dilokthornsakul P, Lloyd-Lavery A, et al. Systemic treatments for eczema: a network meta-analysis. *Cochrane Database Syst Rev*. 2020 Sep 14;9:CD013206.
- Schlessinger J, Shepard JS, Gower R, et al. Safety, effectiveness, and pharmacokinetics of crisaborole in infants aged 3 to < 24 months with mild-to-moderate atopic dermatitis: A phase IV open-label study (CrisADe CARE 1). *Am J Clin Dermatol*. 2020;21(2):275-284.
- Schneider L, Tilles S, Lio P, et al. Atopic dermatitis: a practice parameter update 2012. *J Allergy Clin Immunol*. 2013;131(2):295-9.e1-27.
- Sidbury R, Davis DM, Cohen DE, et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. *J Am Acad Derm*. 2014;71:327-49.
- Siegels D, Heratizadeh A, Abraham S, et al. Systemic treatments in the management of atopic dermatitis: A systematic review and meta-analysis. [online ahead of print]. *Allergy*. 2020 Oct 19. doi: 10.1111/all.14631.
- Sigurgeirsson B, Boznanski A, Todd G, et al. Safety and efficacy of pimecrolimus in atopic dermatitis: a 5-year randomized trial. *Pediatrics*. 2015;135(4):597-606.
- Simpson EL, Bieber T, Guttman-Yassky E, et al, for the SOLO 1 and SOLO 2 Investigators. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med*. 2016;375(24):2335-2348.
- Simpson EL, Bruin-Weller M, Flohr C, et al. When does atopic dermatitis warrant systemic therapy? Recommendations from an expert panel of the International Eczema Council. *J Am Acad Dermatol*. 2017;77(4):623-633.
- Simpson EL, Paller AS, Siegfried EC, et al. Efficacy and safety of dupilumab in adolescents with uncontrolled moderate to severe atopic dermatitis: a phase 3 randomized clinical trial. *JAMA Dermatol*. 2020;156(1):44-56.
- Thyssen JP, de Bruin-Weller MS, Paller AS, et al. Conjunctivitis in atopic dermatitis patients with and without dupilumab therapy - international eczema council survey and opinion. *J Eur Acad Dermatol Venereol*. 2019;33(7):1224-1231.
- Tollefson MM, Bruckner AL; Section on Dermatology. Atopic dermatitis: skin-directed management. *Pediatrics*. 2014;134:e1735-e1744.
- Weston WL, Howe W. Atopic dermatitis (eczema): pathogenesis, clinical manifestations, and diagnosis. UpToDate Web site. www.uptodate.com. Updated July 22, 2021. Accessed September 25, 2021.
- Wollenberg A, Barbarot S, Bieber T, et al. Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: part II. *J Eur Acad Dermatol Venereol*. 2018;32(6):850-878.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Zane LT, Chanda S, Jarnagin K, et al. Crisaborole and its potential role in treating atopic dermatitis: overview of early clinical studies. *Immunotherapy*. 2016;8(8):853-66.

Publication Date: September 28, 2021

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Prior Authorization Guideline

Guideline Name: Cabenuva (cabotegravir and rilpivirine) and Vocabria (cabotegravir)

1 . Indications

Drug Name: Cabenuva (cabotegravir and rilpivirine) Injection
Treatment of HIV-1 Infection Indicated as a complete regimen for the treatment of HIV-1 infection in adults to replace the current antiretroviral regimen in those who are virologically suppressed (HIV-1 RNA less than 50 copies per mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine.

Drug Name: Vocabria (cabotegravir) Tablet
Treatment of HIV-1 Infection Indicated in combination with EDURANT (rilpivirine) for short-term treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable antiretroviral regimen with no history of treatment failure and with no known or suspected resistance to either cabotegravir or rilpivirine, for use as: 1) Oral lead-in to assess the tolerability of cabotegravir prior to administration of Cabenuva extended-release injectable suspensions. 2) Oral therapy for patients who will miss planned injection dosing with Cabenuva.

2. Criteria

Product Name: Cabenuva, Vocabria	
Approval Length	12 month(s)
Guideline Type	Prior Authorization

Approval Criteria

1 - All of the following:

1.1 Diagnosis of HIV-1 infection

AND

1.2 Patient is currently virologically suppressed (HIV-1 RNA less than 50 copies/mL) on a stable, uninterrupted antiretroviral regimen for at least 6 months

AND

1.3 Patient has no history of treatment failure or known/suspected resistance to either cabotegravir or rilpivirine

AND

1.4 Provider attests that patient would benefit from long-acting injectable therapy over standard oral regimens

AND

1.5 Prescribed by or in consultation with a clinician with HIV expertise

AND

1.6 Will not be use concurrently with other ART medications

OR

2 - For continuation of prior therapy

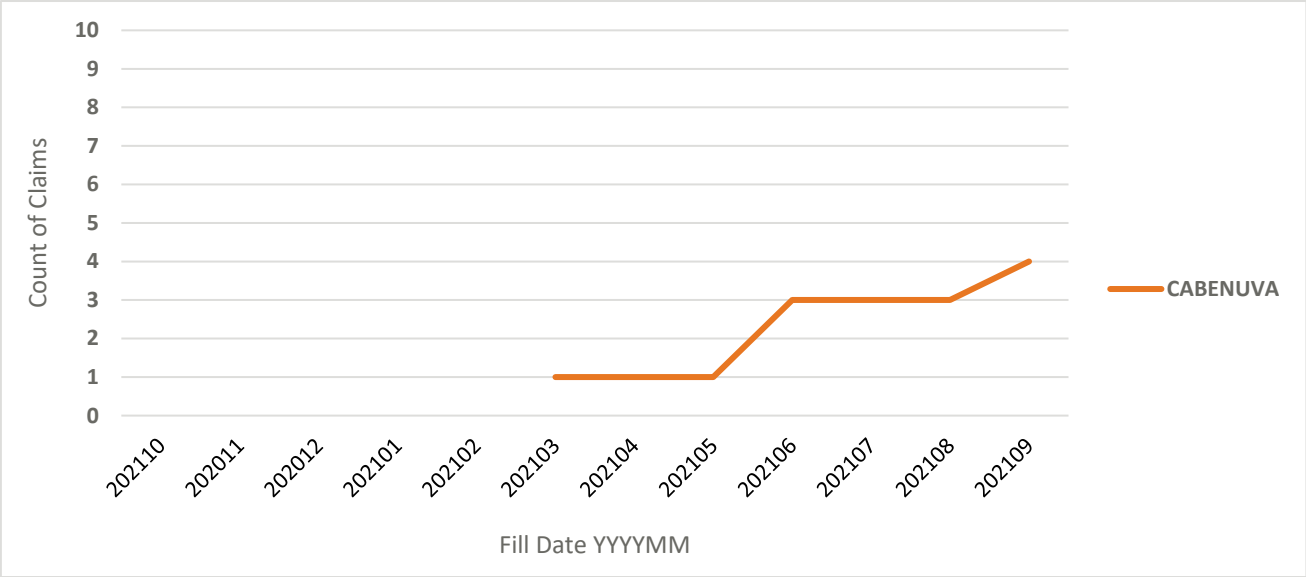
Nevada Medicaid

Utilization

Fee for Service

October 1, 2020 – September 30, 2021

Drug Name	Members	Claims	Total Day Supply	Total Quantity
Cabenuva	5	16	306	74



Therapeutic Class Overview
HIV – Integrase inhibitors (INSTIs)

INTRODUCTION

- Human immunodeficiency virus (HIV) infects cells expressing cluster of differentiation 4 (CD4) receptors, such as T-helper lymphocytes, monocytes, macrophages, dendritic cells, and brain microglia. HIV is characterized by a progressive decline in CD4 cell count, leading to the development of severe immunosuppression which increases the risk for infectious diseases caused by opportunistic pathogens (*Anderson et al 2020, Wood et al 2021*).
- At the end of 2019, there were approximately 1.2 million persons aged ≥ 13 years with diagnosed HIV-1 infection in the United States (US) (*Centers for Disease Control and Prevention [CDC] 2021*).
- The goal of antiretroviral therapy (ART) is multifaceted. Treatment should be continued to maximally suppress plasma HIV, restore and preserve immunologic function, prevent transmission, reduce HIV associated morbidity and mortality, and prolong the duration or quality of survival (*Anderson et al 2020, Department of Health and Human Services [DHHS] 2021[a]*).
- Currently, ART is considered lifelong. As persons living with HIV live longer due to the advent of ART, clinicians are now challenged with treating individuals with co-morbidities. A wide spectrum of complications associated with older age have become common, some of which overlap with adverse events from ART. Management of these complications is constantly evolving (*Anderson et al 2020*).
  - Virologic failure is defined as the inability to achieve or maintain suppression of viral replication to HIV-1 RNA levels ≤ 200 copies/mL (*DHHS 2021[a]*).
- The recommendations for initial treatment of HIV usually include a minimum of 3 antiretroviral (ARV) agents: 1 “anchor” drug and 2 “backbone” drugs. The backbone is usually 2 nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs). The anchor can be a non-nucleoside reverse transcriptase inhibitor (NNRTI), a boosted protease inhibitor (PI), or an integrase strand transfer inhibitor (INSTI). In adults, some 2 drug regimens have also demonstrated efficacy. There is an increased risk for the HIV to select for ARV-resistant variants. Therefore, individuals should be tested for susceptibility via genotypic (preferred) or phenotypic resistance testing at treatment entry and when virologic failure occurs. (*Anderson et al 2020, DHHS 2021[a-c]*).
- More than 30 medications in 6 classes are Food and Drug Administration (FDA)-approved for treatment of HIV infection. Drug classes that are active against the HIV virus include the NRTIs, NNRTIs, PIs, INSTIs, and the entry inhibitors (including a fusion inhibitor, CC chemokine receptor 5 (CCR5) inhibitor, post-attachment or CD4 inhibitor, and a gp120 attachment inhibitor). In addition, 2 drugs, ritonavir (RTV or r) and cobicistat (COBI or c), are used solely as pharmacokinetic (PK) enhancers to improve the PK profiles of some ARV drugs *(DHHS 2021[a])*.
- The focus of this overview will be the INSTIs, which are the only preferred anchor drug regimens for treatment-naïve adults. The INSTIs are divided into first generation INSTIs, which have a lower genetic barrier to resistance and include RAL and EVG. There is a high level of cross-resistance between RAL and EVG. The second generation INSTIs, which have a higher genetic barrier to resistance and include BIC and DTG. It is uncommon for individuals to develop resistance to the NRTIs that are administered with DTG. BIC has retained activity against certain INSTI-resistant strains vs DTG, but this is usually inconsequential due to infrequent resistance with second generation INSTIs. (*Anderson et al 2020, DHHS 2021[a], Clinical Pharmacology 2021, Facts and Comparison 2021*).
  - The 5 FDA-approved INSTIs include bictegravir (BIC), Vocabria (cabotegravir [CAB]), Tivicay or Tivicay PD (dolutegravir [DTG]), elvitegravir (EVG), and Isentress or Isentress HD (raltegravir [RAL]), .
    - BIC and EVG are not available as single drug formulations.
  - The combination, multiple drug formulations include Biktarvy (BIC/emtricitabine [FTC]/tenofovir alafenamide [TAF]), Cabenuva (CAB/rilpivirine [RPV]), Dovato (DTG/lamivudine [3TC]), Genvoya (EVG/c/FTC/TAF), Juluca (DTG/RPV), Stribild (EVG/c/FTC/tenofovir disoproxil fumarate [TDF]), and Triumeq (DTG/abacavir [ABC]/3TC).
  - All the INSTI multiple drug formulations are considered single tablet regimens (STRs) or complete regimens.
    - Cabenuva is the only long-acting HIV-1 formulation available, but also requires the oral lead-in and bridging therapy Vocabria (CAB). Cabenuva is reserved for individuals who are currently virologically suppressed on a stable ARV regimen and no history of treatment failures. Oral Vocabria (CAB) is required as an oral lead-in administered 1 month prior to Cabenuva. In May 2021, ViiV Healthcare announced the submission for a new drug application

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

(NDA) for CAB for the treatment of pre-exposure prophylaxis (PrEP) in transgender women, cisgender men and cisgender women. The NDA is based on results demonstrating CAB was superior to FTC/TDF in PrEP (*Cabenuva prescribing information 2021, ViiV healthcare press release 2021*).

- Cabenuva, Juluca and Dovato are the only 2-drug regimens considered STRs among all HIV therapeutic classes.
- Biktarvy, Triumeq, and Dovato are the only STRs guideline-recommended as preferred in treatment-naïve adults.
  - Dovato has exceptions for use as an initial regimen (ie, HIV RNA > 500,000 copies/mL, hepatitis B virus [HBV] coinfection, or HIV genotypic resistance testing not available).

- Medispan Classes: Anti-infective Agents; Antivirals; Antiretrovirals – Integrase Inhibitors; Anti-infective Agents; Antivirals; Antiretroviral Combinations

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single drug formulations	-
Isentress (raltegravir)	-
Isentress HD (raltegravir)	-
Tivicay (dolutegravir)	-
Tivicay PD (dolutegravir)	-
Vocabria (cabotegravir)	-
Multiple drug formulations or STRs	-
Biktarvy (bictegravir/emtricitabine/tenofovir alafenamide)	-
Cabenuva (cabotegravir/rilpivirine)	-
Dovato (dolutegravir/lamivudine)	-
Genvoya (elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide)	-
Juluca (dolutegravir/rilpivirine)	-
Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate)	-
Triumeq (dolutegravir/abacavir/lamivudine)	-

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

INDICATIONS

Table 2. FDA Approved Indications – Single Drug Formulations

Single Drug formulation	In combination with other ARV agents for the treatment of HIV-1 in adults and pediatric patients	In combination with RPV as a complete regimen for the treatment of HIV-1 infection in adults to replace the current ARV regimen in those who are virologically suppressed (< 50 copies/mL) on a stable ARV regimen (with no history of treatment failure) for at least 6 months	In combination with RPV for short-term treatment of HIV infection in adults who are virologically suppressed (< 50 copies/mL) on a stable ARV regimen with no history of treatment failure and known or suspected resistance to cabotegravir or rilpivirine
Isentress (RAL)	✔ *‡	-	-
Isentress HD (RAL)	✔ †‡	-	-

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Single Drug formulation	In combination with other ARV agents for the treatment of HIV-1 in adults and pediatric patients	In combination with RPV as a complete regimen for the treatment of HIV-1 infection in adults to replace the current ARV regimen in those who are virologically suppressed (< 50 copies/mL) on a stable ARV regimen (with no history of treatment failure) for at least 6 months	In combination with RPV for short-term treatment of HIV infection in adults who are virologically suppressed (< 50 copies/mL) on a stable ARV regimen with no history of treatment failure and known or suspected resistance to cabotegravir or rilpivirine
Tivicay (DTG)	✔ +#	✔ ¶#	-
Tivicay PD (DTG)	✔ +#	✔ ¶#	-
Vocabria (CAB)	-	-	✔

* Pediatric patients weighing ≥ 2 kg
† Pediatric patients weighing ≥ 40 kg
‡ Isentress chewable tablet and oral suspension cannot be substituted for Isentress/Isentress HD 400 mg or 600 mg film-coated tablets
+Pediatric patients ≥ 4 weeks of age and weighing ≥ 3 kg
¶ No known substitutions associated with resistance to either ARV agent
# Tivicay PD is a tablet for oral suspension. Do not interchange tablets and tablets for oral suspension on a mg-per-mg basis.

(*Prescribing information: Isentress/Isentress HD 2021, Tivicay/Tivicay PD 2021, Vocabria 2021*)

Table 3. FDA Approved Indications – Multiple Drug Formulations

Multiple drug formulation/STR	Indicated for the treatment of HIV-1 infection in adults and in pediatric patients	Treatment Naïve: indicated as a complete regimen for the treatment of HIV-1 infection in pediatric patients who have no ARV treatment history	Treatment Naïve: indicated as a complete regimen for the treatment of HIV-1 infection in adults who have no ARV treatment history	Treatment Experienced: to replace the current ARV regimen in those who are virologically suppressed (< 50 copies/mL) on a stable ARV regimen
Biktarvy (BIC/FTC/TAF)	-	✔ *	✔	✔ §||*
Cabenuva (CAB/RPV)	-	-	-	✔ §||
Dovato (DTG/3TC)	-	-	✔	✔ §||
Genvoya (EVG/c/FTC/TAF)	-	✔ *	✔	✔ §||*
Juluca (DTG/RPV)	-	-	-	✔ §||
Stribild (EVG/c/TFC/TDF)	-	✔ ¶	✔	✔ ¶§||
Triumeq (DTG/ABC/3TC)	✔ #**	-	-	-

*Pediatric patients weighing ≥ 25 kg
§ Stable regimen defined as no history of treatment failure
|| No known substitutions associated with resistance to individual ARV components
¶ Pediatric patients ≥ 12 years of age weighing ≥ 35 kg
# Pediatric patients weighing ≥ 40 kg
** not recommended in patients with resistance-associated integrase substitutions or clinically suspected INSTI resistance because the dose of DTG in Triumeq is insufficient in these subpopulations.

(*Prescribing information: Biktarvy 2021, Cabenuva 2021, Dovato 2021, Genvoya 2021, Juluca 2021, Stribild 2020, Triumeq 2021*)

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- 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

RAL

- RAL was the first INSTI approved and has demonstrated durable efficacy through the STARTMRK trial. At week 48, RAL plus TDF/FTC was shown to be non-inferior to efavirenz (EFV) plus TDF/FTC (86.1% vs 81.9%, respectively; difference 4.2%; 95% confidence interval [CI], -1.9 to 10.3) for virologic suppression (HIV-1 RNA < 50 copies/mL) (*Lennox et al 2009*).
  - At 156 weeks, the RAL-containing regimen was non-inferior to the EFV-regimen, with 75.4% given RAL and 68.1% given EFV maintaining viral suppression (difference 7.3%; 95% CI, -0.2 to 14.7) (*Rockstroh et al 2011*).
  - At 5 years (240 weeks), RAL was superior to EFV for virologic efficacy (71% vs 61%; difference 9.5%; 95% CI, 1.7 to 17.3). Twenty-five percent of RAL patients discontinued vs 35% of EFV patients (*Rockstroh et al 2013*).
    - Overall, significantly fewer RAL vs EFV patients experienced neuropsychiatric side effects (39.1% vs 64.2%; p < 0.001) or drug-related clinical AEs (52.0% vs 80.1%; p < 0.001).
- The ACTG A5257 trial evaluated the efficacy of 2 NNRTI/r-boosted regimens vs RAL in treatment-naïve HIV-1 patients. Three regimens were used: atazanavir (ATV)/r, darunavir (DRV)/r, or RAL, each with TDF plus FTC. At 96 weeks, virologic failure (> 1000 copies/mL between 16 and 24 weeks or > 200 copies/mL after 24 weeks) occurred in 12.6% of those given ATR/r, 14.9% given DRV/r, and in 9.0% given RAL; differences in response between groups were within the margin of equivalence (-10% to 10%). Tolerability failure was 0.9% for RAL and 4.7% for DRV/r (with the 2 regimens considered equivalent) and 13.9% for ATV/r (*Lennox 2014*).
- The SPRING-2 trial evaluated the non-inferiority between DTG and RAL. At 48 weeks, non-inferiority for viral suppression was seen between the 2 INSTIs, with 88% in the DTG group and 85% in the RAL group achieving HIV-1 RNA < 50 copies/mL (adjusted difference, 2.5%; 95% CI, -2.2 to 7.1) (*Raffi et al 2013[a]*). At 96 weeks, non-inferiority of viral suppression was maintained in 81% of the DTG group and in 76% of the RAL group (adjusted difference, 4.5%; 95% CI, -1.1 to 10.0) (*Raffi et al 2013[b]*).
- The ONCEMRK trial (N = 797) concluded that RAL 1200 mg once daily was shown to be non-inferior to RAL 400 mg dosed twice daily (both in combination with FTC/TDF), with 81.5% and 80.1% of participants achieving viral suppression (< 40 copies/mL), respectively (difference 1.4%; 95% CI, -4.4 to 7.3) at 96 weeks. Viral resistance to RAL was seen in 0.8% of each group (*Cahn et al 2018*).

BIC

- The GS-US-380-1489 and GS-US-380-1490 were 2 large randomized controlled trials that evaluated the efficacy of BIC/FTC/TAF and also directly compared it to DTG plus 2 NRTI regimens: DTG/ABC/3TC or DTG/FTC/TAF, respectively (*Gallant et al 2017, Sax et al 2017*). At 48 weeks, BIC/FTC/TAF showed non-inferiority to the 2 DTG-regimens for viral suppression (< 50 copies/mL). At 96 weeks, non-inferiority for viral suppression was maintained for BIC/FTC/TAF vs DTG/FTC/TAF (84 vs 86%; respectively; difference -2.3%; 95% CI, -7.9 to 3.2) and vs DTG/ABC/3TC (88 vs 90%; respectively; difference -1.9%; 95% CI, -6.9 to 3.1) (*Stellbrink et al 2019*, *Wohl et al 2019*). No emergence of resistance occurred in either trial. At 144 weeks viral suppression was seen in 82% (difference from DTG/ABC/3TC regimen, -2.6%; 95% CI, -8.5 to 3.4) and 81% (difference from DTG/FTC/TAF regimen, -1.9%; 95% CI, -7.8 to 3.9) of patients given BIC/FTC/TAF vs 84% in DTG-containing regimens, with non-inferiority of the BIC regimen maintained (*Orkin et al 2020[a]*).

DTG

- GEMINI-1 and GEMINI-2 trials evaluated the 2-drug regimen of DTC/3TC to DTC/TDF/3TC for viral suppression (< 50 copies/mL). At 48 weeks, DTC/3TC resulted in viral suppression in 90% (GEMINI-1) and 93% (GEMINI-2) of patients vs 93% and 94%, respectively, with DTC/TDF/3TC, for noninferiority of the 2-drug regimen (*Cahn et al 2019*). A 96-week pooled analysis of the GEMINI-1 and GEMINI-2 trials found the rate of response to be 86% with DTG/3TC vs 90% with DTG/TDF/3TC (adjusted treatment difference, -3.5%; 95% CI, -6.7 to 0.0007) (*Cahn et al 2020*). Non-inferiority of the 2-drug regimen was maintained. No treatment-emergent resistance mutations were seen.
- The SWORD-1 and SWORD-2 trials evaluated the efficacy of DTG/RPV vs a standard 3- or 4-drug regimen. Adult patients on a stable drug regimen for at least 6 months with successful viral suppression (< 50 copies/mL) were randomly assigned to continue their regimen for another 52 weeks or switch for DTG/RPV (early switch group); after

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

week 52, the remaining patients on a 3- or 4-drug regimen were switched to DTG/RPV (late switch group; if viral suppression was maintained) and continued to week 148 (*Aboud et al 2019*). At 100 weeks (snap-shot window), 89% (95% CI, 86 to 92) of the early switch group and 93% (95% CI, 91 to 95) of the late switch group had viral load < 50 copies/mL. Preliminary data from 148 weeks reported viral suppression to be maintained in 84% (95% CI, 81 to 87) in the early switch group and in 90% (95% CI, 87 to 92) in the late switch group (*van Wyk et al 2020*).

- The ADVANCE trial compared DTG/FTC/(TAF or TDF) vs EFV/FTC/TDF as initial treatment for HIV-1 infection. At 96 weeks, viral suppression (< 50 copies/mL) was achieved in 79% of patients given DTG/FTC/TAF, in 79% given DTG/FTC/TDF, and in 74% given EFV/FTC/TDF. The difference in response was 5.1% (98.3% CI, -2.5 to 12.8) between DTC/FTC/TAF and EFV/FTC/TDF, 4.8% (98.3% CI, -2.8 to 12.5) for DTG/FTC/TDF and EFV/FTC/TDF, and 0.3% (98.3% CI, -7.1 to 7.7) between DTG/FTC/TAF and DTG/FTC/TDF (*Venter et al 2020*).
- The efficacy and safety of DTG/FTC/(TAF or TDF) and EFV/FTC/TDF started in pregnancy (at 14 to 28 weeks gestation) were assessed in the IMPAACT 2010/VESTED trial. At delivery, DTG-based regimens resulted in viral suppression (< 200 copies/mL) in 98% of patients and in 91% of patients in the EFV/FTC/TDF regimen (estimated difference, 6.5%; 95% CI, 2.0 to 10.7). A composite adverse pregnancy outcome (spontaneous abortion, stillbirth, preterm delivery, or small for gestation age) occurred in 24% of patients given DTG/FTC/TAF, in 33% of the DTG/FTC/TDF group (estimated difference vs DTG/FTC/TAF, -8.8%; 95% CI, -17.3 to -0.3), and in 33% given EFV/FTC/TDF (estimated difference vs DTG/FTC/TAF, -8.6%; 95% CI, -17.1 to -0.1 ; estimated difference vs DTG/FTC/TDF, 0.2%; 95% CI, -8.8 to 9.1) (*Lockman et al 2021*).

EVG

- The efficacy of EVG with COBI was compared to the same regimen without COBI in a randomized, double-blind, active controlled trial (*Sax et al 2012*). EVG/c/TDF/FTC was found to be non-inferior to EFV/TDF/FTC (87.5% vs 84.1%, respectively; difference 3.6%; 95% CI, -1.6% to 8.8%) for viral suppression (< 50 copies/mL) at 48 weeks. In a second trial, EVG/c/FTC/TDF was compared with ATV/r/TDF/FTC in ART-naïve individuals (*DeJesus et al 2012*). At 48 weeks, viral suppression was seen in 89.5% with EVG/c/FTC/TDF vs 86.8% with ATV/r/TDF/FTC (difference 3%; 95% CI, -1.9% to 7.8%). Similarly, 2 double-blind, placebo-controlled, phase 3 trials demonstrated non-inferiority for viral suppression between EVG/c/FTC/TAF and EVG/c/FTC/TDF coformulations (adjusted difference in viral response, 2.0%; 95% CI, -0.7 to 4.7) at 48 weeks. However, adverse renal and bone effects were significantly reduced in patients given EVG/c/FTC/TAF(*Sax et al 2015*). Similar results were seen at 96 weeks, with viral response in 86.6% with EVG/c/FTC/TAF vs 85.2% with EVG/c/FTC/TDF (difference, 1.5%; 95% CI, -1.8% to 4.8%) (*Wohl et al 2016*). Smaller declines in spine bone mineral density (BMD) were seen with EVG/c/FTC/TAF compared with EVG/c/FTC/TDF (-0.96 vs -2.792), as well as in hip BMD (-0.672 vs -3.275). However, at 144 weeks, EVG/c/FTC/TAF was found to be superior in viral efficacy (as viral suppression) compared to EVG/c/FTC/TDF; 84.2% vs 80.0% (difference, 4.2%, 95% CI, 0.6 to 7.8) (*Arribas et al 2017*). Similar to the 96-week results, declines in spine and hip BMD were smaller with EVG/c/FTC/TAF (-0.9 and -0.8, respectively) compared with EVG/c/FTC/TDF (-3.0 and -3.4, respectively).

CAB/RPV

- The FLAIR trial showed non-inferiority of long-acting CAB/RPV monthly injections vs oral DTG/ABC/3TC in terms of maintaining viral suppression in adults, following induction therapy with DTG/ABC/3TC. At 48 weeks, 2.1% of patients in the CAB/RPV group and 2.5% of patients given DTG/ABC/3TC had loss of viral suppression (≥ 50 copies/mL) (*Orkin et al 2020[b]*). Similar results were seen at 96 weeks, with only 3% of patients in each treatment arm having HIV-1 RNA levels ≥ 50 copies/mL (*Orkin et al 2021*).
- The ATLAS trial compared long-acting CAB/RPV to an oral standard-of-care regimen. Patients had received at least 6 months of a standard-of-care regimen and had HIV-1 RNA levels < 50 copies/mL. At 48 weeks, 1.6% of patients given CAB/RPV and 1% of those given standard-of-care regimens lost viral suppression, with CAB/RPV shown to be non-inferior to oral therapy (adjusted difference, 0.6; 95% CI, -1.2 to 2.5) (*Swindels et al 2020*).
- The ATLAS-2M trial evaluated CAB/RPV given at 2 different dosing interval: every 8 weeks vs every 4 weeks. At 48 weeks, CAB/RPV 600 mg/900 mg every 8 weeks was non-inferior to CAB/RPV 400 mg/600 mg every 4 weeks, with loss of viral suppression in 2% vs 1% of patients (adjusted difference 0.8%; 95% CI, -0.6 to 2.2), respectively (*Overton et al 2021*). An update at 96 weeks reported a total of 9 individuals with virologic failure in the every 8 week arm compared to 2 individuals in the every 4 week arm. The study authors did perform an archived genotype test retroactively and claimed patients had baseline resistance; however, this is not a robust process for correlating between finding resistance mutations and correlating it to drug susceptibility (*Jaeger et al 2020, Cabenuva prescribing information 2021*).

Pediatrics

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Most INSTI-based regimens in children that are guideline recommended have been based on inferred data from adults and adolescents, specifically EVG and RAL. In June 2019, BIC/FTC/TAF was FDA-approved for treatment-naïve or virologically suppressed children weighing ≥ 25 kg. Efficacy was based on 2 cohort studies in 100 children who remained virologically suppressed (HIV RNA < 50 copies/mL) after 24 and 48 weeks for therapy. The authors found that the younger cohort aged 6 to <12 years sustained more variable serum trough concentrations vs adolescents and adults. No grade 3 or 4 AEs were reported and no treatment-emergent resistance was observed (*Biktarvy prescribing information 2019, Cotton et al 2018, DHHS et al 2021[b], Gaur et al 2018, Gaur et al 2019*).

Meta-Analyses

- A meta-analysis (MA)/systematic review (SR) evaluated the efficacy of INSTI vs non-INSTI regimens in 27 trials (N = 25,067). A total of 18,225 individuals were administered an INSTI (BIC: n = 5 trials; DTG: n = 11 trials; EVG: n = 12 trials; RAL: n = 27 trials). In treatment-naïve adults, INSTI-based treatment was favored over non-INSTI treatment for viral suppression to non-detectable levels (odds ratio [OR], 1.48; 95% CI, 1.23 to 1.79; I^2 = 53.8%; p = 0.007). Additionally, significant benefit was observed in virologically suppressed individuals who switched to INSTI vs maintaining non-INSTI therapy (OR, 1.34; 95% CI, 0.91 to 1.97; I^2 = 65.5%; p = 0.003) (*Yang et al 2019*).
  - A subgroup analyses compared each INSTI therapy (BIC, DTG, EVG, and RAL) to each non-INSTI therapy and found no difference between treatments. BIC and DTG were found to maintain antiviral activity against HIV-1 variants resistant to RAL and EVG. The mean odds of resistance at virologic failure was significantly higher for RAL regimens vs non-RAL regimens (OR, 3.14; 95% CI, 1.83 to 5.39; I^2 = 40.3%). The prevalence of resistance at virologic failure was 29.6% for EVG (95% CI, 24.4 to 34.8%) and 33.5% for RAL (95% CI, 25.5 to 41.5%), indicating that drug resistance was prevalent in individuals with virologic failure to these drugs. A pooled analysis of resistance data indicated that development of resistance to DTG and BIC was rare, whereas EVG and RAL had low genetic barriers to resistance.
    - Both RAL and EVG share the Q148 and N155H major resistance pathways, which may confer the emergence of cross-resistance between them.
- An MA/SR found initiating treatment with DTG in treatment-naïve individuals increased the likelihood of achieving viral suppression vs non-DTG regimens (risk difference [RD], 0.06; 95% CI, 0.03 to 0.10; p < 0.0001). Benefit was more pronounced in individuals with a high baseline viral load. The overall rate of discontinuation was lower with DTG vs other ARV regimens (RD, -0.03; p = 0.007); however, the AE discontinuation rate was not significantly different (RD, -0.02; p = 0.10) (*Cruciani et al 2019*).

CLINICAL GUIDELINES

- **DHHS Guidelines for the Use of ARV Agents in Adults and Adolescents with HIV (2021)** (*DHHS 2021[a]*)
  - This guideline recommends ART for all individuals with HIV (**AI**), regardless of CD4 T lymphocyte cell count, and initiated as soon as possible after HIV diagnosis (**AIII**) (see Appendix for ratings of recommendations and evidence). The goals of treatment are:
    - Maximally suppress plasma HIV-1 RNA and maintain a durable response
    - Restore/preserve immunologic function
    - Reduce the morbidity and mortality associated with HIV
    - Prevent HIV transmission
    - Prolong the duration or quality of survival
  - Initial therapy for most people with HIV should be with 2 NRTIs combined with an INSTI, the combination of DTG/3TC or, in some individuals, a combination including 2 NRTIs plus an NNRTI or a boosted PI.
  - Recommendations are based on the virologic potency and durability, short- and long-term toxicity, and dosing convenience of these drugs.
  - Recommended initial INSTI regimens for most people with HIV
    - INSTI plus 2 NRTIs
      - BIC/TAF/FTC (**AI**)
      - DTG/ABC/3TC (**AI**)—if HLA-B*5701 negative
      - DTG plus (TAF or TDF) plus (FTC or 3TC) (**AI**)
    - INSTI plus 1 NRTI
      - DTG/3TC (**AI**), except for individuals with HIV-1 RNA > 500,000 copies/mL, HBV coinfection or in individuals in whom ART is to be started before results of resistance testing or HBV testing are available.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Recommended initial INSTI regimens in certain clinical situations
  - INSTI plus 2 NRTIs
    - EVG/c/(TAF or TDF)/FTC (**BI**)
    - RAL plus (TAF or TDF) plus (FTC or 3TC) (**BI** for TDF/[FTC or 3TC], **BII** for TAF/FTC)
- Regimens to consider when ABC, TAF, and TDF cannot be used or are not optimal
  - DTG/3TC (**AI**), except for individuals with HIV-1 RNA > 500,000 copies/mL, HBV coinfection or in individuals in whom ART is to be started before results of resistance testing or HBV testing are available.
- Note: Because of insufficient data, BIC should not be prescribed if pregnant; TAF and TDF are two forms of tenofovir approved by FDA. TAF has fewer bone and kidney toxicities than TDF, while TDF is associated with lower lipid levels. Lower concentrations of COBI and its boosted drugs EVG, DRV, and ATV have been seen during 2nd and 3rd trimesters, avoid during pregnancy.

- **DHHS Guidelines for the Use of ARV Agents in Pediatric HIV Infection (2021)** *(DHHS 2021[b])*
  - This guideline recommends that ART should be initiated in all infants and children with HIV infection (**AI** for children < 3 months of age, **AI*** for older children).
  - For treatment-naive children, the guideline recommends initiating ART with 3 drugs: a dual-NRTI backbone plus an INSTI, a NNRTI, or a boosted PI (**AI**).
  - In treatment-naïve children living with HIV, ART should be initiated in all infants and children with HIV infection (**AI** for children aged < 3 months, **AI*** for older children), otherwise known as rapid ART initiation (defined as initiating ART immediately or within days of diagnosis). Treatment initiation in young infants with HIV during the early stages of HIV infection may control viral replication before HIV can evolve into diverse and potentially more pathogenic quasi-species. Early therapy also preserves immune function, preventing clinical disease progression.
  - Preferred initial INSTI regimens
    - Infants, birth to age < 14 days
      - Weight ≥ 2 kg: 2 NRTIs plus RAL
    - Neonates ≥ 14 days to age < 4 weeks
      - Weight ≥ 2 kg: 2 NRTIs plus RAL
    - Infants and children age ≥ 4 weeks to < 6 years
      - Weight ≥ 3 kg: 2 NRTIs plus DTG
    - Children age ≥ 6 years
      - Weight ≥ 25 kg: 2 NRTIs plus BIC
      - Weight ≥ 25 kg: 2 NRTIs plus DTG
    - Adolescents aged ≥ 12 years with sexual maturity rating (SMR) 4 to 5
      - Refer to adult and adolescent ARV guidelines (previously summarized above)
  - Alternate INSTI regimens
    - Infants and children age ≥ 4 weeks to < 3 months
      - Weight ≥ 2 kg: 2 NRTIs plus RAL
    - Infants and children age ≥ 3 months to < 3 years
      - Weight no restriction: 2 NRTIs plus RAL
    - Children age ≥ 3 years
      - Weight ≥ 25 kg: 2 NRTIs plus EVG/c
      - Weight no restriction: 2 NRTIs plus RAL
    - Adolescents age ≥ 12 years with SMRs of 1 to 3
      - Weight no restriction: 2 NRTIs plus RAL
      - Weight ≥ 25 kg: 2 NRTIs plus EVG/c

- **DHHS Recommendations for the Use of ARV Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States (2021)** (*DHHS 2021[c]*)
  - This guideline recommends that all pregnant women with HIV should initiate ART as early in pregnancy as possible, regardless of their HIV RNA level or CD4 cell count, to maximize their health and prevent perinatal HIV transmission and secondary sexual transmission (**AI**). Women with HIV should maintain an HIV viral load that is below the limit of

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

detection during pregnancy, postpartum, and throughout their lives (**AII**). Neonates born to women with HIV should receive appropriate ARV drugs (**AI**).
- Preferred INSTI based regimens for pregnant women
  - DTG/ABC/3TC or DTG plus a preferred dual NRTI backbone
    - Although early data suggested an increased risk of neural tube defects with DTG during pregnancy, later analysis indicated that the rate of neural tube defects with DTG was 0.19%, for a difference of 0.09% from other ARVs (*Zash et al 2018, Zash et al 2020, DHHS 2021[c]*); however, risks and benefits of DTG should be discussed with patients prior to initiating therapy. Importantly, the guidline now recommends DTG as the preferred ARV for use throughout pregnancy (**AII**) and for women with HIV who are trying to conceive (**AIII**).
  - RAL plus a preferred dual NRTI backbone (pharmacokinetic data during pregnancy are available for twice daily [400 mg] formulation but not for once daily [1200 mg extended release] formulation)
  - Pregnancy-specific pharmacokinetic data are insufficient to recommend BIC as part of an initial regimen in treatment-naïve women
  - EVG-containing regimens are not recommended as initial treatment during pregnancy due to insufficient data and/or concerns about maternal/fetal safety
- Newborn ARV management according to risk of HIV Infection in the newborn
  - Low risk: ZDV for 4 weeks
  - High risk: ZDV/3TC plus NVP or RAL for 6 weeks
  - With HIV infection: ZDV/3TC plus NVP or RAL as lifelong therapy
    - DTG tablets for oral suspension can be used in place of NVP or RAL in infants ≥ 4 weeks of age and weigh ≥ 3 kg
    - RAL can be used in infants born at postmenstrual age ≥ 37 weeks and weigh ≥ 2 kg

- **International Antiretroviral Society (IAS)-USA Panel (2020)** (*Saag et al 2020*)
  - Treatment should be initiated as soon as possible after HIV diagnosis. Recommendations for therapy selection are genrally consistent with the DHHS guidelines.
  - INSTI-based regimens for adults (see Appendix for ratings of recommendations and evidence)
    - Recommended for most patients with HIV (with recommendation rating)
      - BIC/TAF/FTC (**AIa**)
      - DTG plus TAF/FTC or TDF/FTC or TAF/3TC (**AIa)**
      - DTG/3TC (**AIa**) (not recommended for patients with chronic HBV infection or HIV RNA > 500,000 copies/mL [and possibly CD4 cell count < 200/µL])
    - Recommended in the presence of opportunistic infection treatment
      - DTG or EFV or RAL plus 2 NRTIs (**AIa**) if active tuberculosis and treatment with rifampin
      - BIC is not recommended with rifampin (**AIIa**)
    - Recommended during pregnancy
      - DTG plus TDF/FTC or TDF/3TC (**AIb**)
      - RAL plus TDF/FTC or TDF/3TC (**AIIa**)
  - The following INSTI regimens are recommended for switching in cases of virologic suppression:
    - Switching from a 3-drug regimen to an oral 2-drug regimen is an appropriate strategy to manage toxic effects, intolerance, adherence, or patient preference provided both agents are fully active **(AIa)**.
    - DTG/3TC **(AIa)**
    - DTG/RPV **(AIa)**
    - CAB/RPV every 4 weeks **(AIa)** or every 8 weeks **(BIb)**
      - Note: Only the every 4 week regimen is FDA-approved.
  - The following INSTI regimens are recommended for switching in cases of virologic failure:
    - DTG plus 2 NRTIs (with 1 active drug determined by genotypic testing) is recommended after initial treatment failure with an NNRTI **(AIa)**.
    - DTG (dosed twice daily) plus at least 1 fully active other agent is recommended in the setting of RAL or EVG resistance **(BIII)**.
  - In the setting of viral suppression and archived drug resistance mutations, the following boosted regimens may be prescribed:

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- BIC/FTC/TAF or DTG plus FTC/TAF or ABC/3TC may be effective in patients with an archived M184V/I mutation detected by proviral DNA genotyping **(AIa)**.
- In individuals with archived 2-class drug resistance (3 thymidine analogue–associated resistance mutations but no Q151 mutation complex, T69 insertion complex, or DRV resistance mutations), EVG/c/FTC/TAF (Genvoya) combined with DRV taken once daily effectively maintained viral suppression at rates higher than observed in individuals continuing baseline ART **(AIa)**.

- **Updated US Public Health Service Guidelines for the Management Of Occupational Exposures to HIV and Recommendations for Postexposure Prophylaxis (2018)** (*US Public Health Service 2018[a]*)
  - Start PEP medication regimens as soon as possible after occupational exposure to HIV and continue them for a 4-week duration
  - PEP regimens should contain 3 (or more) ARV drugs
  - Preferred PEP regimen: TDF/FTC plus RAL

- **Updated US Public Health Service Guidelines For ARV Postexposure Prophylaxis After Sexual, Injection Drug Use, or Other Non-Occupational Exposure to HIV (2018)** (*US Public Health Service 2018[b]*)
  - A 28-day course of non-occupational post exposure prophylaxis (nPEP) is recommended for HIV-uninfected persons who seek care ≤ 72 hours after a non-occupational exposure to blood, genital secretions, or other potentially infected body fluids of persons known to be HIV infected or of unknown HIV status when that exposure represents a substantial risk for HIV acquisition.
  - Preferred ARV nPEP Regimens
    - Adults and adolescents aged ≥ 13 years, including pregnant women, with normal renal function:
      - 3 drug regimen: TDF/FTC plus RAL or DTG
    - Adults and adolescents aged ≥ 13 years, including pregnant women, with renal dysfunction (creatinine clearance [CrCL]) < 59 mL/min):
      - 3 drug regimen: ZDV/3TC (renally dose adjusted) plus RAL or DTG
    - Children aged 2 to 12 years:
      - 3 drug regimen: TDF/3TC plus RAL
    - Children aged 4 weeks to < 2 years:
      - 3 drug regimen: ZDV/3TC (oral solutions) plus RAL or lopinavir/RTV (oral solutions)

SAFETY SUMMARY

- **Contraindications**
  - Biktarvy, Dovato, Tivicay/Tivicay PD, Triumeq, Juluca
    - BIC and DTG use with dofetilide increases dofetilide concentrations and associated risk for serious and/or life-threatening events.
  - Biktarvy
    - BIC use with rifampin decreases BIC concentrations and loss of therapeutic effect and potential BIC resistance.
  - Genvoya and Stribild
    - COBI use is contraindicated with drugs that are highly dependent on CYP3A for clearance and can cause elevated plasma concentrations or are strong CYP3A inducers and could lead to lower exposure or loss of efficacy.
  - Juluca and Cabenuva
    - RPV use is contraindicated with drugs that may significantly decrease RPV plasma concentrations, resulting in loss of viral response.
  - Triumeq
    - Presence of HLA-B*5701 allele
    - Moderate or severe hepatic impairment
    - Coadministration with dofetilide
  - Vocabria and Cabenuva
    - CAB use contraindicated with carbamazepine, oxcarbazepine, phenobarbital, phenytoin, rifampin, and rifapentine.
- **Boxed Warning**
  - Dovato

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

        - Patients with HIV-1 should be tested for HBV prior to therapy; emergence of 3TC-resistant HBV has occurred with HIV-1 regimens containing 3TC. Additional treatment for HBV should be considered with co-infection with HBV. Severe acute exacerbations of HBV have been reported in individuals who are co-infected with HBV and HIV-1 and have discontinued 3TC.
    - Biktarvy, Genvoya, Stribild
        - Severe acute exacerbations of HBV have been reported in individuals who are co-infected with HBV and HIV-1 and have discontinued FTC, 3TC, and TDF. Monitor hepatic function closely in these individuals and, if appropriate, initiate anti-HBV treatment.
    - Triumeq
        - Hypersensitivity reactions, including serious and sometimes fatal have been reported with multiple organ involvement, with ABC use. Hypersensitivity reactions can occur in any individuals administered ABC; however, those who carry the HLA-B*5701 allele are at a higher risk. Use is contraindicated in individuals with a prior hypersensitivity reaction to ABC and in HLA-B*5701-positive individuals. Discontinue immediately if a hypersensitivity reaction is suspected, and never restart any ABC-containing product.
        - Severe acute exacerbations of HBV have been reported in individuals who are co-infected with HBV and HIV-1 and have discontinued 3TC. Monitor hepatic function closely in these individuals and, if appropriate, initiate anti-HBV treatment.

- **Warnings and Precautions**
    - Tivicay, Tivicay PD, Dovato, Juluca, Triumeq (DTG-based regimens)
        - Severe hypersensitivity reactions with rash, hepatotoxicity, embryo-fetal toxicity (eg, neural tube defects, which may occur when used at the time of conception and in early pregnancy), and immune reconstitution syndrome when treated with combination ARV
        - Pregnancy testing is recommended prior to starting a DTG-containing regimen, as is consistent use of effective contraception for adolescents and adults of child-bearing potential during treatment
        - Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogues (Dovato, Triumeq)
        - Depressive disorders with use of RPV- or DTG-containing regimens (Juluca)
    - Isentress, Isentress HD
        - Severe, potentially life-threatening and fatal skin reactions, immune reconstitution syndrome
        - 100 mg and 25 mg chewable tablets contain phenylalanine
    - Biktarvy
        - Immune reconstitution syndrome, new or worsening renal impairment, lactic acidosis/severe hepatomegaly with steatosis
    - Genvoya
        - Risk of adverse reactions or loss of virologic response due to drug interactions, immune reconstitution syndrome, new or worsening renal impairment, lactic acidosis/severe hepatomegaly with steatosis
    - Stribild
        - Risk of adverse reactions or loss of virologic response due to drug interactions, immune reconstitution syndrome, new or worsening renal impairment (including renal failure and Fanconi syndrome), lactic acidosis/severe hepatomegaly with steatosis, decreases in BMD
    - Vocabria and Cabenuva
        - Hypersensitivity reactions, hepatotoxicity, and depressive disorders
    - Cabenuva
        - Serious post-injection reactions have been reported with RPV
        - Residual concentrations of CAB and RPV may remain in systemic circulation up to 12 months or longer; an alternative, fully suppressive ARV regimen should be initiated no later than 1 month after final injection of Cabenuva

- **Adverse Effects**
    - *Single drug formulations*
        - Isentress/Isentress HD: the most common AEs of moderate to severe intensity (≥ 2%) were insomnia, headache, dizziness, nausea, and fatigue; creatinine kinase elevations have occurred as have myopathy and rhabdomyolysis

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Tivicay/Tivicay PD: the most common AEs of moderate to severe intensity (≥ 2%) were insomnia, fatigue, and headache
- Vocabria: the most common AEs (all grades) were headache, nausea, abnormal dreams, anxiety, and insomnia

○ *Multiple drug formulations*

- Biktarvy: the most common AEs (≥ 5%, all grades) were diarrhea, nausea, and headache.
- Cabenuva: the most common AEs (≥ 2%, all grades) were injection site reactions, pyrexia, fatigue, headache, musculoskeletal pain, nausea, sleep disorders, dizziness, and rash
- Dovato: the most common AEs (≥ 2%, all grades) were headache, diarrhea, nausea, insomnia, and fatigue
- Genvoya: the most common AEs (≥ 10%, all grades) was nausea
- Juluca: the most common AEs (≥ 2%, all grades) were headache and diarrhea
- Stribild: the most common AEs (≥ 10%, all grades) were nausea and diarrhea
- Triumeq: the most common AEs (≥ 2%, all grades) were headache, insomnia and fatigue

- **Key Drug interactions**
  - Drug–drug interactions between ARVs and concomitant medications are common and may lead to increased or decreased drug exposure (DHHS 2021[a]). Consider the potential for drug interactions prior to and throughout ART and refer to package labeling and the DHHS HIV guidelines for steps to prevent or manage possible and known significant drug interactions, including dosing recommendations.
  - *Single drug formulations*
    - Isentress/Isentress HD: drugs that are strong inducers of UGT1A1, such as rifampin, may decrease RAL concentrations
    - Tivicay/Ticivay PD: metabolic inducers may decrease the plasma concentrations of DTG, cation-containing products (eg, laxatives, antiacids, sulcrafate or supplements)
    - Vocabria: drugs that induce UGT1A1 may decrease plasma concentrations of CAB
  - *Multiple drug formulations*
    - Cabenuva: drugs that induce UGT1A1 may decrease plasma concentrations of CAB, drugs with a known risk of Torsade de Pointes
    - Dovato: an additional DTG tablet should be taken 12 hours from the dose of Dovato if it is coadministered with carbamazepine or rifampin
    - Genvoya, Stribild: drugs metabolized by CYP3A or CYP2D6 or drugs that induce CYP3A
    - Juluca: drugs that induce or inhibit CYP3A4 or UGT1A1, drugs that increase gastric pH or contain polyvalent cations, drugs with a known risk of Torsade de Pointes
    - Triumeq: drugs that induce UGT1A1 or CYP3A

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single drug formulations				
Isentress (RAL)	Film-coated tablet Chewable tablet Oral suspension	Oral	Once or twice daily	Can be administered with or without food. Do not substitute chewable tablets or oral suspension for the 400 mg or 600 mg film-coated tablet.
Isentress HD (RAL)	Film-coated tablet	Oral	Once or twice daily	Can be administered with or without food. Do not substitute chewable tablets or oral suspension for

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				the 400 mg or 600 mg film-coated tablet.
Tivicay (DTG)	Tablet	Oral	Once or twice daily	May be taken without regard to food. Perform pregnancy testing before initiation in adolescents and adults of childbearing potential. Do not use oral tablets in patients weighing 3 to 14 kg.
Tivicay PD (DTG)	Tablet for oral suspension	Oral	Once or twice daily	May be taken without regard to food. Do not interchange tablets and tablets for oral suspension on a mg-per-mg basis. Perform pregnancy testing before initiation in adolescents and adults of childbearing potential.
Vocarbia (CAB)	Tablet	Oral	Once daily	Given for approximately 1 month as lead-in dose to Cabenuva, with concurrent RPV. When given as replacement for Cabenuva, start approximately 1 month after last dose of Cabenuva; as daily oral therapy to replace up to 2 consecutive months of injection visits for Cabenuva.
Multiple drug formulations or STRs				
Biktarvy (BIC/FTC/TAF)	Tablet	Oral	Once daily	May be taken without regard to food. Test for HBV infection prior to or when initiating. Renal impairment: Not recommended in patients with CrCL 15 to < 30 mL/min; CrCL < 15 mL/min without hemodialysis; or CrCL < 15 mL/min with no history of antiretroviral therapy.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				On hemodialysis days, administer after hemodialysis. Not recommended in patients with severe hepatic impairment.
Cabenuva (CAB/RPV)	Injection	Intramuscular	Monthly	Initial injections on last day of oral lead-in therapy with Vocarbia plus RPV. Oral therapy with Vocarbia plus RPV should be given for planned missed injection visit by more than 7 days. Administer CAB/RPV as separate gluteal intramuscular injections.
Dovato (DTG/3TC)	Tablet	Oral	Once daily	Test for HBV infection prior to or when initiating. Perform pregnancy testing before initiation in adolescents and adults of childbearing potential. May be taken without regard to food. Renal impairment: not recommended in patients with CrCL < 30 mL/min. Not recommended in patients with severe hepatic impairment.
Genvoya (EVG/c/FTC/TAF)	Tablet	Oral	Once daily	Test for HBV infection prior to or when initiating. For patients weighing ≥ 25 kg and CrCL ≥ 30 mL/min. Can be given to adult patients with CrCL < 15 mL/min if on dialysis; on days of hemodialysis, administer after hemodialysis. Renal impairment: Not recommended in patients with

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				CrCL 15 to 30 mL/min or < 15 mL/min who are not receiving chronic hemodialysis. Not recommended in patients with severe hepatic impairment.
Juluca (DTG/RPV)	Tablet	Oral	Once daily	Take with a meal. Perform pregnancy testing before initiation in adolescents and adults of childbearing potential. Rifabutin coadministration: Take an additional 25 mg tablet of RPV with Juluca once daily with a meal for the duration of the rifabutin coadministration.
Stribild (EVG/c/TFC/TDF)	Tablet	Oral	Once daily	Take with food. Test for HBV infection prior to or when initiating. Renal impairment: Not recommended in patients with CrCL < 70 mL/min. Discontinue if CrCL < 50 mL/min.
Triumeq (DTG/ABC/3TC)	Tablet	Oral	Once daily	May be taken without regard to food. Before initiating, screen for the HLA-B*5701 allele because Truimeq contains ABC. Perform pregnancy testing before initiation in adolescents and adults of childbearing potential. An additional dose of DTG is needed in the presence of UGT1A or CYP3A inducers. Renal impairment: Not recommended in patients with CrCL < 30 mL/min

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Not recommended with hepatic impairment, or in patients that may require dose adjustments.

See the current prescribing information for full details.

CONCLUSION

- Current clinical evidence supports the use of an initial ARV regimen that consists of an INSTI plus 2 NRTIs agent (eg, BIC- or DTG-containing regimens) and are are considered as one of the preferred therapies for treatment-naïve HIV-positive individuals.
- STRs are considered the standard of care and mitigate any potential issues with incomplete or missed dosing that can occur with multiple tablet regimens. Incomplete or missed dosing can result in drug resistance and more costly therapies, so adherence is important in treating HIV and reducing transmission.
- The INSTIs have demonstrated virologic potency, durability, and tolerability in many individuals. The INSTIs are divided into first generation INSTIs, which have a lower genetic barrier to resistance and include RAL and EVG. There is a high level of cross-resistance between RAL and EVG. The second generation INSTIs, which have a higher genetic barrier to resistance and include BIC and DTG. It is uncommon for individuals to develop resistance to the NRTIs that are administered with DTG. BIC has retained activity against certain INSTI-resistant strains vs DTG, but this is usually inconsequential due to infrequent resistance with second generation INSTIs.
- There are currently 5 FDA-approved INSTIs: bictegravir (BIC), cabotegravir (CAB), dolutegravir (DTG), elvitegravir (EVG), and raltegravir (RAL). BIC and EVG are not available as single drug formulations. INSTIs are the only HIV class to include 2-drug STRs, Dovato (DTG/3TC), Cabenuva (CAB/RPV), and Juluca (DTG/RPV). Other 3-drug STR options include Biktarvy (BIC/FTC/TAF), Genvoya (EVG/c/FTC/TAF), Stribild (EVG/c/FTC/TDF), and Triumeq (DTG/ABC/3TC).
  - Cabenuva is the only long-acting HIV-1 formulation available, but also requires the oral lead-in and bridging therapy Vocabria (CAB). Cabenuva is reserved for individuals who are currently virologically suppressed on a stable ARV regimen and no history of treatment failures. Oral Vocabria (CAB) is required as an oral lead-in administered 1 month prior to Cabenuva. Prior to starting CAB, patients should be carefully selected for their ability for adherence and counseled on the importance of adherence to scheduled dosing visits to help maintain viral suppression and reduce the risk of viral rebound and potential development of resistance with missed doses.
    - In May 2021, ViiV Healthcare announced the submission for a NDA for CAB for the treatment of PrEP in transgender women, cisgender men, and cisgender women. The NDA is based on results demonstrating CAB was superior to FTC/TDF in PrEP.
  - Cabenuva, Juluca and Dovato are the only 2-drug regimens considered STRs among all HIV therapeutic classes.
  - Biktarvy, Triumeq, and Dovato are the only STRs guideline-recommended as preferred in treatment-naïve adults.
    - Dovato has exceptions for use as an initial regimen (ie, HIV RNA > 500,000 copies/mL, HBV coinfection, or HIV genotypic resistance testing not available).
    - Triumeq contains ABC and those individuals who carry the HLA-B*5701 allele are at a higher risk for hypersensitivity reactions. Use of Triumeq is contraindicated in individuals with a prior hypersensitivity reaction to ABC and in HLA-B*5701-positive individuals.
  - Stribild, Isentress HD, and Juluca have fewer places in therapy. Genvoya and Stribild are considered alternative STR options for pediatric patients and recommended in certain clinical situations in adults per guidelines. Genvoya may be reserved for patients who have virologic failure as part of a salvage regimen.
- Alternative formulations (chewable tablets and packets for oral suspension) are available for Isentress (RAL). Ticivay PD (DTG) is available as a tablet for oral suspension.
- The INSTIs have demonstrated virologic potency and durability through key clinical trials for many individuals living with HIV. The INSTIs are divided into first generation INSTIs (RAL and EVG), which have a lower genetic barrier, while the second generation INSTIs (BIC, CAB, and DTG) have a higher genetic barrier to resistance.
- RAL is the preferred INSTI agent for children aged < 4 weeks, DTG is the preferred INSTI agent for children aged ≥ 4 weeks to < 6 years, and BIC or DTG are preferred regimen options in children aged ≥ 6 years per the current US perinatal treatment guidelines.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Treatment of individuals living with HIV requires an individualized approach. Management of these complications is constantly evolving. An importance is placed on access in order to manage complications and prevent resistance.

APPENDIX

- **Rating scheme for DHHS 2021 Guidelines for the for the Use of ARV Agents in Adults and Adolescents with HIV** *(DHHS 2021[a])*
  - Rating of Recommendations: A = Strong; B = Moderate; C = Optional
  - Rating of Evidence: I = Data from randomized controlled trials; II = Data from well-designed nonrandomized trials, observational cohort studies with long-term clinical outcomes, relative bioavailability/bioequivalence studies, or regimen comparisons from randomized switch studies; III = Expert opinion
- **Rating scheme for DHHS 2021 Guidelines for the use of ARV Agents in Pediatric HIV Infection** *(DHHS 2021[b])*
  - Rating of Recommendations: A = Strong; B = Moderate; C = Optional
  - Rating of Evidence:I = One or more randomized trials in children with clinical outcomes and/or validated laboratory endpoints; I* = One or more randomized trials in adults, with clinical outcomes and/or validated laboratory endpoints plus accompanying data in children from 1 or more well designed, non-randomized trials or observational cohort studies with long-term clinical outcomes; II = One or more well-designed, nonrandomized trials or observational cohort studies in children with long-term clinical outcomes; II* = One or more well-designed, nonrandomized trials or observational cohort studies in adults with long-term clinical outcomes plus accompanying data in children from 1 or more smaller nonrandomized trials or cohort studies with clinical outcome data; III = Expert opinion
- **Rating scheme for DHHS 2021 Recommendations for the Use of ARV Drugs in Pregnant Women with HIV Infection and Interventions to Reduce Perinatal HIV Transmission in the United States** (DHHS 2021[c])
  - Rating of Recommendations: A = Strong; B = Moderate; C = Optional
  - Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies with long-term clinical outcomes; III = Expert opinion
- **Rating scheme for IAS-USA Panel 2020 Guidelines for Use ARVs in Treatment and Prevention of HIV in Adults (*Saag 2020*)**
  - Rating of Recommendations: A = Strong; B = Moderate; C = Limited or weak
  - Quality of Evidence: Ia = Evidence from ≥ 1 RCTs in peer-reviewed literature; Ib = Evidence from ≥ 1 RCTs presented in abstract form at peer-reviewed meeting; IIa = Evidence from cohort or case-controlled studies published in peer-reviewed literature; IIb = Evidence from cohort or case-controlled studies presented in abstract form at peer-reviewed meeting; III = Based on panel's analysis of available evidence

REFERENCES

- Anderson PL, Yager J, Fletcher CV. Pharmacotherapy: A Pathophysiologic Approach. Chapter 143: Human Immunodeficiency Virus Infection. *New York: McGraw-Hill Medical*, 2020.
- Arribas JR, Thompson M, Sax PE, et al. Brief report: randomized, double-blind comparison of tenofovir alafenamide (TAF) vs tenofovir disoproxil fumarate (TDF), each coformulated with elvitegravir, cobicistat, and emtricitabine (E/C/F) for initial HIV-1 treatment: week 144 results. *J Acquir Immune Defic Syndr*. 2017;75(2):211-218. doi: 10.1097/QAI.0000000000001350.
- Biktarvy [package insert]. Foster City, CA: Gilead Sciences, Inc; May 2021.
- Cabenuva [package insert]. Research Triangle Park: ViiV Healthcare; January 2021.
- Cahn P, Sax PE, Squires K, Molina JM et al. Raltegravir 1200 mg once daily vs 400 mg twice daily, with emtricitabine and tenofovir disoproxil fumarate, for previously untreated hiv-1 infection: week 96 results from ONCEMRK, a randomized, double-blind, noninferiority trial. *J Acquir Immune Defic Syndr*. 2018; 78(5):589-598.
- Cahn P, Madero JS, Arribas JR, et al. Dolutegravir plus lamivudine vs dolutegravir plus tenofovir disoproxil fumarate and emtricitabine in antiretroviral-naive adults with HIV-1 infection (GEMINI-1 and GEMINI-2): week 48 results from two multicentre, double-blind, randomised, non-inferiority, phase 3 trials. *Lancet*. 2019;393(10167):143-155. doi: 10.1016/S0140-6736(18)32462-0.
- Cahn P, Madero JS, Arribas JR, et al. Durable efficacy of dolutegravir plus lamivudine in antiretroviral treatment-naive adults with hiv-1 infection: 96-week results from the Gemini-1 and Gemini-2 randomized clinical trials. *J Acquir Immune Defic Syndr*. 2020;83(3):310-318.
- CDC. HIV Surveillance Report. June 24, 2021. Website. https://www.cdc.gov/hiv/statistics/overview/index.html. Accessed July 12, 2021.
- Clinical Pharmacology. Gold Standard, Inc.; 2021. https://www.clinicalpharmacology.com. Accessed July 12, 2021.
- Cotton MF, Liberty A, Rodriguez CA, et al. Pharmacokinetics, safety, and efficacy of bictegravir/emtricitabine/tenofovir alafenamide (B/F/TAF) single-tablet regimen in children (6 to <12 years) living with HIV-1. Presented at: 22nd International AIDS Conference. Amsterdam, Netherlands; Website: http://www.natap.org/2018/IAC/IAC_39.htm. July 23 to 27, 2018. Accessed July 12, 2021.
- Cruciani M, Parisi SG. Dolutegravir based antiretroviral therapy compared to other combined antiretroviral regimens for the treatment of HIV-infected naive patients: A systematic review and meta-analysis. *PLoS One*. 2019;14(9):e0222229.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- DeJesus E, Rockstroh J, Henry K, et al. Coformulated elvitegravir, cobicistat, emtricitabine and tenofovir disoproxil fumarate vs ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet*. 2012;379:2429–2438.
- DHHS panel on antiretroviral guidelines for adults and adolescents. Guidelines for the use of antiretroviral agents in adults and adolescents living with HIV 2021[a]. Updated June 3, 2021. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/AdultandAdolescentGL.pdf. Accessed July 12, 2021.
- DHHS panel on antiretroviral guidelines for pediatric ARV. Guidelines for the use of antiretroviral agents in pediatric HIV infection. Updated April 7, 2021[b]. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/PedARV_GL.pdf. Accessed July 12, 2021.
- DHHS panel on antiretroviral guidelines for perinatal ARV. Guidelines for the use of antiretroviral drugs in pregnant women with HIV infection and interventions to reduce perinatal HIV transmission in the United States. Updated February 10, 2021[c]. https://clinicalinfo.hiv.gov/sites/default/files/guidelines/documents/Perinatal_GL.pdf. Accessed July 12, 2021.
- Dovato [package insert]. Research Triangle Park, NC: GlaxoSmithKline; March 2021.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed July 12, 2021.
- Facts & Comparisons Website. https://fco.factsandcomparisons.com. Accessed June 29, 2021.
- Fletcher CV. Overview of antiretroviral agents used to treat HIV. UpToDate Website. www.uptodate.com. Updated March 3, 2021. Accessed July 6, 2021.
- Gallant J, Lazzarin A, Mills A, et al. Bictegravir, emtricitabine, and tenofovir alafenamide vs dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection (GS-US-380-1489): a double-blind, multicentre, phase 3, randomised controlled non-inferiority trial. *Lancet* 2017;390(10107):2063-2071. doi: 10.1016/S0140-6736(17)32299-7
- Gaur A, Rodriguez C, McGrath EJ, et al. Bictegravir/FTC/TAF single-tablet-regimen in adolescents: week 24 results. Presented at: Conference on retroviruses and opportunistic infections. http://www.croiconference.org/sessions/bictegravirftctaf-single-tablet-regimen-adolescents-week-24-results. 2018. Boston, Massachusetts. Accessed July 12, 2021.
- Gaur A, Rodriguez C, McGrath EJ, et al. Bictegravir/FTC/TAF single-tablet-regimen in adolescents & children: week 48 results. Presented at: Conference on retroviruses and opportunistic infections. https://www.croiconference.org/sessions/bictegravirftctaf-single-tablet-regimen-adolescents-children-week-48-results. 2019. Seattle, Washington. Accessed July 12, 2021.
- Genvoya [package insert]. Foster City, CA: Gilead Sciences, Inc.; March 2021.
- Isentress [package insert]. Whitehouse station, NJ: Merck and Co, Inc; May 2021.
- Jaeger H, Overton ET, Richmond G, et al. Week 96 efficacy and safety of cabotegravir + rilpivirine every 2 months: ATLAS-2M. [abstract 401]. Conference on Retroviruses and Opportunistic Infections (CROI). March 6 to 10, 2021. Virtual.
- Juluca [package insert]. Research Triangle Park, NC: GlaxoSmithKline; March 2021.
- Lennox JL, DeJesus E, Lazzarin A, et al. Safety and efficacy of raltegravir-based vs efavirenz-based combination therapy in treatment-naive patients with HIV-1 infection: a multicentre, double-blind randomised controlled trial. *Lancet*. 2009;374(9692):796-806.
- Lennox JL, Landovitz RJ, Ribaudo HJ, et al. Efficacy and tolerability of 3 nonnucleoside reverse transcriptase inhibitor-sparing antiretroviral regimens for treatment-naive volunteers infected with HIV-1: a randomized, controlled equivalence trial. *Ann Intern Med*. 2014;161:461-471.
- Lockman S, Brummel SS, Ziemba L, et al. Efficacy and safety of dolutegravir with emtricitabine and tenofovir alafenamide fumarate or tenofovir disoproxil fumarate, and efavirenz, emtricitabine, and tenofovir disoproxil fumarate HIV antiretroviral therapy regimens started in pregnancy (IMPAACT 2010/VESTED): a multicentre, open-label, randomised, controlled, phase 3 trial. *Lancet*. 2021;397(10281):1276-1292. doi: 10.1016/S0140-6736(21)00314-7.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed July 12, 2021.
- Orkin C, DeJesus E, Sax PE, et al. Fixed-dose combination bictegravir, emtricitabine, and tenofovir alafenamide vs dolutegravir-containing regimens for initial treatment of HIV-1 infection: week 144 results from two randomised, double-blind, multicentre, phase 3, non-inferiority trials. *Lancet HIV* 2020[a]. 7(6):e389-e400. doi: 10.1016/S2352-3018(20)30099-0.
- Orkin C, Arasteh K, Górgolas Hernández-Mora M, et al. Long-acting cabotegravir and rilpivirine after oral induction for HIV-1 infection. *N Engl J Med*. 2020[b];382(12):1124-1135. doi:10.1056/NEJMoa1909512.
- Orkin C, Oka S, Philibert P, et al. Long-acting cabotegravir plus rilpivirine for treatment in adults with HIV-1 infection: 96-week results of the randomised, open-label, phase 3 FLAIR study. *Lancet* 2021;8(4):e185-196. doi: 10.1016/S2352-3018(20)30340-4.
- Overton Et, Richmond G, Rizzardini G, et al. Long-acting cabotegravir and rilpivirine dosed every 2 months in adults with HIV-1 infection (ATLAS-2M), 48-week results: a randomised, multicentre, open-label, phase 3b, non-inferiority study. *Lancet*. 2021;396(10267):1994-2005. doi: 10.1016/S0140-6736(20)32666-0.
- Raffi F, Rachlis A, Stellbrink HJ, et al. Once-daily dolutegravir vs raltegravir in antiretroviral-naive adults with HIV-1 infection: 48 week results from the randomised, double-blind, non-inferiority SPRING-2 study. *Lancet*. 2013[a];381:735-743.
- Raffi F, Jaeger H, Quiros-Roldan E, et al. Once-daily dolutegravir vs twice-daily raltegravir in antiretroviral-naive adults with HIV-1 infection (SPRING-2 study): 96 week results from a randomised, double-blind, non-inferiority trial. *Lancet Infect Dis*. 2013[b];13(11):927-935. doi:10.1016/S1473-3099(13)70257-3.
- Rockstroh JK, Lennov JL, DeJesus E, et al. Long-term treatment with raltegravir or efavirenz combined with tenofovir/emtricitabine for treatment-naive human immunodeficiency virus-1-infected patients: 156-week results from STARTMRK. *Clin Infect Dis*. 2011;53(8):807-816. doi:10.1093/cid/cir510.
- Rockstroh JK, DeJesus E, Lennox JL, et al. Durable efficacy and safety of raltegravir vs efavirenz when combined with tenofovir/emtricitabine in treatment-naive HIV-1-infected patients: final 5-year results from STARTMRK. *J Acquir Immune Defic Syndr*. 2013; 63(1):77-85.
- Saag MS, Gandhi RT, Hoy JF, et al. Antiretroviral drugs for treatment and prevention of HIV infection in adults 2020 recommendations of the International Antiviral Society-USA panel. *JAMA*. 2020;324(16):1651-1669. doi:10.1001/jama.2020.17025.
- Sax PE, DeJesus E, Mills A, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir vs co-formulated efavirenz, emtricitabine, and tenofovir for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3 trial, analysis of results after 48 weeks. *Lancet*. 2012;379:2439–2448.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Sax PE, Wohl D, Yin MT, et al. Tenofovir alafenamide vs tenofovir disoproxil fumarate, coformulated with elvitegravir, cobicistat, and emtricitabine, for initial treatment of hiv-1 infection: two randomised, double-blind, phase 3, non-inferiority trials. *Lancet*. 2015;385(9987):2606-2615.
- Sax PE, Pozniak A, Montes M, et al. Coformulated bictegravir, emtricitabine, and tenofovir alafenamide vs dolutegravir with emtricitabine and tenofovir alafenamide, for initial treatment of HIV-1 infection (GS-US-380-1490): a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet*. 2017;390(101007): 2073-2082. doi: 10.1016/S0140-6736(17)32340-1
- Stellbrink H, Arribas J, Stephens JL, et al. Co-formulated bictegravir, emtricitabine, and tenofovir alafenamide vs dolutegravir with emtricitabine and tenofovir alafenamide for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3, non-inferiority trial. *Lancet HIV*. 2019;6(6):e364-372. Doi:10.1016/S2352-3018(19)300800-3.
- Stribild [package insert].]. Foster City, CA: Gilead Sciences, Inc; August 2020.
- Swindells S, Andrade-Villanueva JF, Richmond GJ, et al. Long-acting cabotegravir and rilpivirine for maintenance of HIV-1 suppression. *N Engl J Med*. 2020;382(12):111201123. doi:10.1056/NEJMoa1904398.
- Tivicay [package insert]. Research Triangle Park, NC: GlaxoSmithKline; March 2021.
- Triumeq [package insert]. Research Triangle Park, NC: GlaxoSmithKline; March 2021.
- US Public Health Service. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HIV and recommendations for postexposure prophylaxis. Updated May 23, 2018[a]. Website. https://stacks.cdc.gov/view/cdc/20711. Accessed July 12, 2021.
- US Public Health Service. Updated guidelines for antiretroviral postexposure prophylaxis after sexual, injection drug use, or other nonoccupational exposure to HIV. Updated May 23, 2018[b]. Website. https://stacks.cdc.gov/view/cdc/38856. Accessed July 12, 2021.
- Venter WDF, Sokhela S, Simmons B, et al. Dolutegravir with emtricitabine and tenofovir alafenamide or tenofovir disoproxil fumarate vs efavirenz, emtricitabine, and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection (ADVANCE): week 96 results from a randomised, phase 3, non-inferiority trial. *Lancet HIV*. 2020;7(10):e666-e676. doi: 10.1016/S2352-3018(20)30241-1.
- ViiV Healthcare press release. ViiV Healthcare initiates rolling submission of new drug application with US FDA for long-acting cabotegravir for prevention of HIV. May 4, 2021. https://viivhealthcare.com/en-gb/media/press-releases/2021/may/viiv-healthcare-initiates-rolling/. Accessed August 20, 2021.
- Vocarbia [package insert]. Research Triangle Park, NC: ViiV Healthcare; January 2021.
- van Wyk J, Orkin C, Rubio R, et al. Brief Report: Durable suppression and low rate of virologic failure 3 years after switch to dolutegravir + rilpivirine 2-drug regimen: 148-week results from the SWORD-1 and SWORD-2 randomized clinical trials. *J Acquir Immune Defic Syndr*. 2020;85(3):325-330. doi: 10.1097/QAI.0000000000002449.
- Wohl D, Oka S, Clumeck N, et al. Brief report: a randomized, double-blind comparison of tenofovir alafenamide vs tenofovir disoproxil fumarate, each coformulated with elvitegravir, cobicistat, and emtricitabine for initial HIV-1 treatment week 96 results. *J Acquir Immune Defic Syndr*. 2016;72(1):58-64. doi: 10.1097/QAI.0000000000000940.
- Wohl DA, Yazdanpanah Y, Baumgarten A, et al. Bictegravir combined with emtricitabine and tenofovir alafenamide vs dolutegravir, abacavir, and lamivudine for initial treatment of HIV-1 infection: week 96 results from a randomised, double-blind, multicentre, phase 3,non-inferiority trial. *Lancet HIV*. 2019;6(6):e355-363. doi: 10.1016/S2352-3018(19)30077-3.
- Wood BR. The natural history and clinical features of HIV infection in adults and adolescents. UpToDate Website. www.uptodate.com. Updated March 8, 2021. Accessed July 12, 2021.
- Yang LL, Li Q, Zhou LB, et al. Meta-analysis and systematic review of the efficacy and resistance for human immunodeficiency virus type 1 integrase strand transfer inhibitors. *Int J Antimicrob Agents*. 2019; 54(5):547-555. doi: 10.1016/j.ijantimicag.2019.08.008.
- Zash R, Makhema J, Shapiro R, et al. Neural-tube defects with dolutegravir treatment from the time of conception. *N Engl J Med*. 2018; 379(10):979-981.
- Zash R, Holmes L, Diseko M, et al. Antiretroviral exposure in the Tsepamo Study, Botswana. IAC July 6-10, 2020. https://www.natap.org/2020/IAC/IAC_112.htm. Accessed July 12, 2021.

Date of publication: August 20, 2021

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Prior Authorization Guideline

Guideline Name Targeted Immunomodulators

1. Criteria

Product Name: **Zeposia**	
Diagnosis	Ulcerative Colitis (UC)
Approval Length	12 months

Approval Criteria

1 - Prescribed by or in consultation with a gastroenterologist

AND

2 - Patient has a diagnosis of moderately to severely active ulcerative colitis (UC)

AND

3 - Inadequate response after a 90-day trial of ONE of the following conventional therapies:

- 6-mercaptopurine
- Aminosalicylates (e.g., mesalamine, balsalazide, olsalazine)
- Sulfasalazine
- Azathioprine
- Corticosteroids (i.e., budesonide, high dose steroids: 40-60 mg of prednisone daily)

AND

4 - Patient has tried and failed two preferred immunomodulator therapies indicated for moderately to severely active UC.

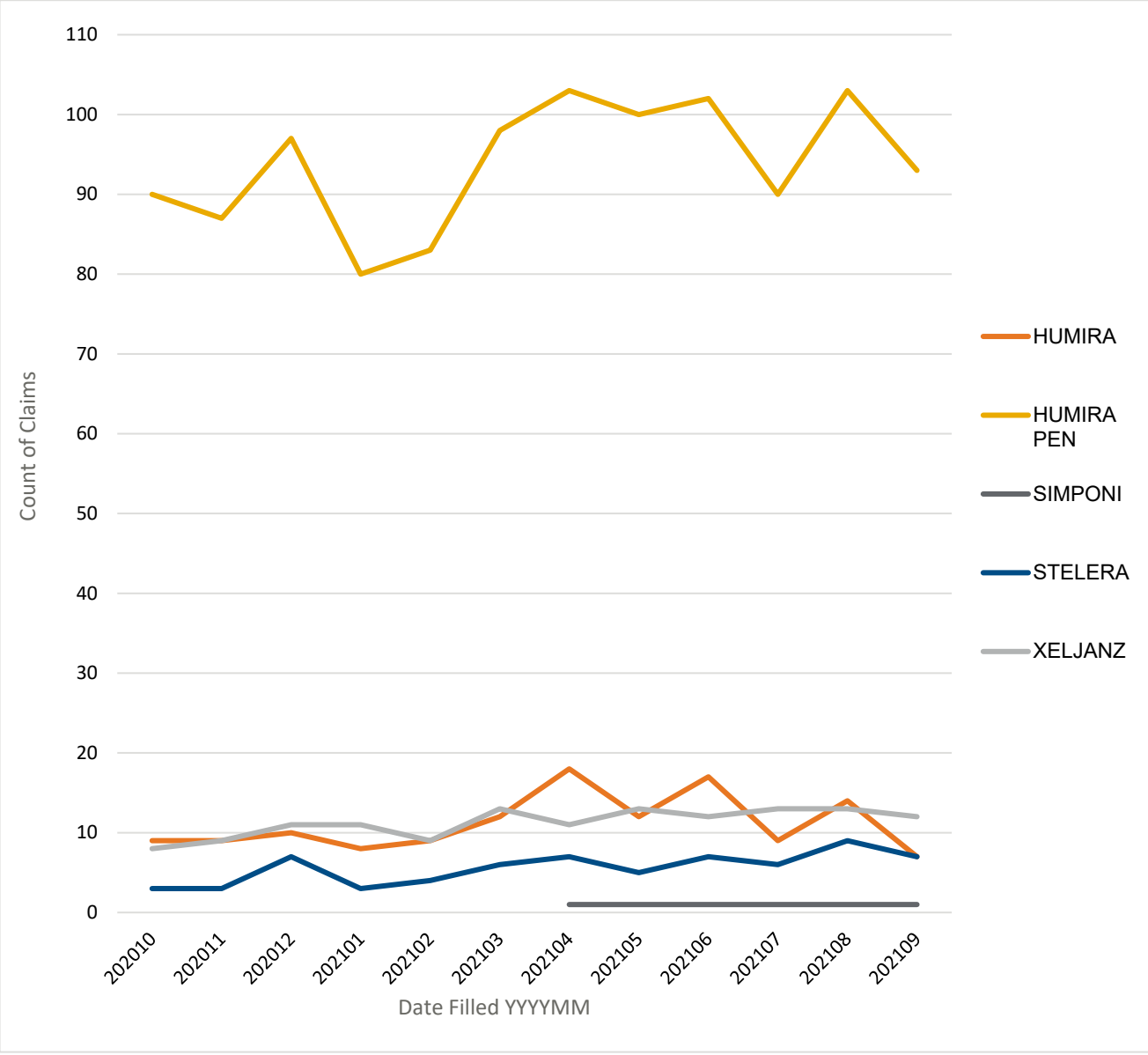
Nevada Medicaid

Utilization

Fee for Service

October 1, 2020 – September 30, 2021

Drug Name	Members	Claims	Total Day Supply	Total Quantity
HUMIRA	23	134	3,884	350
HUMIRA PEN	167	1,126	32,215	2,736
SIMPONI	1	6	180	3
STELERA	21	67	3,623	58
XELJANZ	22	135	4,230	6,150



Therapeutic Class Overview
Inflammatory Bowel Disease Agents

INTRODUCTION

- Inflammatory bowel disease (IBD) is a spectrum of chronic idiopathic inflammatory intestinal conditions that cause gastrointestinal symptoms including diarrhea, abdominal pain, bleeding, fatigue, and weight loss. The exact cause of IBD is unknown; however, proposed etiologies involve a combination of infectious, genetic, and lifestyle factors *(Peppercorn and Cheifetz 2021, Peppercorn and Kane 2020[b]).*
- Complications of IBD include hemorrhage, rectal fissures, fistulas, peri-rectal and intra-abdominal abscesses, and colon cancer. Possible extra-intestinal complications include hepatobiliary complications, anemia, arthritis and arthralgias, uveitis, skin lesions, and mood and anxiety disorders *(Peppercorn and Kane 2020[a], Peppercorn and Kane 2020[b]).*
- Ulcerative colitis (UC) and Crohn's disease (CD) are 2 forms of IBD that differ in pathophysiology and presentation; as a result of these differences, the approach to the treatment of each condition often differs *(Peppercorn and Cheifetz 2021).*
- UC is characterized by recurrent episodes of inflammation of the mucosal layer of the colon. The inflammation, limited to the mucosa, commonly involves the rectum and may extend in a proximal and continuous fashion to affect other parts of the colon. The hallmark clinical symptom is an inflamed rectum accompanied by urgency, bleeding, and tenesmus *(Peppercorn and Kane 2020[b], Rubin et al 2019).*
- CD can involve any part of the gastrointestinal tract and is characterized by transmural inflammation and "skip areas." Transmural inflammation may lead to fibrosis, strictures, sinus tracts, and fistulae *(Peppercorn and Kane 2020[a]).*
- The immune system is known to play a critical role in the underlying pathogenesis of IBD. It is suggested that abnormal responses of both innate and adaptive immunity mechanisms induce aberrant intestinal tract inflammation in IBD patients *(Geremia et al 2014).*
- Precise incidence and prevalence estimates of CD and UC have been limited by a lack of gold standard criteria for diagnosis, inconsistent case ascertainment, and disease misclassification. The existing data suggest that the United States (U.S.) incidence rate of UC varies between 2.2 to 19.2 per 100,000 person-years and the incidence of CD varies from 3.1 to 20.2 per 100,000 person-years. As many as 3 million persons in the U.S. suffer from IBD *(Molodecky et al 2012, Shivashankar et al 2017, Centers for Disease Control and Prevention [CDC] 2021).*
- Some risk factors for IBD include age, gender, race, ethnicity, genetics, smoking status, and dietary considerations (*Peppercorn and Cheifetz 2021*).
  - The typical age of onset of IBD is between 15 and 30 years, while a second peak between ages 50 and 80 years has been noted.
  - Caucasians tend to have a higher incidence of IBD compared to Hispanic and Black populations. Additionally, ethnic and racial differences may be related to environmental and lifestyle factors as well as underlying genetic differences.
  - Smoking status affects CD and UC differently, being associated with an increased risk with CD and a decreased risk with UC.
  - Dietary factors have been associated with risk factors since food antigens are believed to activate an immune response. Although specific pathogenic antigens have not been conclusively identified, intake of animal fat and polyunsaturated fatty acids is associated with an increased risk of developing CD and UC. Vitamin D deficiency is commonly present among patients with IBD.
- Genetic susceptibility to IBD is not completely understood; however, it is estimated that first-degree relatives of patients with IBD are 3 to 20 times more likely to develop IBD compared with the general population (*Snapper et al 2021*).
- The goals of treatment for IBD include resolution of intestinal inflammation and healing of the mucosa; elimination of symptoms while minimizing side effects; maintenance of corticosteroid-free remission; prevention of complications, hospitalization, and surgery; and maintenance of good nutritional status *(Bernstein et al 2015).*
- Current pharmacotherapy for UC includes 5-aminosalicylic acid (5-ASA) derivatives, glucocorticoids, conventional immunomodulators (azathioprine, 6-mercaptopurine [6-MP], and methotrexate), immunomodulator biologic agents (eg, Remicade [infliximab], Humira [adalimumab]), Zeposia (ozanimod: a sphingosine 1-phosphate [S1P] receptor modulator) and Xeljanz (tofacitinib; a small molecule targeting Janus-associated kinase [JAK] pathways) *(Micromedex 2021; Bernstein et al 2015).* Budesonide and injectable biologic agents are also approved for CD (*Lichtenstein et al 2018).*

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

  - Choice of therapy is based on several factors, including disease severity, anatomic extent, response to prior therapies, and prognosis *(Lichtenstein et al 2018, Rubin et al 2019).*
- The oral 5-ASA derivatives include balsalazide, mesalamine, olsalazine, and sulfasalazine; mesalamine is the only 5-ASA derivative that has rectal formulations *(Hashash et al 2021)*. Mesalamine is available in several formulations and is also the active component of balsalazide and olsalazine (*Prescribing information: Colazal 2021, Dipentum 2021)*. The 5-ASA preparations have comparable efficacy to sulfasalazine for the management of IBD but a better tolerability profile. Oral 5-ASAs have not shown differences in safety or efficacy. The choice of treatment agent should be based on indication, disease location, expected patient compliance with the treatment regimen, patient preference, and drug availability *(Cheifetz 2020)*.
- Budesonide (Uceris) is available in an extended-release tablet, which delays the release of budesonide until it reaches the site of action (*Uceris tablet prescribing information 2020)*. Budesonide is also available as a rectal foam (Uceris). Budesonide extended-release capsules (Entocort EC and Ortikos) are approved for the treatment and maintenance of remission of CD. (*Prescribing information: Entocort EC 2020, Ortikos 2019)*. Budesonide rectal foam is indicated for the induction of remission in patients with active mild to moderate distal UC extending up to 40 cm from the anal verge (*Uceris rectal foam prescribing information 2020*).
- Sulfasalazine (Azulfidine EN-tabs) is also Food and Drug Administration (FDA)-approved for the treatment of rheumatoid arthritis nonresponsive to salicylates and nonsteroidal anti-inflammatory drugs (NSAIDs) and for pediatric polyarticular-course juvenile rheumatoid arthritis (*Prescribing information: Azulfidine EN-Tabs 2021)*.
- T cells, B cells, and cytokines such as tumor necrosis factor (TNF), interleukin-1 (IL-1), and interleukin-6 (IL-6) play a key role in the inflammatory and immune process (*Choy et al 2001*). This has led to the development of biologic agents to target these areas. The FDA has currently approved 4 originator TNF inhibitors for IBD indications: Cimzia (certolizumab), Humira (adalimumab), Remicade (infliximab), and Simponi (golimumab). Three infliximab biosimilars are also on the market: Avsola (infliximab-axxq), Inflectra (infliximab-dyyb), and Renflexis (infliximab-abda). Other immunomodulators targeting different cells and cytokines in the inflammatory and immune process are also FDA-approved for IBD indications: Entyvio (vedolizumab) targets α4β7 integrin, preventing leucocyte translocation from the blood into the inflamed gut tissue, and Stelara (ustekinumab) targets the IL-12 and IL-23 cytokines (*Prescribing information: Entyvio 2020, Stelara 2020*).
- Two oral immunomodulators for UC are also on the market. Xeljanz/Xeljanz XR (tofacitinib) targets JAK pathways, reducing the ability of cytokines to produce inflammation (*Xeljanz/Xeljanz XR prescribing information 2020)*. Zeposia (ozanimod) is an S1P receptor modulator that also has an approval for multiple sclerosis (MS) *(Zeposia prescribing information 2021).* S1P receptor agonism is a novel strategy for the treatment of UC that targets lymphocyte recirculation by preventing lymphocytes from exiting the lymph nodes and circulating to the intestinal tissue.
- Tysabri (natalizumab), an integrin receptor antagonist, is approved for CD for patients who have had an inadequate response to, or are unable to tolerate conventional therapies and TNF inhibitors; because of its safety concerns, it is not included as a drug product in this review (*Tysabri prescribing information 2020*).Tysabri is included in the MS review.
- The scope of this review will focus upon the oral, topical, and injectable agents outlined in Table 1 for their respective FDA-approved, gastrointestinal-related indications.
- Medispan Therapeutic Class: Inflammatory Bowel Agents

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Oral	
Apriso (mesalamine) ER capsule	✔
Asacol HD (mesalamine) DR tablet	✔
Azulfidine (sulfasalazine) tablet	✔
Azulfidine EN-tabs (sulfasalazine) DR tablet	✔
Colazal (balsalazide) capsule	✔
Delzicol (mesalamine) DR capsule	✔
Dipentum (olsalazine) capsule	-
Entocort EC (budesonide) DR capsule	✔
Lialda (mesalamine) DR tablet	✔
Ortikos (budesonide) ER capsule	-

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Drug	Generic Availability
Pentasa (mesalamine) CR capsule	-
Uceris (budesonide) ER tablet	✔
Xeljanz/ Xeljanz XR (tofacitinib) tablet, ER tablet, oral solution	-
Zeposia (ozanimod) capsule	-
Topical	
Canasa (mesalamine) rectal suppository	✔
Rowasa (mesalamine) rectal enema suspension	✔
sfRowasa (mesalamine) rectal enema suspension (sulfite-free)	-
Uceris (budesonide) rectal foam	-
Injectable	
Avsola (infliximab-axxq) injection	N/A*
Cimzia (certolizumab) injection	-
Entyvio (vedolizumab) injection	-
Humira (adalimumab) injection	-
Inflectra (infliximab-dyyb) injection	N/A*
Remicade (infliximab) injection	-
Renflexis (infliximab-abda) injection	N/A*
Simponi (golimumab) injection	-
Stelara (ustekinumab) injection	-

CR = controlled release, DR = delayed release, EC = enteric coated, ER = extended release, N/A = not applicable.
*Inflectra (infliximab-dyyb), Renflexis (infliximab-abda), and Avsola (infliximab-axxq) have been FDA-approved as biosimilar agents to Remicade (infliximab). None of these agents are FDA-approved as an interchangeable biologic.

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

INDICATIONS

Table 2. FDA Approved Indications for Oral and Topical Agents for IBD

Indication	Balsalazide	Budesonide	Mesalamine	Olsalazine	Ozanimod	Sulfasalazine	Tofacitinib
Treatment of mild to moderate active CD involving the ileum and/or the ascending colon in patients ≥ 8 years of age		✔ (Entocort EC; Ortikos)					
Treatment of mildly to moderately active UC in patients ≥ 5 years of age	✔ (Colazal)†		✔ (Delzicol)				
Treatment of moderately active UC in adults			✔ (Asacol HD)*				
Induction of remission in adults with		✔ (Uceris tablet)	✔ (Lialda)				

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

active, mild to moderate UC							
Induction of remission in adults with active mild to moderate distal UC extending up to 40 cm from the anal verge		✔ (Uceris rectal foam)					
Maintenance of remission of mild to moderate CD involving the ileum and/or ascending colon for up to 3 months in adults		✔ (Entocort EC; Ortikos)***					
Maintenance of remission of UC in adults			✔ (Apriso; Delzicol; Lialda)				
Maintenance of remission of UC in patients who are intolerant of sulfasalazine				✔			
Induction of remission and for the treatment of patients with mildly to moderately active UC			✔ (Pentasa)				
Treatment of mildly to moderately active ulcerative proctitis			✔ (Canasa)				
Treatment of active mild to moderate distal UC, proctosigmoiditis or proctitis			✔ (Rowasa; sfRowasa)				
Treatment of mildly to moderately active UC in pediatric patients weighing at least 24 kg			✔ (Lialda)				
Treatment of mild to moderate UC,						✔ (Azulfidine;	

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

and as adjunctive therapy in severe UC						Azulfidine EN-tabs**)	
Prolongation of the remission period between acute attacks of UC						✔ (Azulfidine; Azulfidine EN-tabs**)	
Treatment of moderately to severely active UC					✔		✔ ††
Treatment of patients with rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs (eg, an insufficient therapeutic response to, or intolerance of, an adequate trial of full doses of 1 or more NSAIDs)						✔ (Azulfidine EN-tabs)	
Treatment of pediatric patients with polyarticular-course juvenile rheumatoid arthritis who have responded inadequately to salicylates or other NSAIDs						✔ (Azulfidine EN-tabs)	

*Safety and effectiveness of Asacol HD beyond 6 weeks have not been established.
**Azulfidine EN-tabs are specifically indicated in patients with UC who cannot tolerate sulfasalazine tablets due to gastrointestinal intolerance when the gastrointestinal intolerance is not primarily due to high blood levels of sulfapyridine and its metabolites.
***Taper to complete cessation after 3 months; continued treatment for more than 3 months has not been shown to provide substantial clinical benefit.
†Safety and effectiveness of balsalazide beyond 8 weeks in children (ages 5 to 17 years) and 12 weeks in adults have not been established.
††For use in patients with inadequate response to TNF inhibitors. The use of tofacitinib in combination with biological therapies for UC or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.

(Prescribing information: Apriso 2020, Asacol HD 2020, Azulfidine 2021, Azulfidine EN-Tabs 2021, Canasa 2020, Colazal 2021, Delzicol 2020, Dipentum 2021, Entocort EC 2020, Lialda 2021, Ortikos 2019, Pentasa 2021, Rowasa 2021, sfRowasa 2020, Uceris tablet 2020, Uceris rectal foam 2020, Xeljanz/Xeljanz XR 2020, Zeposia 2021)

Table 3. FDA Approved Indications for Injectable Agents for IBD

Indication*	Humira (adalimumab)	Cimzia (certolizumab)	Simponi (golimumab)	Remicade (infliximab); Avsola	Stelara (ustekinumab)	Entyvio (vedolizumab)

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

				(infliximab-axxq); Inflectra (infliximab-dyyb); Renflexis (infliximab-abda)		
CD: treatment of moderately to severely active disease	✔ (6 years and older)				✔	✔
CD: reducing signs and symptoms and maintaining clinical response in patients with moderately to severely active disease who have had an inadequate response to conventional therapy		✔		✔ (6 years and older)		
CD: reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing disease				✔		
UC: treatment of moderately to severely active disease	✔ † (5 years and older)		✔ ‡		✔	✔
UC: reducing signs and symptoms and inducing and maintaining clinical remission in patients with moderately to severely active disease who have had an inadequate response to				✔ § (6 years of age and older)		

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

conventional therapy						

*Indications are for adult patients unless otherwise noted.
†Effectiveness has not been established in patients who have lost response to or were intolerant to TNF inhibitors.
‡ Simponi (golimumab) is indicated in adult patients with moderately to severely active UC who have demonstrated corticosteroid dependence or who have had an inadequate response to or failed to tolerate oral aminosalicylates, oral corticosteroids, azathioprine, or 6-MP for inducing and maintaining clinical response, improving endoscopic appearance of the mucosa during induction, inducing clinical remission, and achieving and sustaining clinical remission in induction responders.
§In the setting of UC in adults, infliximab products are also indicated for inducing and maintaining mucosal healing and eliminating corticosteroid use.

(Prescribing information: Avsola 2019, Cimzia 2019, Entyvio 2020, Humira 2021, Inflectra 2021, Remicade 2020, Renflexis 2021, Simponi 2019, Stelara 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

Oral therapy

- Multiple systematic reviews have been published evaluating randomized clinical trials of mesalamine products for UC. No significant differences in safety or efficacy between the mesalamine products have been found in the systematic reviews.
  - In a 2013 Cochrane review of 17 randomized clinical trials (N = 2925), the efficacy and safety of oral mesalamine products used for induction and maintenance of remission of UC were evaluated. The primary outcomes were failure to induce global or clinical remission or improvement, and failure to maintain global or clinical remission (relapse). Products included balsalazide, olsalazine, Pentasa, Asacol, Lialda, and 3 mesalamine products which are not available in the U.S. For the endpoint of failure to induce global or clinical remission in mild to moderately active UC, there was no significant difference between the 5-ASA formulations (balsalazide, Pentasa, olsalazine, Lialda, mesalamine, and 5-ASA micropellets) and the comparator group (Asacol and 2 mesalamine formulations) (11 studies, N = 1968, 50% vs 52%, pooled relative risk [RR] 0.94, 95% confidence interval [CI], 0.86 to 1.02, $I^2 = 0\%$, p = 0.11). For failure to induce global or clinical remission or improvement, a total of 8 studies with 1647 patients were evaluated, and results demonstrated that there was no difference between the 5-ASA products (balsalazide, Pentasa, olsalazine, Lialda, and 5-ASA micropellets) and the 5-ASA comparators (Asacol, 2 mesalamine formulations, and Pentasa) (30% vs 35%, pooled RR 0.89, 95% CI, 0.77 to 1.01, $I^2 = 0\%$, p = 0.08) using a fixed-effects model. Note that Pentasa was on both sides of the comparison for this endpoint. For the failure to maintain global or clinical or endoscopic remission at 12 months, there was no difference between the 5-ASA formulations (balsalazide, Pentasa, and olsalazine) and the comparators (Asacol, mesalamine) in 5 studies (N = 457) (38% vs 37%, pooled RR 1.01, 95% CI, 0.80 to 1.28, $I^2 = 39\%$, p = 0.95). The incidences of adverse events (AEs) between the various formulations were not significantly different. Risk of bias was low for most study factors; however, 1 study was single-blind, and 3 were open-label. There were numerous products in this systematic review which are not currently available in the U.S. *(Feagan et al 2013[a]).*
  - A 2020 Cochrane review of 54 studies with 9612 patients with UC evaluated oral 5-ASA preparations for the induction of active UC remission. The newer 5-ASA derivatives were “superior” to placebo with 71% of 5-ASA patients failing to enter clinical remission compared to 83% for placebo (11 studies; N = 2387; RR 0.86, 95% CI, 0.82 to 0.89). No statistically significant differences in efficacy between 5-ASA and sulfasalazine were observed, with 54% of 5-ASA-treated patients and 58% of sulfasalazine-treated patients failing to enter remission (8 studies; N = 526; RR 0.90, 95% CI, 0.77 to 1.04). Adherence did not appear to be enhanced by once daily dosing in the clinical trials; however, it is not known if once daily dosing would improve adherence in the community setting. Failure to enter clinical remission rates were 60% for once daily vs 61% for conventional dosing regimens (5 studies; N = 1761; RR 0.99, 95% CI, 0.93 to 1.06). No significant differences among the 5-ASA products for safety and efficacy were found (*Murray et al 2020[a]*).
  - In a 2020 Cochrane review of 44 studies with 9967 patients, 5-ASA formulations were more effective than placebo for maintenance of clinical or endoscopic remission of UC. Relapse rates were 37% for 5-ASA-treated patients and 55% for placebo-treated patients (8 studies; N = 1555; RR 0.68, 95% CI, 0.6 to 0.76). Sulfasalazine was found to have a statistically significant benefit over 5-ASA in the maintenance of UC when looking at all trials at study endpoint (12 studies; N = 1655; RR 1.14, 95% CI, 1.03 to 1.27); however, when only trials of 12 months or longer were evaluated, there was no longer a difference between sulfasalazine and 5-ASA (8 studies; N = not reported; RR 1.10, 95% CI,

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

0.98 to1.23). No significant difference in efficacy was demonstrated between once daily and conventional dosing regimens; 37% of once daily-treated patients relapsed over 12 months vs 39% of conventionally dosed patients (10 studies; N = 3910; RR 0.91, 95% CI, 0.88 to 1.01). No significant difference in efficacy was found when comparing the various 5-ASA formulations. Relapse rate was 44% in the 5-ASA group vs 41% in the 5-ASA comparator group (6 studies; N = 707; RR 1.08, 95% CI, 0.91 to 1.28). No statistically significant differences were found for the incidence of AEs between 5-ASA and placebo, 5-ASA and sulfasalazine, once daily and conventionally dosed 5-ASA, and 5-ASA and comparator 5-ASA formulations *(Murray et al 2020[b]).*

- A network meta-analysis evaluated the comparative efficacy and tolerability of agents used to treat mild to moderate UC. The analysis included 75 trials (12,215 patients) that evaluated either sulfasalazine, diazo-bonded 5-ASA, mesalamine, or budesonide, alone or in combination with rectal 5-ASA therapy. Agents were ranked using surface under the cumulative ranking curve (SUCRA) probabilities. For the induction of remission, combined oral and rectal 5-ASAs (SUCRA, 0.99) and high-dose mesalamine (> 3 g/day; SUCRA, 0.82) were the highest ranked therapies; both were also found to be superior to standard-dose mesalamine. For the maintenance of remission, all therapies were found to be superior to placebo, but high-dose mesalamine was not superior to standard-dose mesalamine (*Nguyen et al 2018*).
- Another systematic review evaluated once daily oral mesalamine compared to conventional dosing regimens of oral mesalamine for induction and maintenance of remission of UC in 11 studies with 4070 patients. Of the 11 studies, 5 studies were single-blind, and 1 study was performed in an open-label manner. Products assessed were Lialda, Asacol, Pentasa, and Salofalk (mesalazine - not available in the U.S.). Failure to induce global or clinical remission was not different between once daily and conventional dosing of mesalamine (3 studies, N = 738; pooled RR 0.95, 95% CI, 0.82 to 1.10; I^2 = 0%). No difference was observed between dosing regimens in failure to maintain global or clinical remission at 12 months (5 studies, N = 1394; pooled RR 0.92, 95% CI, 0.83 to 1.03, I^2 = 40.9%). Rates of medication adherence or AEs between once daily and conventional dosing regimens of mesalamine were not significantly different. The authors noted that adherence rates in clinical trials may be higher than real world usage *(Feagan & MacDonald 2012).*
- A meta-analysis of 10 studies that evaluated mesalamine once daily vs multiple daily dosing regimens in 3410 patients with quiescent UC was conducted to determine the efficacy in preventing a relapse. The intention to treat analysis found that mesalamine once daily (26.3%) was as effective as multiple daily doses (26.5%) (8 studies, RR 1.00, 95% CI, 0.89 to 1.12, I^2 = 41%, p = 0.105). An analysis of the efficacy of once daily vs multiple daily dosing of mesalamine for inducing remission in active UC found that remission was not observed in 29.8% of patients on once daily mesalamine and 37.8% of patients receiving multiple daily doses. The risk of failure to achieve remission was higher with multiple daily doses (2 studies, RR 0.80, 95% CI, 0.64 to 0.99, I^2 = 21.6%, p = 0.259). When evaluating the same outcome on a per-protocol analysis, there was no significant difference between the 2 groups. No significant differences in AEs were observed between the 2 groups *(Tong et al 2012).*
- In another 2012 meta-analysis, 9 of 10 studies included in the Tong et al analysis were evaluated by another group *(Zhu et al 2012).* There were no significant differences for once daily compared to more frequent dosing (twice or 3 times daily) of mesalamine for UC for the maintenance of clinical remission, endoscopic remission, maintenance of combined clinical and endoscopic remission, and the overall incidence of AEs.

- A Cochrane review evaluated oral budesonide for induction of remission in UC. A total of 6 studies (N = 1808) were evaluated. Budesonide multi-matrix (MMX) (Uceris) 9 mg was superior to placebo for inducing remission at 8 weeks (15% vs 7%, respectively; 3 studies, N = 900; RR 2.25, 95% CI, 1.50 to 3.39; moderate quality of evidence). An analysis of 2 studies with budesonide MMX 6 mg showed that it was not superior to placebo for induction of remission (11% vs 6%, respectively; 2 studies, N = 440; RR 1.80, 95% CI, 0.94 to 3.42; low quality of evidence). Budesonide (Entocort EC) was significantly less likely to induce clinical remission than oral mesalamine after 8 weeks (1 study, N = 343; RR 0.72, 95% CI, 0.57 to 0.91; moderate quality of evidence). However, another study found no difference in remission rates between budesonide MMX 9 mg and mesalamine (1 study; N = 247; RR 1.48, 95% CI, 0.81 to 2.71; low quality of evidence). In a comparison of the 2 budesonide formulations, there was no difference in remission rates between budesonide MMX 9 mg and budesonide 9 mg (1 study, N = 212; RR 1.38, 95% CI, 0.72 to 2.65; low quality of evidence) *(Sherlock et al 2015).*
- A network meta-analysis of 15 trials compared oral budesonide MMX to oral mesalamine in 4083 patients with mild-to-moderate UC. Budesonide MMX 9 mg/day and mesalamine > 2.4 g/day showed no statistically significant difference for induction of remission, but mesalamine had a better safety profile (*Bonovas et al 2019*).
- A Cochrane review of 14 trials compared the efficacy and safety of oral 5-ASA agents to placebo, no treatment, or any other active treatment for maintenance of surgically-induced remission in CD (N = 1867). Patients receiving 5-ASA had lower rates of relapse during a follow-up period of 12 to 72 months compared with placebo (36% vs 43%, respectively;

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

RR 0.83, 95% CI, 0.72 to 0.96; I^2 = 0%; moderate certainty evidence). At 12 months, 17% (17/101) of the 4 g/day mesalamine group relapsed compared to 26% (27/105) of the 2.4 g/day group (RR 0.65, 95% CI, 0.38 to 1.13; moderate certainty evidence). During a follow-up period of 18 to 36 months, sulfasalazine and placebo showed no statistically significant difference in the relapse rate. Adverse event rates were similar between 5-ASA and placebo or biologics (*Gjuladin-Hellon et al 2019*).

- Two Cochrane reviews have evaluated oral budesonide for induction and maintenance of remission in CD.
  - For induction of remission, budesonide was found to be superior to placebo at 8 weeks (47% vs 22%, respectively; 3 studies, N = 379; RR 1.93, 95% CI, 1.37 to 2.73; moderate quality of evidence). Budesonide was found to be significantly less effective than conventional steroids (52% vs 61%, respectively; 8 studies, N = 750; RR 0.85, 95% CI, 0.75 to 0.97; moderate quality of evidence), but treatment with budesonide resulted in significantly fewer AEs (RR 0.64, 95% CI, 0.54 to 0.76) (*Rezaie et al 2015*).
  - For maintenance of remission, budesonide 6 mg daily was not found to be more effective than placebo at 3, 6, or 12 months. The authors concluded that budesonide is not effective for maintenance of remission in CD, particularly when used longer than 3 months following the induction of remission (*Kuenzig et al 2014*).
- A multicenter, randomized, double-blind study established the effectiveness of Lialda (mesalamine) in patients aged 5 to 17 years weighing ≥ 24 kg with mildly to moderately active UC. This study was conducted in 2 phases, with 53 patients in the first phase and 87 patients in the second phase. During each phase, patients were randomized to receive a low or a high weight-based dosage. The primary endpoint for both phases was partial UC Disease Activity Index score ≤ 1 with rectal bleeding equal to 0, stool frequency ≤ 1, and Physician's Global Assessment (PGA) score equal to 0. In the initial 8-week phase, the primary endpoint was achieved in 65.4% of patients receiving the high weight-based dose compared to 37.0% of patients receiving the low weight-based dose. Fewer patients in the high weight-based dose group discontinued the drug due to UC (0/26 [0%] patients vs 8/27 [30%] patients in the low weight-based dose group). During the second 26-week phase, the primary endpoint was achieved in 54.8% of low weight-based dose patients and 53.3% of high weight-based dose patients (*ClinicalTrials.gov Web site, Lialda prescribing information 2021*).
- The efficacy and safety of Zeposia (ozanimod) were evaluated in 2 multicenter, double-blind, placebo-controlled, randomized trials in adult patients with moderately to severely active UC (*Zeposia prescribing information 2021)*. In the trials, patients were randomized to oral ozanimod 0.92 mg daily or placebo. All patients received an initial dose escalation of ozanimod or placebo prior to receiving their assigned dose on day 8. Patients with moderately or severely active UC were included if they had an inadequate response or were intolerant to previous therapies, including oral aminosalicylates, corticosteroids, immunomodulators, or biologic agents. In UC Study 1, patients (N = 645) received induction treatment for 10 weeks. In UC Study 2, patients who achieved a clinical response in UC Study 1 or an open-label arm at week 10 (N = 457) were re-randomized to maintenance treatment with ozanimod or placebo for 42 additional weeks (52 weeks total). Use of corticosteroids or aminosalicylates was allowed in UC Study 1, while patients had to be tapered from corticosteroids for entry into UC Study 2. The primary endpoint was clinical remission at week 10 in UC Study 1 and at 52 weeks in UC Study 2. Clinical remission was defined as a 3-component Mayo score (without the physician global assessment), which included the rectal bleeding subscore, stool frequency subscore, and endoscopy subscore.
  - In UC Study 1, clinical remission was achieved by 18% with ozanimod and 6% of patients with placebo at 10 weeks (treatment difference 12%, 95% CI, 8 to 17%; $p < 0.0001$). In addition, the following secondary endpoints were improved with ozanimod vs placebo, respectively: clinical response (48% vs 26%; $p < 0.0001$), endoscopic improvement (27% vs 12%; $p < 0.0001$), and endoscopic-histologic mucosal improvement (13% vs 4%; $p < 0.001$).
  - In UC Study 2, clinical remission was achieved by 37% of patients with ozanimod and 19% of patients with placebo at 52 weeks (treatment difference 19%, 95% CI, 11 to 26%). In addition, the following secondary endpoints were improved with ozanimod vs placebo, respectively: clinical response (60% vs 41%; $p < 0.0001$), endoscopic improvement (46% vs 26%; $p < 0.0001$), corticosteroid-free clinical remission (32% vs 17%; $p < 0.001$), and endoscopic-histologic mucosal improvement (30% vs 14%; $p < 0.001$).
- The efficacy of Xeljanz (tofacitinib) for UC was evaluated in two 8-week induction trials followed by a 52-week maintenance trial. In the induction trials, patients were assigned to tofacitinib 10 mg twice daily or placebo (*Sandborn et al 2017*). At week 8, remission occurred in 18.5% vs 8.2% of patients in the tofacitinib and placebo groups, respectively, in the OCTAVE 1 trial and 16.6% vs 3.6% of patients in the tofacitinib and placebo groups, respectively, in the OCTAVE 2 trial. In the OCTAVE Sustain maintenance trial, patients who achieved a clinical response were continued on either tofacitinib 5 mg, tofacitinib 10 mg, or placebo. At week 52, remission occurred in 34.3%, 40.6%, and 11.1% of patients in the tofacitinib 5 mg, tofacitinib 10 mg, and placebo groups, respectively.

Topical therapy

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- According to a meta-analysis of 38 studies comparing rectal 5-ASA therapy to either placebo or other active agents for the treatment of active distal UC, rectal 5-ASA was superior to placebo and rectal corticosteroids for inducing symptomatic improvement and remission. Rectal 5-ASA was not superior to oral 5-ASA for symptomatic improvement. *(Marshall et al 2010).* A 2012 smaller meta-analysis found that rectal 5-ASA therapy was superior to placebo and similar to oral 5-ASA on rates of symptomatic remission and endoscopic remission. No dose response relationship for 5-ASA enemas or other rectal dosage forms has been observed *(Marshall et al 2012).*
- A meta-analysis of 7 trials of patients with quiescent UC (3 trials of patients with disease confined to the rectum, 1 of patients with proctitis or proctosigmoiditis, 2 of patients with left-sided colitis only, and 1 which also included patients with extensive disease) found greater efficacy with topical mesalamine than placebo for the prevention of relapse, with a number needed to treat (NNT) of 3. Time to relapse was longer with topical mesalamine in the 2 trials, and there was a trend toward a greater effect size with continuous topical therapy compared to intermittent therapy *(Ford et al 2012).*
- Budesonide rectal foam was compared to placebo in 2 randomized, phase 3 trials in patients with mild to moderate ulcerative proctitis or ulcerative proctosigmoiditis. Compared to placebo, a significantly greater proportion of patients receiving budesonide rectal foam experienced remission, resolution of rectal bleeding, and endoscopic improvement at week 6 ($p < 0.05$ for all comparisons in both trials) *(Sandborn et al 2015).* Additionally, in a randomized, phase 3 trial in patients with mild to moderate UC with distal active inflammation, significantly more patients who received budesonide rectal foam experienced clinical remission and complete mucosal healing of distal lesions compared to placebo ($p = 0.0035$ and $p = 0.0003$, respectively) *(Naganuma et al 2017).*
- A meta-analysis of 74 studies showed that the highest induction of histologic remission rates for UC was with topical 5-ASA (37.2%; 95% CI, 29.0 to 46.3) and 5-ASA suppositories (44.9%; 95% CI, 28.9 to 62.3). Compared with placebo, 5-ASA enemas (RR 4.14; 95% CI, 2.35 to 7.31), 5-ASA suppositories (RR 3.94; 95% CI, 1.26 to 12.32), and budesonide MMX (RR 3.94; 95% CI, 1.26 to 12.32) had higher histologic remission rates (*Battat et al 2019*).

Oral vs topical mesalamine

- A meta-analysis of 63 clinical trials (40 for induction and 23 for maintenance) of 5-ASA in patients with UC found topical 5-ASA or the combination of oral and topical 5-ASA to be superior to oral 5-ASA for induction of remission. However, combination therapy or high-dose oral therapy was more efficacious than topical therapy for maintenance treatment *(Barberio et al 2021).*

Injectable therapy for CD

- In a trial evaluating Remicade (infliximab) for induction of remission, significantly more patients achieved remission at 4 weeks with infliximab compared to placebo ($p < 0.005$) (*Targan et al 1997*). In a placebo-controlled trial, significantly more patients treated with infliximab 5 and 10 mg/kg had a reduction ≥ 50% in the number of fistulas compared to patients treated with placebo ($p = 0.002$ and $p = 0.02$, respectively) (*Present et al 1999*). In an open-label trial evaluating the use of infliximab in pediatric CD patients, 88.4% responded to the initial induction regimen, and 58.6% were in clinical remission at week 10 (*Hyams et al 2007*). More recently, an international, randomized, double-blind, phase 3, study revealed biosimilar infliximab (Inflectra) to be non-inferior to infliximab in patients with active CD with similar response rates (*Ye et al 2019*).
- The safety and efficacy of Entyvio (vedolizumab) was demonstrated in 2 trials of CD in patients who responded inadequately to immunomodulator therapy, TNF inhibitors, and/or corticosteroids. In 1 trial, a significantly higher percentage of vedolizumab-treated patients achieved clinical response and remission at week 52 compared to placebo. In the second trial, in patients with prior TNF antagonist failure, the primary endpoint of proportion of patients in clinical remission at week 6 was not met (15.2% for vedolizumab vs 12.1% for placebo; $p = 0.433$). However, in a secondary analysis, greater proportions of vedolizumab-treated patients than placebo-treated patients were in clinical remission at week 10 (26.6% vs 12.1%; $p = 0.001$) (*Sandborn et al 2013, Sands et al 2014*).
- A meta-analysis evaluating Cimzia (certolizumab) use over 12 to 26 weeks for the treatment of CD demonstrated that the agent was associated with an increased rate of induction of clinical response (RR, 1.36; $p = 0.004$) and remission (RR, 1.95; $p < 0.0001$) over placebo. However, risk of infection was higher with certolizumab use (*Shao et al 2009*).
- Additionally, Humira (adalimumab), Cimzia (certolizumab) and Remicade (infliximab) demonstrated the ability to achieve clinical response (RR, 2.69; $p < 0.00001$; RR, 1.74; $p < 0.0001$ and RR, 1.66; $p = 0.0046$, respectively) and maintain clinical remission (RR, 1.68; $p = 0.000072$ with certolizumab and RR, 2.5; $p = 0.000019$ with infliximab; adalimumab, data not reported) over placebo in patients with CD. Adalimumab and infliximab also had a steroid-sparing effect (*Behm et al 2008*). Other systematic reviews have further demonstrated the efficacy of these agents in CD (*Singh et al 2014, Fu et al 2017*). In a 2021 meta-analysis by Wu et al that included 29 RCTs, infliximab and adalimumab were superior to certolizumab pegol and tofacitinib for induction of remission in CD (*Wu et al 2021*).

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- In a systematic review of patients with CD who had failed a trial with Remicade (infliximab), the administration of Humira (adalimumab) was associated with remission rates of 19% to 68% at 1 year. Serious cases of sepsis, cellulitis, and fungal pneumonia occurred in 0% to 19% of patients in up to 4 years of treatment (*Ma et al 2009*).
- The use of Stelara (ustekinumab) for the treatment of CD was evaluated in the UNITI-1, UNITI-2, and IM-UNITI studies (*Feagan et al 2016*). All were Phase 3, double-blind, placebo-controlled trials.
  - UNITI-1 (n = 741) was an 8-week induction trial that compared single IV doses of ustekinumab 130 mg IV, weight-based ustekinumab (~6 mg/kg), and placebo in patients with nonresponse or intolerance to ≥ 1 TNF inhibitors. The primary endpoint was clinical response at week 6, which was defined as a decrease from baseline in the clinical disease activity index (CDAI) of ≥ 100 points or a CDAI score of < 150. A clinical response was achieved by 34.4%, 33.7%, and 21.5% of patients in the ustekinumab 130 mg, weight-based ustekinumab, and placebo groups, respectively (p = 0.002 for 130 mg dose vs placebo; p = 0.003 for weight-based dose vs placebo). Benefits were also demonstrated on all major secondary endpoints, which included clinical response at week 8, clinical remission (CDAI < 150) at week 8, and CDAI decrease of ≥ 70 points at weeks 3 and 6.
  - UNITI-2 (n = 628) had a similar design to UNITI-1, but was conducted in patients with treatment failure or intolerance to immunosuppressants or glucocorticoids (with no requirement for prior TNF inhibitor use). In this trial, a clinical response was achieved by 51.7%, 55.5%, and 28.7% of patients in the ustekinumab 130 mg, weight-based ustekinumab, and placebo groups, respectively (p < 0.001 for both doses vs placebo). Benefits were also demonstrated on all major secondary endpoints.
  - IM-UNITI was a 44-week maintenance trial that enrolled patients completing UNITI-1 and UNITI-2. Of 1281 enrolled patients, there were 397 randomized patients (primary population); these were patients who had had a clinical response to ustekinumab induction therapy and were subsequently randomized to ustekinumab 90 mg SQ every 8 or 12 weeks or placebo. The primary endpoint, clinical remission at week 44, was achieved by 53.1%, 48.8%, and 35.9% of patients in the ustekinumab every 8 week, ustekinumab every 12 week, and placebo groups, respectively (p = 0.005 for every 8 week regimen vs placebo; p = 0.04 for every 12 week regimen vs placebo). Numerical and/or statistically significant differences for ustekinumab vs placebo were observed on key secondary endpoints including clinical response, maintenance of remission, and glucocorticoid-free remission.

Injectable therapy for UC

- Two trials (ACT 1 and ACT 2) evaluated Remicade (infliximab) compared to placebo for the treatment of UC. In both trials, clinical response at week 8 was significantly higher in infliximab 5- and 10 mg/kg-treated patients compared to placebo-treated patients (all p < 0.001). A significantly higher clinical response rate in both infliximab groups was maintained throughout the duration of the studies (*Rutgeerts et al 2005*). A randomized open-label trial evaluated infliximab at different dosing intervals for the treatment of pediatric UC. At week 8, 73.3% of patients met the primary endpoint of clinical response (95% CI, 62.1 to 84.5%) (*Hyams et al 2012*).
- In the ULTRA 2 study, significantly more patients taking Humira (adalimumab) 160 mg at week 0, 80 mg at week 2, and then 40 mg every other week for 52 weeks achieved clinical remission and clinical response vs patients taking placebo (*Sandborn et al 2012*). These long-term results confirm the findings of ULTRA 1. This 8-week induction trial demonstrated that adalimumab in same dosage as in ULTRA 2 was effective for inducing clinical remission (*Reinisch et al 2011*). In ULTRA 1, significant differences between the adalimumab and placebo groups were only achieved for 2 of the secondary endpoints at week 8, ie, rectal bleeding and Physician's global assessment (PGA) subscores. Conversely, in ULTRA 2, significantly greater proportions of adalimumab-treated patients achieved almost all secondary end points at week 8. This may have been because of the high placebo response rates in ULTRA 1. A meta-analysis of 3 randomized trials comparing adalimumab to placebo demonstrated that adalimumab increased the proportion of patients with clinical responses, clinical remission, mucosal healing, and inflammatory bowel disease questionnaire responses in the induction and maintenance phases. It also increased the proportion of patients with steroid-free remission in the maintenance phase (*Zhang et al 2016*).
- Simponi (golimumab) was studied in 1064 patients with moderate to severe UC. Patients receiving golimumab 200 mg then 100 mg or golimumab 400 mg then 200 mg at weeks 0 and 2 were compared to patients receiving placebo. At week 6, significantly greater proportions of patients in the golimumab 200/100 mg and golimumab 400/200 mg groups (51.8%, and 55%, respectively) were in clinical response than patients assigned to placebo (29.7%; p < 0.0001 for both comparisons) (*Sandborn et al 2014[c]*). In a study enrolling patients who responded in a prior study with golimumab, the proportion of patients who maintained a clinical response through week 54 was greater for patients treated with golimumab 100 mg and 50 mg compared to placebo (49.7% and 47% vs 31.2%; p < 0.001 and p = 0.01, respectively) (*Sandborn et al 2014[b]*).

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- The safety and efficacy of Entyvio (vedolizumab) was evaluated in a trial for UC in patients who responded inadequately to previous therapy. A higher percentage of vedolizumab-treated patients achieved or maintained clinical response and remission over placebo at weeks 6 and 52, as measured by stool frequency, rectal bleeding, endoscopic findings, and PGA (*Feagan et al 2013[b]*). A systematic review and meta-analysis (n = 606; 4 trials) demonstrated that vedolizumab was superior to placebo for clinical response (RR 0.82, 95% CI, 0.75 to 0.91), induction of remission (RR, 0.86; 95% CI, 0.80 to 0.91), and endoscopic remission (RR 0.82, 95% CI, 0.75 to 0.91) (*Bickston et al 2014, Mosli et al 2015*).
- Entyvio (vedolizumab) was directly compared to Humira (adalimumab) in the double-blind, double-dummy, randomized, multicenter, VARSITY trial (*Sands et al 2019[a]*). VARSITY enrolled 769 adults with moderate-to-severe UC and randomized them to vedolizumab (n = 383) 300 mg IV on day 1 and at weeks 2, 6, 14, 22, 30, 38, and 46 (plus placebo injections) or adalimumab (n = 386) 160 mg SQ at week 1, 80 mg at week 2, and 40 mg every 2 weeks thereafter (plus placebo infusions) until week 50. Results revealed that clinical remission at week 52 occurred in significantly more patients in the vedolizumab group (31.3% vs 22.5%; difference 8.8%, 95% CI, 2.5 to 15; p = 0.0006). Endoscopic improvement was also significantly improved with vedolizumab (39.7% vs 27.7%; difference 11.9%, 95% CI, 5.3 to 18.5; p < 0.001). However, corticosteroid-free clinical remission was better with adalimumab (12.6% vs 21.8%; difference, -9.3%; 95%, -18.9 to 0.4).
- The efficacy of Stelara (ustekinumab) as induction and maintenance therapy in 961 patients with moderate-to-severe UC was evaluated in the UNIFI study (*Sands et al 2019[b]*). The study involved 8-week induction and 44-week maintenance phases. Patients were randomly assigned to receive an IV induction dose of either ustekinumab 130 mg (n = 320), a weight-range-based ustekinumab dose that approximated 6 mg/kg (n = 322), or placebo (n = 319). Patients with an induction response were then randomly assigned to ustekinumab 90 mg SQ every 12 weeks (n = 172), every 8 weeks (n = 176), or placebo (n = 175) for maintenance. Results revealed a significantly higher clinical remission at week 8 with ustekinumab 130 mg (15.6%) or 6 mg/kg (15.5%) as compared to placebo (5.3%; p < 0.001 for both comparisons). At the end of maintenance, the percentage of patients who had clinical remission was also significantly increased in both ustekinumab groups (38.4% for every 12 weeks vs 43.8% for every 8 weeks vs 24% for placebo; p = 0.002 and p < 0.001, respectively).
- A network meta-analysis of 12 trials of biologic-naïve patients with moderate-severe UC ranked infliximab and vedolizumab highest for induction of clinical remission and mucosal healing among tofacitinib, vedolizumab, golimumab, adalimumab, and infliximab (*Singh et al 2018*). Among patients with prior exposure to TNF inhibitors (4 trials), the results ranked tofacitinib the highest for induction of clinical remission and mucosal healing.
- A Cochrane review examined the evidence for oral JAK inhibitors in the maintenance of UC remission (*Davies et al 2020*). Only 1 randomized controlled trial met criteria for inclusion. In this trial, tofacitinib was superior to placebo for maintenance of clinical and endoscopic remission in patients with moderate to severe UC. The authors concluded that further studies are required to assess long-term effectiveness and safety of tofacitinib as maintenance therapy.

CLINICAL GUIDELINES

UC

- A 2019 guideline from the American College of Gastroenterology (ACG) recommends 5-ASA therapy for induction of remission in mildly active UC, and budesonide, systemic corticosteroids, TNF inhibitor therapy (adalimumab, golimumab, or infliximab), vedolizumab, and tofacitinib for induction of remission in moderately to severely active disease. Vedolizumab and tofacitinib are recommended for induction of remission in patients who have failed previous TNF inhibitor therapy. For maintenance of remission in patients with previously mildly active disease, 5-ASA therapy is recommended, and in patients with previously moderately to severely active disease, continuation of TNF inhibitor therapy, vedolizumab, or tofacitinib is recommended after induction of remission with these agents (*Rubin et al 2019*).
- A 2019 guideline from the American Gastroenterological Association (AGA) recommends standard-dose mesalamine or 5-ASA (balsalazide, olsalazine) as first-line options for most patients with mild to moderate disease (*Ko et al 2019*). For adult outpatients with moderate to severe UC, a 2020 AGA guideline strongly recommends using infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or ustekinumab over no treatment (*Feuerstein et al 2020*). However, for patients with less severe disease who place a higher value on the safety of 5-ASA therapy and a lower value on the efficacy of biologic agents, it is reasonable to choose gradual step therapy with 5-ASA.
- The European Crohn's and Colitis Organization (ECCO) recommends thiopurine, TNF inhibitors, vedolizumab, or methotrexate for patients with UC who have active steroid-dependent disease. In the case of further treatment failure, an alternative TNF inhibitor, vedolizumab, or colectomy can be considered. TNF inhibitors and vedolizumab are also treatment options for patients who have steroid- or immunomodulator-refractory disease (*Harbord et al 2017*).

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

CD

- A 2018 ACG guideline on the management of CD in adults recommends controlled ileal release budesonide at a dose of 9 mg once daily for induction of symptomatic remission for patients with mild to moderate ileocecal CD. The guideline also recommends against the use of oral mesalamine to treat patients with active CD, since it has not consistently been shown effective for inducing remission and achieving mucosal healing when compared to placebo. Sulfasalazine is recommended for symptoms of mild to moderate colonic CD. For patients with more severe disease, the ACG states that the TNF inhibitors adalimumab, certolizumab, and infliximab are effective in the treatment of moderate to severely active CD in patients who are resistant to corticosteroids or are refractory to thiopurines or methotrexate. These agents can be considered for treating perianal fistulas, and infliximab can also treat enterocutaneous and rectovaginal fistulas in CD. Adalimumab, certolizumab, and infliximab are effective for the maintenance of TNF inhibitor-induced remission; due to the potential for immunogenicity and loss of response, combination with azathioprine/6-MP or methotrexate should be considered. The combination of infliximab with an immunomodulator (thiopurine) is more effective than monotherapy with individual agents in patients with moderate to severe CD and who are naïve to both agents. Infliximab can also treat fulminant CD. Vedolizumab with or without an immunomodulator can be used for induction and maintenance of remission in patients with moderate to severe CD. Patients are candidates for ustekinumab therapy, including for the maintenance of remission, if they have moderate to severe CD and have failed corticosteroids, thiopurines, methotrexate, or TNF inhibitors. The guideline acknowledges the effectiveness of biosimilar infliximab and biosimilar adalimumab for the management of moderate to severe CD (*Lichtenstein et al 2018*).
- A 2021 AGA guideline on the medical management of moderate to severe CD strongly recommends the use of biologic monotherapy over thiopurine monotherapy for the induction of remission in adult outpatients and recommends TNF inhibitors or ustekinumab over no treatment for induction and maintenance of remission. In patients who are naïve to biologic drugs, infliximab, adalimumab, or ustekinumab are recommended over certolizumab pegol for the induction of remission and vedolizumab is suggested over certolizumab pegol. In patients who never responded to TNF inhibitors, the use of ustekinumab is recommended and the use of vedolizumab is suggested over no treatment for the induction of remission. In patients who previously responded to infliximab, the use of adalimumab or ustekinumab is recommended and the use of vedolizumab is suggested over no treatment for the induction of remission. The AGA recommends against the use of 5-ASA or sulfasalazine over no treatment for the induction or maintenance of remission. In patients with CD and active perianal fistula, infliximab is recommended over no treatment for the induction and maintenance of fistula remission. In patients with CD and active perianal fistula without perianal abscess, the use of biologic agents in combination with an antibiotic over a biologic drug alone is recommended for the induction of fistula remission (*Feuerstein et al 2021*).
- The 2020 ECCO guideline on medical treatment in CD recommends the use of TNF inhibitors (infliximab, adalimumab, and certolizumab pegol) to induce remission in patients with moderate-to-severe CD who have not responded to conventional therapy (*Torres et al 2020*). Other immunomodulator-related recommendations within the guideline include:
  - Suggesting against the combination of adalimumab and thiopurines over adalimumab alone to achieve clinical remission and response.
  - Recommending combination therapy with a thiopurine when starting infliximab to induce remission in patients with moderate-to-severe CD, who have had an inadequate response to conventional therapy.
  - Recommending ustekinumab for induction of remission in patients with moderate-to-severe CD with inadequate response to conventional therapy and/or to TNF inhibitors.
  - Recommending vedolizumab for induction of response and remission in patients with moderate-to-severe CD with inadequate response to conventional therapy and/or to TNF inhibitors.
  - Equally suggesting the use of either ustekinumab or vedolizumab for the treatment of moderate-to-severe active luminal CD in patients who have previously failed TNF inhibitors.
- The AGA supports the use of TNF inhibitors and/or thiopurines as pharmacologic prophylaxis in patients with surgically-induced CD remission (*Nguyen et al 2017*).
- An AGA Institute clinical decision tool for CD notes the importance of controlling both symptoms and the underlying inflammation, and makes recommendations for treatments (budesonide, azathioprine, 6-MP, prednisone, methotrexate, a TNF inhibitor, or certain combinations) based on the patient's risk level (*Sandborn 2014[a]*).

Preventive care and pregnancy

- The ACG released a clinical guideline addressing preventive care in IBD. According to published data, patients with IBD do not receive preventive care services at the same rate as general medical patients. Increased coordination between gastroenterology and primary care providers is recommended, as well as proper age-appropriate immunization, cervical

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

and skin cancer screenings, depression and anxiety screening, and smoking cessation counseling for patients with CD *(Farraye et al 2017)*.

- The AGA pregnancy care pathway for IBD recommends that aminosalicylates may be continued during pregnancy, delivery, and during the postpartum period. For maintenance therapy in pregnancy, monotherapy is preferred. The pathway notes that Azulfidine EN-tabs contain phthalates, which may be better to avoid in pregnancy, and all mesalamine preparations are phthalate-free. Both mesalamine and sulfasalazine are compatible with breastfeeding, though mesalamine is preferred. Regarding biologic therapy, the AGA recommends continuing therapy during pregnancy and delivery as the benefits of maintaining disease remission outweigh any risks associated with biologic maintenance therapy. The pathway does note that infliximab and adalimumab have the greatest amount of safety data. (*Mahadevan et al 2019*).
- Another statement for the management of IBD in pregnancy, coordinated by the Canadian Association of Gastroenterology, states that TNF inhibitor treatment does not appear to be associated with unfavorable pregnancy outcomes and should generally be continued during pregnancy. Because of the low risk of transfer across the placenta, certolizumab may be preferred in women who initiate TNF inhibitor therapy during pregnancy (*Nguyen et al 2016)*.

SAFETY SUMMARY

Oral and topical treatments

- The safety profile of ozanimod and tofacitinib are found in the sections below.
- Contraindications include hypersensitivity to salicylates or any component for the drugs in this class. Sulfasalazine is contraindicated in patients with intestinal or urinary obstruction or in patients with porphyria, as sulfonamides may precipitate an acute attack.
- Warnings include mesalamine acute intolerance syndrome, exacerbations of colitis, nephrolithiasis, and caution using drugs in this class in patients with hepatic or renal impairment. The aminosalicylate products may cause photosensitivity in patients with atopic dermatitis or eczema and have recently been reported to cause nephrolithiasis. These products may interfere with laboratory tests for normetanephrine. Rectal mesalamine may cause oligospermia and pancolitis. The brand mesalamine product, Apriso, and its branded generic product manufactured by Bausch Health contain phenylalanine, which may be harmful to patients with phenylketonuria; the generic for Apriso manufactured by Mylan Pharmaceuticals does not contain phenylalanine.
- Due to the potential for severe blood dyscrasias, complete blood counts, including differential white cell count, and liver function tests should be performed before starting sulfasalazine therapy (Azulfidine and Azulfidine EN-tabs) and every second week during the first 3 months of therapy; tests should be repeated once monthly for 3 months, then once every 3 months, and as clinically indicated. Serious skin and hypersensitivity reactions have also occurred with sulfasalazine products.
- Budesonide may cause hypercorticism, adrenal axis suppression, and increased risk of infection.
- Concurrent use of NSAIDs with mesalamine products may increase the risk of nephrotoxicity; use with caution. Mesalamine products should not be used with 6-MP and azathioprine due to decreased thiopurine metabolism; an increased risk of myelosuppression may result.
- In general, the IBD agents are most commonly associated with gastrointestinal-related AEs.

Ozanimod

- Contraindications:
  - Patients that have experienced myocardial infarction, unstable angina, stroke, transient ischemic attack, Class III/IV HF, or decompensated HF requiring hospitalization in the past 6 months.
  - Patients with Mobitz type II second- or third-degree atrioventricular block, sick sinus syndrome, or sinoatrial attack unless the patient has a functioning pacemaker.
  - Patients with severe, untreated sleep apnea and those taking a monoamine oxidase inhibitor.
- Warnings/Precautions:
  - Infections; obtain a complete blood count before initiation of treatment and monitor for infection throughout treatment and 3 months after discontinuation.
  - Bradyarrhythmia, atrioventricular conduction delays, increased blood pressure: check electrocardiogram before starting treatment and monitor blood pressure during therapy.
  - Hepatoxicity: obtain liver function tests before starting treatment and discontinue if liver injury is confirmed.
  - Fetal toxicity: women of childbearing potential should use effective contraception during and for 3 months after stopping ozanimod.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Respiratory effects and decline in pulmonary function: assess pulmonary function as needed.
- Macular edema: assess for changes in vision as needed.

- Adverse Effects:
  - Upper respiratory tract infection
  - Increased hepatic transaminases
  - Headache
- Drug interactions
  - Do not give with live (including attenuated) vaccines; additionally, non-live vaccines may not elicit a sufficient immune response.
  - Initiating treatment with ozanimod after alemtuzumab is not recommended because of the characteristics and duration of alemtuzumab immune suppressive effects.
  - Consult with a cardiologist before using ozanimod with a heart rate lowering calcium channel blocker (eg, verapamil, diltiazem) and a beta blocker, an antiarrhythmic, or a drug with QT interval prolonging effects.
  - Not recommended for use with:
    - Drugs that increase norepinephrine or serotonin (opioids, selective-serotonin reuptake inhibitors, etc.)
    - Drugs that are strong cytochrome P450 (CYP) 2C8 inhibitors or inducers

Injectable treatments and tofacitinib

- Contraindications:
  - Avsola (infliximab-axxq), Cimzia (certolizumab), Entyvio (vedolizumab), Inflectra (infliximab-dyyb), Remicade (infliximab), Renflexis (infliximab-abda), and Stelara (ustekinumab): use in patients with hypersensitivity to any component of the product.
  - Remicade (infliximab), Avsola (infliximab-axxq), Inflectra (infliximab-dyyb), and Renflexis (infliximab-abda): use in patients with hypersensitivity to murine proteins; and doses > 5 mg/kg in patients with moderate to severe heart failure (HF).
- Boxed Warnings:
  - Avsola (infliximab-axxq), Cimzia (certolizumab), Humira (adalimumab), Inflectra (infliximab-dyyb), Remicade (infliximab), Renflexis (infliximab-abda), Simponi (golimumab), and Xeljanz/Xeljanz XR (tofacitinib) all have warnings for serious infections such as active tuberculosis, which may present with pulmonary or extrapulmonary disease; invasive fungal infections; and bacterial, viral, and other infections due to opportunistic pathogens.
  - In addition, Avsola (infliximab-axxq), Cimzia (certolizumab), Humira (adalimumab), Inflectra (infliximab-dyyb), Remicade (infliximab), Renflexis (infliximab-abda), Simponi (golimumab), and Xeljanz (tofacitinib) all have warnings for increased risk of malignancies.
  - Xeljanz/Xeljanz XR (tofacitinib) have boxed warnings for increased risk of thrombosis and death, including sudden cardiovascular death, with the 10 mg twice daily dose, which is used in patients with UC.
    - On September 1, 2021, the FDA issued a drug safety communication for tofacitinib (Xeljanz and Xeljanz XR). Based on review of a large randomized clinical safety trial comparing tofacitinib with a TNF inhibitor in patients with rheumatoid arthritis, the FDA concluded that there is an increased risk of serious heart-related events such as heart attack or stroke, cancer, blood clots, and death. The trial's final results also showed an increased risk of blood clots and death with the lower dose (5 mg twice daily, also used for UC) of Xeljanz. The FDA is requiring revisions to the boxed warning, for Xeljanz/Xeljanz XR to include information about the risks of serious heart-related events, cancer, blood clots, and death.
- Warnings/Precautions (applying to some or all of the agents in the class).
  - Reactivation of hepatitis B virus (HBV) or other viral infections
  - Serious infections including tuberculosis
  - New onset or exacerbation of central nervous system demyelinating disease and peripheral demyelinating disease
  - Pancytopenia
  - Worsening and new onset congestive HF
  - Hypersensitivity reactions
  - Lupus-like syndrome
  - Malignancy and lymphoproliferative disorders
  - Avoiding live vaccinations
  - Noninfectious pneumonia with Stelara (ustekinumab)
  - Increased lipid parameters and liver function tests with Xeljanz/Xeljanz XR (tofacitinib)
  - Infusion-related and hypersensitivity reactions with Entyvio (vedolizumab)

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Gastrointestinal perforations with Xeljanz/Xeljanz XR (tofacitinib)
- Progressive multifocal leukoencephalopathy (PML) with Entyvio (vedolizumab)
- Cardiovascular and cerebrovascular reactions during and after infusion (infliximab)
- Posterior reversible encephalopathy syndrome (PRES) with Stelara (ustekinumab)
- Consult prescribing information for other drug-specific warnings/precautions

- Adverse Effects:
  - Infusion site reactions, diarrhea, nausea/vomiting, abdominal pain, infections, hypertension, headache, upper respiratory tract infection.
  - Consult prescribing information for other drug-specific AEs
- Risks of Long-Term Treatment: As it becomes accepted practice to treat patients with IBD for long-term, it is imperative to assess the long-term safety of these products. Because these agents suppress the immune system, serious infections and malignancies are a concern. Several long-term efficacy and safety studies support several agents in this class. The extension studies were performed in an open-label manner and were subject to attrition bias.
  - One study looked at 23,458 patients who were treated with Humira (adalimumab) for several autoimmune conditions including CD. Patients received adalimumab for up to 12 years. No new safety signals were observed from this analysis. Rates of malignancies and infections were similar to the general population and also similar to rates reported in other shorter-term trials for TNF inhibitors (*Burmester et al 2013*).
  - A total of 18 multicenter, placebo-controlled, randomized trials evaluated the safety profile of certolizumab pegol monotherapy or in combination with disease-modifying antirheumatic drugs in several autoimmune conditions including CD (*Capogrosso Sansone et al 2015).* All but 1 trial was conducted in a double-blind manner. The overall pooled risk ratios for all doses of certolizumab pegol were reported as follows: AEs (defined as AE reported but not evaluated for causality) 1.09 (95% CI, 1.04 to 1.14), serious AEs 1.50 (95% CI, 1.21 to 1.86), adverse drug reactions (defined as an AE possibly related to drug treatment by investigators) 1.20 (95% CI, 1.13 to 1.45), infectious AEs 1.28 (95% CI, 1.13 to 1.45), infectious serious AEs 2.17 (95% CI, 1.36 to 3.47), upper respiratory tract infections 1.34 (95% CI, 1.15 to 1.57), neoplasms 1.04 (95% CI, 0.49 to 2.22), and tuberculosis 2.47 (95% CI, 0.64 to 9.56). Rare AEs may not have been captured by the studies due to limiting the reporting of most AEs to those occurring in > 3 to 5%.
  - The safety of ustekinumab was examined in a pooled analysis of 12 trials in patients with several autoimmune conditions including CD. A total of 5584 patients were evaluated, equating to 4521 patient-years (PYs). Respective incidences per 100 PY of infections (125.4 vs 129.4), major cardiovascular AEs (0.5 vs 0.3), malignancies (0.4 vs 0.2), and death (0.1 vs 0.0) were similar between ustekinumab and placebo, respectively (*Ghosh et al 2019*).
- Drug interactions:
  - Do not give with live (including attenuated) vaccines; additionally, non-live vaccines may not elicit a sufficient immune response.
  - Do not give 2 immunomodulators together.
  - For Xeljanz/Xeljanz XR (tofacitinib), adjust dose with potent inhibitors of CYP3A4 and medications that result in both moderate inhibition of CYP3A4 and potent inhibition of CYP2C19. Coadministration with potent CYP3A4 inducers and potent immunosuppressive drugs is not recommended.

DOSING AND ADMINISTRATION

Table 4. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Oral and topical agents				
Balsalazide	Capsule (Colazal): 750 mg	Oral	Capsule (Colazal): 3 times daily	Capsule (Colazal): approved for use in children 5 to 17 years old
Budesonide	Delayed-release capsule (Entocort EC): 3 mg Extended-release capsule (Ortikos): 6 mg, 9 mg	Oral, Rectal	Extended-release capsule and delayed-release capsule: once daily Extended-release tablet: once daily	Extended-release capsules (Ortikos) and delayed-release capsules (Entocort EC) is approved for active CD (children ≥ 8

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
	Extended-release tablet (Uceris): 9 mg Rectal foam (Uceris): 2 mg/actuation		Rectal foam: once to twice daily	years of age); Uceris is approved for active UC Patients with moderate to severe hepatic impairment should be monitored for signs and symptoms of hypercorticism
Mesalamine	Controlled-release capsule (Pentasa): 250 mg, 500 mg Delayed-release capsule (Delzicol): 400 mg Delayed-release tablet 800 mg (Asacol HD), 1.2 g (Lialda) Extended-release capsule (Apriso): 0.375 g Rectal suppository (Canasa): 1000 mg Rectal enema (Rowasa, sfRowasa): 4 g/60 mL	Oral, Rectal	Controlled-release capsule (Pentasa): 4 times daily Delayed-release capsule (Delzicol): twice to 4 times daily Delayed-release tablet (Asacol HD): 3 times daily Delayed-release tablet (Lialda): once daily with food Extended-release capsules (Apriso): once daily Rectal suppository (Canasa): once daily at bedtime Rectal enema (Rowasa; sfRowasa): once daily at bedtime	Delayed-release capsule (Delzicol): approved for use in children ≥ 5 years of age Delayed-release tablet (Lialda): approved for use in pediatric patients weighing ≥ 24 kg Complete blood counts should be periodically monitored in elderly patients. Renal function should be evaluated prior to initiation of most mesalamine products; use with caution in patients with a history of or known renal dysfunction. Two Delzicol 400 mg capsules have not been shown to be interchangeable or substitutable with one Asacol HD tablet.
Olsalazine (Dipentum)	Capsule: 250 mg	Oral	Twice daily	
Ozanimod (Zeposia)	Capsule: 0.23 mg, 0.46 mg, 0.92 mg	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.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

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.
Sulfasalazine	Tablet (Azulfidine): 500 mg Delayed-release tablet: (Azulfidine EN-tabs) 500 mg	Oral	Tablet and delayed-release tablet: twice to 4 times daily	Sulfasalazine products may cause an orange-yellow discoloration of the urine or skin. Safety and effectiveness for UC in patients < 2 years of age have not been established. FDA-approved for rheumatoid arthritis in adults and juvenile rheumatoid arthritis for children ≥ 6 years of age. (Azulfidine EN-tabs only)
Tofacitinib (Xeljanz/Xeljanz XR)	Tablet: 5 mg, 10 mg Extended-release Tablet: 11 mg, 22 mg Oral solution: 1 mg/mL	Oral	Induction: 10 mg twice daily or 22 mg once daily for 8 weeks, then, if needed, continue 10 mg twice daily or 22 mg once daily for a maximum of 16 weeks. Discontinue therapy after 16 weeks if an adequate therapeutic response is not achieved. Maintenance: 5 mg twice daily or 11 mg once daily; for patients with loss of response during maintenance, 10 mg twice daily or 22 mg once daily may be considered and limited to the shortest duration.	Patients may switch from Xeljanz 5 mg twice daily to Xeljanz XR 11 mg once daily the day following the last dose of Xeljanz 5 mg. Patients may switch from Xeljanz 10 mg twice daily to Xeljanz XR 22 mg once daily the day following the last dose of Xeljanz 10 mg. Xeljanz XR is not interchangeable or substitutable with Xeljanz oral solution. Dose adjustment needed in patients taking CYP450 inhibitors and in

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				lymphopenia, neutropenia, and anemia. May take with or without food. Swallow Xeljanz XR tablets whole; do not crush, split, or chew. Xeljanz oral solution should not be initiated in patients with absolute lymphocyte count < 500 cells/mm^3, absolute neutrophil count < 1000 cells/mm^3, or hemoglobin < 9 g/dL. Administer Xeljanz oral solution with the included press-in bottle adapter and oral dosing syringe.
Injectable agents				
Humira (adalimumab)	Prefilled syringe: 10 mg/0.1 mL 10 mg/0.2 mL 20 mg/0.2 mL 20 mg/0.4 mL 40 mg/0.4 mL 40 mg/0.8 mL 80 mg/0.8 mL Single-use pen: 80 mg/0.8 mL 40 mg/0.8 mL 40 mg/0.4 mL Single-use vial: 40 mg/0.8 mL	SQ	160 mg on day 1 (given in 1 day or split over 2 consecutive days), followed by 80 mg 2 weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40 mg every other week. **CD in pediatric patients ≥ 6 years of age:** • 17 kg to < 40 kg: 80 mg on day 1 and 40 mg 2 weeks later (on day 15); maintenance dose is 20 mg every other week starting at week 4 (on day 29). • ≥ 40 kg: 160 mg on day 1 (given in 1 day or split over 2 consecutive days) and 80 mg 2 weeks later (on day 15); maintenance dose is 40 mg every other week starting at week 4. **UC in pediatric patients ≥ 5 years of age:** • 20 kg to < 40 kg: 80 mg on day 1, 40 mg 1 week later (on day 8), and 40 mg 1 week	Aminosalicylates and/or corticosteroids may be continued. Azathioprine, 6-MP or methotrexate may be continued if necessary. Needle cover of the syringe contains dry rubber (latex). Patients may be taught to self-inject. Injections should occur at separate sites in the thigh or abdomen. Rotate injection sites. May bring to room temperature prior to injecting. UC: The recommended pediatric dosage should be continued in patients who turn 18 years of age and who are well controlled on their adalimumab regimen.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			after that (on day 15); maintenance dose is 40 mg every other week or 20 mg every week starting at week 4 (on day 29). • ≥ 40 kg: 160 mg on day 1 (given in 1 day or split over 2 consecutive days), 80 mg 1 week later (on day 8), and 80 mg 1 week after that (day 15); maintenance dose is 80 mg every other week or 40 mg every week starting at week 4 (on day 29).	
Cimzia (certolizumab)	Powder for reconstitution: 200 mg Prefilled syringe: 200 mg/mL	SQ	400 mg initially and at weeks 2 and 4. Maintenance dose is 400 mg every 4 weeks.	When a 400 mg dose is required, give as two 200 mg SQ injections in separate sites in the thigh or abdomen. Patients can self-inject with the prefilled syringe.
Simponi (golimumab)	SmartJect® autoinjector: 50 mg/0.5 mL and 100 mg/mL Prefilled syringe: 50 mg/0.5 mL and 100 mg/mL	SQ	200 mg at week 0; then 100 mg at week 2; then 100 mg every 4 weeks.	Patients may be taught to self-inject the SQ dose. For SQ, injection sites should be rotated. For SQ, bring to room temperature for 30 minutes prior to injecting. Needle cover of the syringe contains dry rubber (latex).
Avsola (infliximab-axxq); Inflectra (infliximab-dyyb); Remicade (infliximab); Renflexis (infliximab-abda)	Vial: 100 mg	IV	5 mg/kg IV at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks. In adults with CD who lose response, can increase dose to 10 mg/kg every 8 weeks.	CD: If no response by week 14, consider discontinuation. Premedication to help stop infusion reactions can include antihistamines (anti-H1 ± anti-H2), acetaminophen and/or corticosteroids. Use 250 mL 0.9% sodium chloride for infusion. Infuse over 2 hours.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				Do not administer with other drugs. Doses > 5 mg/kg are contraindicated in moderate to severe HF.
Stelara (ustekinumab)	Prefilled syringe: 45 mg/0.5 mL and 90 mg/mL Vial: 45 mg/0.5 mL and 130 mg/26 mL	IV, SQ	Initial single IV dose: ≤ 55 kg, 260 mg; > 55 kg to ≤ 85 kg, 390 mg; > 85 kg, 520 mg; followed by 90 mg SQ every 8 weeks (irrespective of body weight).	Needle cover of the syringe contains dry rubber (latex). Patients may be taught to self-inject using the prefilled syringes. In pediatric patients, it is recommended that Stelara be administered by a healthcare provider. Stelara for IV infusion must be diluted, prepared and infused by a healthcare professional; it is diluted in 0.9% sodium chloride or 0.45% sodium chloride for a final volume of 250 mL and infused over at least 1 hour. Rotate injection sites.
Entyvio (vedolizumab)	Lyophilized cake for injection in 300 mg single-dose vial	IV	300 mg administered by IV infusion at time 0, 2, and 6 weeks, and then every 8 weeks thereafter.	CD and UC: Discontinue therapy if there is no evidence of therapeutic benefit by week 14. All immunizations should be up to date according to current guidelines prior to initial dose. Entyvio should be reconstituted at room temperature and prepared by a trained medical professional. It should be used as soon as possible after reconstitution and dilution.

See the current prescribing information for full details

CONCLUSION

- Treatment goals of IBD are to resolve acute inflammatory processes, resolve systemic complications, alleviate systemic manifestations, and maintain remission from acute inflammation.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- For induction of remission of UC, no differences in efficacy among the oral 5-ASA formulations have been identified *(Murray et al 2020[a])*.
- No overall differences in efficacy or safety among the oral 5-ASA formulations have been observed for the maintenance of UC remission *(Murray et al 2020[b])*. Once daily dosing and traditional dosing of oral 5-ASA regimens were similarly effective for maintenance of UC remission *(Feagan and MacDonald 2012, Feagan et al 2013[a])*.
- Topical rectal therapies are the formulations of choice for distal disease and have been shown to be more effective than oral sulfasalazine therapy. In a meta-analysis, rectal 5-ASA therapy was shown to be superior to placebo and rectal corticosteroids for inducing symptomatic improvement and remission; however, rectal 5-ASA therapy was not superior to oral 5-ASA for symptomatic improvement or remission rates *(Marshall et al 2010)*. For maintenance of symptomatic and endoscopic remission of UC, rectal 5-ASA was not significantly different compared to oral 5-ASA. It has also been shown in clinical trials that topical mesalamine is more effective than placebo for the prevention of relapse of disease activity in quiescent UC *(Ford et al 2012)*. Similarly, trials showed budesonide rectal foam was more effective than placebo in inducing remission in patients with mild to moderate ulcerative proctitis and ulcerative proctosigmoiditis and patients with mild to moderate UC with distal active inflammation *(Sandborn et al 2015; Naganuma et al 2017)*.
- For induction of remission of CD, a Cochrane review found that budesonide was significantly less effective than conventional steroids, but treatment with budesonide resulted in significantly fewer AEs (*Rezaie et al 2015*). For maintenance of remission budesonide 6 mg daily was not found to be more effective than placebo (*Kuenzig et al 2014*).
- A network meta-analysis of 12 trials of biologic-naïve patients with moderate-severe UC ranked infliximab and vedolizumab highest for induction of clinical remission and mucosal healing among tofacitinib, vedolizumab, golimumab, adalimumab, and infliximab (*Singh et al 2018*). The VARSITY trial compared vedolizumab and adalimumab in patients with moderate to severe UC; vedolizumab was superior for clinical remission at week 52 and endoscopic improvement, while adalimumab was superior for corticosteroid-free remission (*Sands et al 2019[a]*).
- A 2021 meta-analysis that included 25 randomized trials found that infliximab and adalimumab were superior to certolizumab pegol and tofacitinib for induction of remission in CD (*Wu et al 2021*).
- Ozanimod has not been compared to any other agents for UC management. Two pivotal trials demonstrated ozanimod's efficacy vs placebo in achievement of clinical remission in UC (*Zeposia prescribing information 2021*).
- A 2019 guideline from the ACG recommends 5-ASA therapy for induction of remission in mildly active UC, and budesonide, systemic corticosteroids, TNF inhibitor therapy (adalimumab, golimumab, or infliximab), vedolizumab, and tofacitinib for induction of remission in moderately to severely active disease (*Rubin et al 2019*).
- A 2019 AGA guideline on the management of UC recommends standard-dose mesalamine or 5-ASA (balsalazide, olsalazine) as first-line options for most patients with mild to moderate disease (*Ko et al 2019*). For adult outpatients with moderate to severe UC, a 2020 AGA guideline strongly recommends using infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or ustekinumab (*Feuerstein et al 2020*).
- A 2018 ACG guideline on the management of CD in adults recommends controlled ileal release budesonide at a dose of 9 mg once daily for induction of symptomatic remission for patients with mild to moderate ileocecal CD. Sulfasalazine is recommended for symptoms of mild to moderate colonic CD. For patients with more severe disease, the ACG states that the TNF inhibitors adalimumab, certolizumab, and infliximab are effective in the treatment of moderate to severely active CD in patients who are resistant to corticosteroids or are refractory to thiopurines or methotrexate. Vedolizumab with or without an immunomodulator can be used for induction and maintenance of remission in patients with moderate to severe CD. Patients are candidates for ustekinumab therapy, including for the maintenance of remission, if they have moderate to severe CD and have failed corticosteroids, thiopurines, methotrexate, or TNF inhibitors. The guideline acknowledges the effectiveness of biosimilar infliximab and biosimilar adalimumab for the management of moderate to severe CD (*Lichtenstein et al 2018*).
- A 2021 AGA guideline on the management of moderate to severe CD strongly recommends the use of biologic monotherapy over thiopurine monotherapy for the induction of remission in adult outpatients and recommends TNF inhibitors or ustekinumab for induction and maintenance of remission. In patients who never responded to TNF inhibitors, the use of ustekinumab is recommended and the use of vedolizumab is suggested for the induction of remission. In patients with CD and active perianal fistula, infliximab is recommended for the induction and maintenance of fistula remission. In patients with CD and active perianal fistula without perianal abscess, the use of biologic agents in combination with an antibiotic over a biologic drug alone is recommended for the induction of fistula remission (*Feuerstein et al 2021*).
- The differences in oral and topical drug therapies (ie, pH-dependent parameters) allow for the tailoring of treatment based upon an individual's disease location and severity. For injectable treatments, selection of an agent may be determined by approved indications, response, administration method, tolerability, AE profile, and cost of the agent.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Adalimumab and infliximab (including biosimilars) carry approvals for use in pediatric patients with CD and UC. All of the injectable biologic agents in this review are given by subcutaneous injection and/or intravenous infusion. Administration schedule varies among the injectable agents in the class. Ozanimod and tofacitinib are given orally.

- Overall, conventional oral therapies are generally well tolerated; however, AEs often limit the use of sulfasalazine in favor of the newer 5-ASA therapy options given their local mechanism of action compared to the systemic absorption of sulfasalazine. Ozanimod has unique safety concerns regarding its use in patients with underlying or recent cardiovascular events. Tofacitinib is an oral immunomodulator with safety concerns similar to those of injectable biologics. Caution is warranted with these biologic agents due to severe infections and malignancies that can occur with their use. TNF inhibitors have boxed warnings regarding a risk of serious infections and an increased risk of malignancies.

REFERENCES

- Apriso [package insert], Bridgewater, NJ: Salix Pharmaceuticals, Inc.; October 2020.
- Asacol HD [package insert], Irvine, CA: Allergan USA, Inc.; October 2020.
- Avsola [package insert], Amgen, Inc. Thousand Oaks, CA. December 2019.
- Azulfidine EN-tabs [package insert], New York, NY: Pfizer; May 2021.
- Azulfidine [package insert], New York, NY: Pfizer; May 2021.
- Barberio B, Segal JP, Quraishi MN, Black CJ, Savarino EV, Ford AC. Efficacy of oral, topical, or combined oral and topical 5-aminosalicylates, in ulcerative colitis: systematic review and network meta-analysis. *J Crohns Colitis*. 2021;15(7):1184-1196. doi: 10.1093/ecco-jcc/jjab010.
- Battat R, Duijvestein M, Guizzetti L, et al. Histologic healing rates of medical therapies for ulcerative colitis: a systematic review and meta-analysis of randomized controlled trials. *Am J Gastroenterol*. 2019;114(5):733-745. doi: 10.14309/ajg.0000000000000111.
- Behm BW, Bickston SJ. Tumor necrosis factor-alpha antibody for maintenance of remission in Crohn's disease. *Cochrane Database Sys Rev* 2008, Issue 1. Art. No.: CD006893. doi: 10.1002/14651858. CD006893.
- Bernstein C, Eliakim A, Fedail S, et al. World Gastroenterology Organisation global guidelines on inflammatory bowel disease. Updated August 2015. http://www.worldgastroenterology.org/UserFiles/file/guidelines/inflammatory-bowel-disease-english-2015.pdf. Accessed August 19, 2021.
- Bickston SJ, Behm BW, Tsoulis DJ, et al. Vedolizumab for induction and maintenance of remission in ulcerative colitis (review). *Cochrane Database Syst Rev*. 2014;8:CD007571. doi: 10.1002/14651858.
- Bonovas S, Nikolopoulos GK, Piovani D, et al. Comparative assessment of budesonide-MMX and mesalamine in active, mild-to-moderate ulcerative colitis: A systematic review and network meta-analysis. *Br J Clin Pharmacol*. 2019;85(10):2244-2254. doi: 10.1111/bcp.14051.
- Burmester GR, Panaccione R, Gordon KB, et al. Adalimumab: long-term safety in 23,458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. *Ann Rheum Dis*. 2013;72:517–24. doi: 10.1136/annrheumdis-2011-201244.
- Canasa [package insert], Irvine, CA: Allergan USA, Inc.; October 2020.
- Centers for Disease Control and Prevention (CDC). Data and Statistics – Inflammatory Bowel Disease (IBD) in the United States. July 9, 2021. https://www.cdc.gov/ibd/data-statistics.htm. Accessed August 19, 2021.
- Cheifetz AS, Cullen GJ. Sulfasalazine and 5-aminosalicylates in the treatment of inflammatory bowel disease. UpToDate Web site. www.uptodate.com. Updated September 21,2020. Accessed August 19, 2021.
- Choy EH, Panayi GS. Cytokine pathways and joint inflammation in rheumatoid arthritis. *N Engl J Med*. 2001;344(12):907-16. doi: 10.1056/NEJM200103223441207.
- Cimzia [package insert], UCB, Inc. Smyrna, GA. September 2019.
- ClinicalTrials.gov Web site. https://clinicaltrials.gov/. Accessed August 19, 2021.
- Colazal [package insert], Bridgewater, NJ: Salix Pharmaceuticals, Inc.; August 2021.
- Capogrosso Sansone A, Mantarro S, Tuccori M, et al. Safety profile of certolizumab pegol in patients with immune-mediated inflammatory diseases: a systematic review and meta-analysis. *Drug Saf*. 2015;38:869-888. doi: 10.1007/s40264-015-0336-2.
- Davies SC, Hussein IM, Nguyen TM, Parker CE, Khanna R, Jairath V. Oral Janus kinase inhibitors for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2020;1(1):CD012381. doi:10.1002/14651858.CD012381.pub2.
- Delzicol [package insert], Irvine, CA: Allergan USA, Inc.; October 2020.
- Dipentum [package insert], Somerset, NJ: Meda Pharmaceuticals, Inc.; June 2021.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed August 19, 2021.
- Entocort EC [package insert], Allegan, MI: Perrigo Pharma International; July 2020.
- Entyvio [package insert], Takeda Pharmaceuticals America, Inc. Lexington, MA. July 2020.
- Farraye FA, Melmed GY, Lichtenstein GR, et al. ACG clinical guideline: preventive care in inflammatory bowel disease. *Am J Gastroenterol.* 2017;112:241-58.
- Feagan BG, Chande N, MacDonald JK. Are there differences in the efficacy and safety of different formulations of oral 5-ASA used for induction and maintenance of remission in ulcerative colitis? Evidence from Cochrane Reviews. *Inflamm Bowel Dis*. 2013[a];19(9):2031-40.
- Feagan BG, Rutgeerts P, Sands B, et al. Vedolizumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2013[b];369(8):699-710. doi: 10.1056/NEJMoa1215734.
- Feagan BG, MacDonald JK. Once daily oral mesalamine compared to conventional dosing for induction and maintenance of remission in ulcerative colitis: A systematic review and meta-analysis. *Inflamm Bowel Dis*. 2012;18:1785-1794.
- Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2016;375:1946-60. doi: 10.1056/NEJMoa1602773.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Feuerstein JD, Isaacs KL, Schneider Y, et al. AGA clinical practice guidelines on the management of moderate to severe ulcerative colitis. *Gastroenterology*. 2020;158(5):1450-1461. doi: 10.1053/j.gastro.2020.01.006.
- Feuerstein JD, Ho EY, Shmidt E, et al. AGA Clinical Practice Guidelines on the medical management of moderate to severe luminal and perianal fistulizing Crohn's disease. *Gastroenterology*. 2021;160(7):2496-2508. doi:10.1053/j.gastro.2021.04.022.
- Ford AC, Khan KJ, Sandborn WJ, et al. Efficacy of topical 5-aminosalicylates in preventing relapse of quiescent UC: a meta-analysis. *Clin Gastroenterol Hepatol*. 2012;10:513-9.
- Fu YM, Chen M, Liao AJ. A meta-analysis of adalimumab for fistula in Crohn's Disease. *Gastroentero Res Pract*. 2017;2017:1745692. doi: 10.1155/2017/1745692.
- Geremia A, Biancheri P, Allan P, et al. Innate and adaptive immunity in inflammatory bowel disease. *Autoimmun Rev*. 2014 Jan;13(1):3-10.
- Gjuladin-Hellon T, Gordon M, Iheozor-Ejiofor Z, Akobeng AK. Oral 5-aminosalicylic acid for maintenance of surgically-induced remission in Crohn's disease. *Cochrane Database Syst Rev*. 2019:CD008414. doi: 10.1002/14651858.CD008414.pub3.
- Ghosh S, Gensler LS, Yang Z, et al. Ustekinumab safety in psoriasis, psoriatic arthritis, and Crohn's disease: an integrated analysis of phase II/III clinical development programs. *Drug Saf*. 2019;42(6):751-768. doi: 10.1007/s40264-019-00797-3.
- Harbord M, Eliakim R, Bettenworth D, et al. Third European Evidence-based Consensus on diagnosis and management of ulcerative colitis. Part 2: current management. *J Crohns Colitis*. 2017;11(7):769-784. doi: 10.1093/ecco-jcc/jjx009.
- Hashash JA, Regueiro M. Medical management of low-risk adult patients with mild to moderate ulcerative colitis. UpToDate Web site. www.uptodate.com. Updated January 19, 2021. Accessed August 19, 2021.
- Humira [package insert], AbbVie Inc. North Chicago, IL. February 2021.
- Hyams J, Crandall W, Kugathasan S, et al; REACH Study Group. Induction and maintenance infliximab therapy for the treatment of moderate-to-severe Crohn's disease in children. *Gastroenterology*. 2007;132(3):863-73; quiz 1165-6. doi: 10.1053/j.gastro.2006.12.003.
- Hyams JS, Damaraju L, Blank M, et al. Induction and maintenance therapy with infliximab for children with moderate to severe ulcerative colitis. *Clin Gastroenterol Hepatol*. 2012;10(4):391-399. doi: 10.1016/j.cgh.2011.11.026.
- Inflectra [package insert], Hospira. Lake Forest, IL. June 2021.
- Ko CW, Singh S, Feuerstein JD, et al. AGA clinical practice guidelines on the management of mild-to-moderate ulcerative colitis. *Gastroenterology*. 2019;156(3):748-764. doi: 10.1053/j.gastro.2018.12.009.
- Kuenzig ME, Rezaie A, Seow CH, et al. Budesonide for maintenance of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2014, Issue 8. Art. No.: CD0002913. doi: 10.1002/14651858.CD002913.pub3.
- Lialda [package insert], Lexington, MA: Shire US, Inc.; May 2021.
- Lichtenstein GR, Loftus EV, Isaacs, KL, Regueiro, MD, Gerson, LB, Sands, BE. ACG clinical guideline: management of Crohn's disease in adults. *Am J Gastroenterol.* 2018;113(4):481-517. doi: 10.1038/ajg.2018.27.
- Ma C, Panaccione R, Heitman SJ, et al. Systematic review: the short-term and long-term efficacy of adalimumab following discontinuation of infliximab. *Aliment Pharmacol Ther*. 2009;30:977-86. doi: 10.1111/j.1365-2036.2009.04101.x.
- Mahadevan U, Robinson C, Bernasko N, et al. Inflammatory bowel disease in pregnancy clinical care pathway: a report from the American Gastroenterological Association IBD Parenthood Project Working Group. *Gastroenterology*. 2019;156(5):1508-1524. doi: 10.1053/j.gastro.2018.12.022.
- Marshall JK, Thabane M, Steinhart AH, et al. Rectal 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2012, Issue 11. Art No.: CD004118. doi: 10.1002/14651858.CD004118.pub2.
- Marshall JK, Thabane M, Steinhart AH, et al. Rectal 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2010, Issue 1. Art. No.: CD004115. doi: 10.1002/14651858.CD004115.pub2.
- Micromedex Healthcare Series Web site. http://www.micromedexsolutions.com/home/dispatch. Accessed August 19, 2021.
- Molodecky NA, Soon IS, Rabi DM, et al. Increasing incidence and prevalence of the inflammatory bowel diseases with time, based on systematic review. *Gastroenterology*. 2012;142(1):46-54. doi: 10.1053/j.gastro.2011.10.001.
- Mosli MH, MacDonald JK, Bickston SJ, et al. Vedolizumab for induction and maintenance of remission in ulcerative colitis: a Cochrane systemic review and meta-analysis. *Inflamm Bowel Dis*. 2015;21:1151-9. doi: 10.1097/MIB.0000000000000396.
- Murray A, Nguyen TM, Parker CE, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2020[a];8:CD000543. doi: 10.1002/14651858.CD000543.pub5.
- Murray A, Nguyen TM, Parker CE, Feagan BG, MacDonald JK. Oral 5-aminosalicylic acid for maintenance of remission in ulcerative colitis. *Cochrane Database Syst Rev*. 2020[b];8:CD000544. doi: 10.1002/14651858.CD000544.pub5.
- Naganuma M, Aoyama N, Tada T, et al. Complete mucosal healing of distal lesions induced by twice-daily budesonide 2-mg foam promoted clinical remission of mild-to-moderate ulcerative colitis with distal active inflammation: double-blind, randomized study. *J Gastroenterol*. 2018;53(4):494-506. doi: 10.1007/s00535-017-1376-4.
- Nguyen NH, Fumery M, Dulai PS, et al. Comparative efficacy and tolerability of pharmacological agents for management of mild to moderate ulcerative colitis: a systematic review and network meta-analyses. *Lancet Gastroenterol Hepatol*. 2018;3(11):742-753. doi: 10.1016/S2468-1253(18)30231-0.
- Nguyen GC, Loftus EV, Hirano I, et al. American Gastroenterological Institute guideline on the management of Crohn's disease after surgical resection. *Gastroenterology*. 2017;152(1):271-5. doi: 10.1053/j.gastro.2016.10.038.
- Nguyen GC, Seow CH, Maxwell C, et al. The Toronto Consensus Statements for the management of inflammatory bowel disease in pregnancy. *Gastroenterology*. 2016;150:734-57. doi: 10.1053/j.gastro.2015.12.003.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed August 19, 2021.
- Ortikos [package insert], Cranbury, NJ: Sun Pharmaceutical Industries, Inc; October 2019.
- Pentasa [package insert], Lexington, MA: Takeda Pharmaceuticals, Inc.; May 2021.
- Peppercorn MA, Cheifetz AS. Definition, epidemiology, and risk factors in inflammatory bowel disease. UpToDate Web site. www.uptodate.com. Updated August 10, 2021. Accessed August 19, 2021.
- Peppercorn MA, Kane SV. Clinical manifestations, diagnosis, and prognosis of Crohn disease in adults. UpToDate Web site. www.uptodate.com. Updated November 30, 2020[a]. Accessed August 19, 2021.
- Peppercorn MA, Kane SV. Clinical manifestations, diagnosis, and prognosis of ulcerative colitis in adults. UpToDate Web site. www.uptodate.com. Updated January 20, 2020[b]. Accessed August 19, 2021.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Present DH, Rutgeerts P, Targan S, et al. Infliximab for the treatment of fistulas in patients with Crohn's disease. *N Engl J Med.* 1999;6;340(18):1398-405. doi: 10.1056/NEJM199905063401804.
- Reinisch W, Sandborn WJ, Hommes DW, et al. Adalimumab for induction of clinical remission in moderately to severely active ulcerative colitis: results of a randomised controlled trial. *Gut.* 2011;60:780–7. doi: 10.1136/gut.2010.221127.
- Remicade [package insert], Janssen Biotech. Horsham, PA. May 2020.
- Renflexis [package insert], Merck Sharpe & Dohme Corp. Kenilworth, NJ. February 2021.
- Rezaie A, Kuenzig ME, Benchimol E, et al. Budesonide for induction of remission in Crohn's disease. *Cochrane Database Syst Rev*. 2015, Issue 6. Art. No.: CD000296. doi: 10.1002/14651858.CD000296.pub4.
- Rowasa [package insert], Somerset, NJ: Meda Pharmaceuticals, Inc.; June 2021.
- Rubin DT, Ananathakrishnan AN, Siegel CA, Sauer BG, Long MD. ACG clinical guideline: ulcerative colitis in adults. *Am J Gastroenterol*. 2019;114(3):384-413. doi: 10.14309/ajg.0000000000000152.
- Rutgeerts P, Sandborn WJ, Feagan BG, et al. Infliximab for induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2005;353(23):2462-76. doi: 10.1056/NEJMoa050516.
- Sandborn WJ, Bosworth B, Zakko S, et al. Budesonide foam induces remission in patients with mild to moderate ulcerative proctitis and ulcerative proctosigmoiditis. *Gastroenterology*. 2015;148(4):740-750.
- Sandborn WJ. Crohn's Disease Evaluation and Treatment: Clinical Decision Tool. *Gastroenterology*. 2014[a];147:702-5. doi: 10.1053/j.gastro.2014.07.022.
- Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab induces clinical response and remission in patients with moderate to severe ulcerative colitis. *Gastroenterology*. 2014[b];146(1):96-109. doi: 10.1053/j.gastro.2013.05.048.
- Sandborn WJ, Feagan BG, Marano C, et al. Subcutaneous golimumab maintains clinical response in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2014[c];146:96-109. doi: 10.1053/j.gastro.2013.06.010.
- Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med*. 2013;369(8):711-721. doi: 10.1056/NEJMoa1215739.
- Sandborn WJ, Su C, Sands BE, et al. Tofacitinib as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2017;376(18):1723-1736. doi: 10.1056/NEJMoa1606910.
- Sandborn WJ, Van Assche G, Reinisch W, et al. Adalimumab induces and maintains clinical remission in patients with moderate-to-severe ulcerative colitis. *Gastroenterology*. 2012;142:257–65. doi: 10.1053/j.gastro.2011.10.032.
- Sands BE, Feagan BG, Rutgeerts P, et al. Effects of vedolizumab induction therapy for patients with Crohn's disease in whom tumor necrosis factor antagonist treatment failed. *Gastroenterology*. 2014;147:618-627.
- Sands BE, Peyrin-Boulet L, Loftus EV, et al, for the VARSITY study group. Vedolizumab versus adalimumab for moderate-to-severe ulcerative colitis. *N Engl J Med*. 2019[a];381(13):1215-1226. doi: 10.1056/NEJMoa1905725.
- Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. *N Engl J Med*. 2019[b];381(13):1201-1214. doi: 10.1056/NEJMoa1900750.
- sfRowasa [package insert], Somerset, NJ: Meda Pharmaceuticals, Inc.; October 2020.
- Shao L-M, Chen M-Y, Chen Q-Y, et al. Meta-analysis: the efficacy and safety of certolizumab pegol in Crohn's disease. *Aliment Pharmacol Ther.* 2009;29(6):605-14. doi: 10.1111/j.1365-2036.2009.03929.x.
- Sherlock ME, MacDonald JK, Griffiths AM, et al. Oral budesonide for induction of remission in ulcerative colitis. *Cochrane Database Syst Rev.* 2015, Issue 10. Art. No.: CD007698. DOI: 10.1002/14651858.CD007698.pub3.
- Shivashankar R, Tremaine WJ, Harmsen WS, Loftus EV Jr. Incidence and prevalence of Crohn's disease and ulcerative colitis in Olmsted county, Minnesota from 1970 through 2010. *Clin Gastroenterol Hepatol*. 2017;15(6):857-863. doi: 10.1016/j.cgh.2016.10.039.
- Simponi [package insert], Janssen Biotech, Inc. Horsham, PA. September 2019.
- Singh S, Fumery M, Sandborn WJ, and Murad MH. Systematic review with network meta-analysis: first- and second-line pharmacotherapy for moderate-severe ulcerative colitis. *Aliment Pharmacol Ther*. 2018;47(2):162-175. doi:10.1111/apt.14422.
- Singh S, Kumar S, Pardi D, et al. Comparative efficacy of biologic therapy in biologic naïve patients with Crohn's disease: a systematic review and network meta-analysis. *Mayo Clin Proc*. 2014;89:1621-35. doi: 10.1016/j.mayocp.2014.08.019.
- Snapper SB, McGovern DPB. Genetic factors in inflammatory bowel disease. UpToDate Web site. www.uptodate.com. Updated January 25, 2021. Accessed August 19, 2021.
- Stelara [package insert], Janssen Biotech. Horsham, PA. December 2020.
- Targan SR, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med.* 1997;337(15):1029-35. doi: 10.1056/NEJM199710093371502.
- Tong JL, Huang ML, Xu XT, et al. Once-daily vs multiple-daily mesalamine for patients with ulcerative colitis: a meta-analysis. *J Dig Dis*. 2012;13:200-7.
- Torres J, Bonovas S, Doherty G, et al. ECCO guidelines on therapeutics in Crohn's disease: medical treatment. *J Crohns Colits*. 2020;14(1):4-22. doi: 10.1093/ecco-jcc/jjz180.
- Tysabri [package insert], Biogen, Inc. Cambridge, MA. June 2020.
- Uceris extended-release tablet [package insert], Bridgewater, NJ: Salix Pharmaceuticals, Inc; April 2020.
- Uceris rectal foam [package insert], Bridgewater, NJ: Salix pharmaceuticals, Inc.; April 2020.
- Wu G, Yang Y, Liu M, Wang Y, Guo Q. Systematic review and network meta-analysis: comparative efficacy and safety of biosimilars, biologics and JAK1 inhibitors for active Crohn disease. *Front Pharmacol*. 2021;12:655865. doi:10.3389/fphar.2021.655865.
- Xeljanz / Xeljanz XR/Xeljanz oral solution [package insert], Pfizer, Inc. New York, NY. October 2020.
- Ye RD, Pesegova M, Alexeeva O, et al. Efficacy and safety of biosimilar CT-P13 compared with originator infliximab in patients with active Crohn's disease: an international, randomized, double-blind, phase 3 non-inferiority study. *Lancet*. 2019;393(10182):1699-1707. doi: 10.1016/S0140-6736(18)32196-2.
- Zeposia [package insert], Summit, NJ: Celgene Corporation; May 2021.
- Zhang ZM, Li W, Jiang XL. Efficacy and safety of adalimumab in moderately to severely active cases of ulcerative colitis: a meta-analysis of published placebo-controlled trials. *Gut Liver*. 2016;10(2):262-74. doi: 10.5009/gnl15042.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Zhu Y, Ren-kuan T, Zhao P, et al. Can oral 5-aminosalicyclic acid be administered once daily in the treatment of mild-to-moderate ulcerative colitis? A meta-analysis of randomized-controlled trials. *Eur J Gastroenterol Hepatol*. 2012;24:487-494.

Publication Date: September 24, 2021

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Prior Authorization Guideline

Guideline Name: Respiratory Monoclonal Antibody Agents

1. Criteria

Product Name: **Cinqair**	
Approval Length	12 month(s)
Guideline Type	Prior Authorization

Approval Criteria

1 - The recipient will not use the requested antiasthmatic monoclonal antibody in combination with other antiasthmatic monoclonal antibodies

AND

2 - The recipient must have a diagnosis of severe eosinophilic-phenotype asthma

AND

3 - The recipient is 18 years of age or older

AND

4 - The prescriber must be either a pulmonologist or allergist/immunologist

AND

5 - The recipient must be uncontrolled on current therapy including high dose corticosteroid and/or on a secondary asthma inhaler

AND

6 - There is documentation of the recipient's vaccination status

AND

7 - The requested dose is 3 mg/kg via intravenous infusion of 20 to 50 minutes every four weeks

Product Name: **Dupixent**	
Approval Length	6 Months for Asthma, 12 Months for Atopic Dermatitis and CRSwNP
Therapy Stage	Initial Authorization

Approval Criteria

1 - Diagnosis of moderate to severe atopic dermatitis and all of the following:

1.1 Prescribed by or in consultation with a dermatologist or allergist/immunologist

AND

1.2 One of the following:

1.2.1 Trial and failure, contraindication, or intolerance to one medium to high potency topical corticosteroid (e.g. betamethasone, tramcinolone)

OR

1.2.2 Trial and failure or intolerance to one of the following, unless the recipient is not a candidate for therapy (e.g. immunocompromised):

- Elidel (pimecrolumus) topical cream
- Tacrolimus topical ointment

OR

2 - Diagnosis of moderate to severe asthma and all of the following:

2.1 Recipient is 6 years of age or older

AND

2.2 One of the following:

2.2.1 The recipient is currently dependent on oral corticosteroids for the treatment of asthma
- One or more asthma exacerbations requiring systemic corticosteroids within the past 12 months
- Any prior intubation for an asthma exacerbation
- Prior asthma-related hospitalization within the past 12 months

OR

2.2.2 All of the following:

2.2.2.1 Asthma is an eosinophilic phenotype as defined by a baseline (pre-treatment) peripheral blood eosinophil level greater than or equal to 150 cells per microliter

AND

2.2.2.2 The recipient has one of the following:

- One or more asthma exacerbations requiring systematic corticosteroid within the past 12 months
- Any prior intubation for an asthma exacerbation
- Prior asthma-related hospitalization within the past 12 months

AND

2.3 Recipient is currently being treated with one of the following (or there is a contraindication or intolerance to all of these medications):

2.3.1 Both a high-dose inhaled corticosteroid (ICS) (e.g., greater than 500 mcg fluticasone propionate equivalent/day) and an additional asthma controller medication (e.g., leukotriene receptor antagonist, long-acting beta-2 agonist (LABA), theophylline)

OR

2.3.2 One maximally dosed combination ICS/LABA product (e.g., Advair [fluticasone propionate/salmeterol], Dulera [mometasone/formoterol], Symbicort [budesonide/formoterol])

AND

2.4 Prescribed by or in consultation with a pulmonologist or allergy/immunology specialist

OR

3 - Diagnosis of Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP) and all of the following:

3.1 Unless contraindicated, the recipient has had an inadequate response to two months of treatment with an intranasal corticosteroid (e.g., fluticasone, mometasone) [Document drug(s), dose, duration and date of trial]

AND

3.2 The medication will not be used in combination with another agent for CRSwNP

AND

3.3 Prescribed by or in consultation with an allergist/immunologist

Product Name: **Dupixent**	
Approval Length	12 month(s)
Therapy Stage	Reauthorization

Approval Criteria

1 - Diagnosis of moderate to severe atopic dermatitis and all of the following:

1.1 Documentation of positive clinical response to Dupixent therapy

OR

2 - Diagnosis of moderate to severe eosinophilic asthma or oral corticosteroid-dependent asthma and all of the following:

2.1 Documentation of a positive clinical response to Dupixent therapy (e.g., reduction in exacerbations, improvement in FEV1, reduction in oral corticosteroid dose)

AND

2.2 Recipient is currently being treated with one of the following (or there is a contraindication or intolerance to all of these medications):

2.2.1 Both an inhaled corticosteroid (ICS) and an additional asthma controller medication (e.g., leukotriene receptor antagonist, long-acting beta-2 agonist (LABA), theophylline)

OR

2.2.2 A combination ICS/LABA product (e.g., Advair (fluticasone propionate/salmeterol), Dulera (mometasone/formoterol), Symbicort (budesonide/formoterol))

AND

2.3 Prescribed by or in consultation with a pulmonologist or allergy/immunology specialist

OR

3 - Diagnosis of Chronic Rhinosinusitis with Nasal Polyposis (CRSwNP) and all of the following:

3.1 Documentation of a positive clinical response to therapy

AND

3.2 The medication will not be used in combination with another agent for CRSwNP

AND

3.3 Prescribed by or in consultation with an allergist/immunologist

Product Name: **Fasenra**	
Approval Length	12 month(s)
Therapy Stage	Initial Authorization

Approval Criteria

1 - The recipient will not use the requested antiasthmatic monoclonal antibody in combination with other antiasthmatic monoclonal antibodies

AND

2 - The recipient has a diagnosis of severe eosinophilic phenotype asthma

AND

3 - The recipient is 12 years of age or older

AND

4 - Recipient has one of the following:

- One or more asthma exacerbations requiring systemic corticosteroids within the past 12 months
- Any prior intubation for an asthma exacerbation
- Prior asthma-related hospitalization within the past 12 months

AND

5 - Recipient is currently being treated with one of the following (or there is a contraindication or intolerance to all of these medications):

5.1 Both a high-dose inhaled corticosteroid (ICS) (e.g., greater than 500 mcg fluticasone propionate equivalent/day) and an additional asthma controller medication (e.g., leukotriene receptor antagonist, long-acting beta-2 agonist (LABA), theophylline)

OR

5.2 One maximally dosed combination ICS/LABA product (e.g., Advair (fluticasone propionate/salmeterol), Dulera (mometasone/formoterol), Symbicort (budesonide/ formoterol))

AND

6 - Prescribed by or in consultation with a pulmonologist or allergy/immunology specialist

Product Name: **Fasenra**	
Approval Length	12 month(s)
Therapy Stage	Reauthorization

Approval Criteria

1 - There is documentation of a positive clinical response (e.g., reduction in exacerbation)

AND

2 - Recipient is currently being treated with one of the following (or there is a contraindication or intolerance to all of these medications):

2.1 Both an inhaled corticosteroid (ICS) and an additional asthma controller medication (e.g., leukotriene receptor antagonist, long-acting beta-2 agonist (LABA), theophylline)

OR

2.2 A combination ICS/LABA product (e.g., Advair (fluticasone propionate/salmeterol), Dulera (mometasone/formoterol), Symbicort (budesonide/formoterol))

AND

3 - Prescribed by or in consultation with a pulmonologist or allergy/immunology specialist

Product Name: **Nucala**	
Approval Length	6 Months for Asthma, 12 Months for EGPA
Therapy Stage	Initial Authorization

Approval Criteria

1 - The recipient has diagnosis of severe asthma and all of the following:

1.1 The asthma is an eosinophilic phenotype as defined by one of the following:

- Baseline (pre-treatment) peripheral blood eosinophil level greater than or equal to 150 cells/microliter
- Peripheral blood eosinophil levels were greater than or equal to 300 cells/microliter within the past 12 months

AND

1.2 Recipient has one of the following:

- One or more asthma exacerbations requiring systemic corticosteroid within the past 12 months
- Any prior intubation for an asthma exacerbation
- Prior asthma-related hospitalization within the past 12 months

AND

1.3 Recipient is currently being treated with one of the following (or there is a contraindication or intolerance to all of these medications):

1.3.1 Both a high-dose inhaled corticosteroid (ICS) (e.g., greater than 500 mcg fluticasone propionate equivalent/day) and an additional asthma controller medication (e.g., leukotriene receptor antagonist, long-acting beta-2 agonist (LABA), theophylline)

OR

1.3.2 One maximally dosed combination ICS/LABA product (e.g., Advair (fluticasone propionate/salmeterol), Dulera (mometasone/formoterol), Symbicort (budesonide/ formoterol))

AND

1.4 Recipient is 6 years of age or older

AND

1.5 Prescribed by or in consultation with a pulmonologist or allergist/immunologist

OR

2 - The recipient has diagnosis of Eosinophilic Granulomatosis with Polyangiitis (EGPA) and all of the following:

2.1 The recipient's disease has relapsed or is refractory to standard of care therapy (i.e. corticosteroid treatment with or without immunosuppressive therapy)

AND

2.2 The recipient is currently receiving corticosteroid therapy

AND

2.3 Prescribed by or in consultation with one of the following:
- Pulmonologist
- Rheumatologist
- Allergist/Immunologist

Product Name: **Nucala**	
Approval Length	12 month(s)
Therapy Stage	Reauthorization

Approval Criteria

1 - The recipient has diagnosis of severe eosinophilic-phenotype asthma and all of the following:

1.1 Documentation of positive clinical response to therapy (e.g. reduction in exacerbations, improvement in forced expiratory volume in one second [FEV1], decreased use of rescue medications)

AND

1.2 Recipient is currently being treated with one of the following (or there is a contraindication or intolerance to all of these medications):

1.2.1 Both an inhaled corticosteroid (ICS) and an additional asthma controller medication (e.g., leukotriene receptor antagonist, long-acting beta-2 agonist (LABA), theophylline)

OR

1.2.2 A combination ICS/LABA product (e.g., Advair [fluticasone propionate/salmeterol], Dulera [mometasone/formoterol], Symbicort [budesonide/formoterol])

AND

1.3 Prescribed by or in consultation with a pulmonologist or allergist/immunologist

OR

2 - The recipient has diagnosis of Eosinophilic Granulomatosis with Polyangiitis (EGPA) and all of the following:

2.1 Documentation of positive clinical response to therapy (e.g. increase in remission time)

Product Name: **Xolair**	
Approval Length	12 month(s)
Guideline Type	Prior Authorization

Approval Criteria

1 - The recipient will not use the requested antiasthmatic monoclonal antibody in combination with other antiasthmatic monoclonal antibodies

AND

2 - One of the following:

2.1 Diagnosis of moderate to severe persistent asthma and all of the following:

2.1.1 The recipient must be six years of age or older

AND

2.1.2 The recipient must have a history of a positive skin test or Radioallergosorbent (RAST) test to a perennial aeroallergen

AND

2.1.3 The prescriber must be either a pulmonologist or allergist/immunologist

AND

2.1.4 The recipient must have had an inadequate response, adverse reaction or contraindication to inhaled corticosteroids

AND

2.1.5 The recipient must have had an inadequate response, adverse reaction or contraindication to a leukotriene receptor antagonist

AND

2.1.6 The recipient must have had a pretreatment serum total Immunoglobulin E (IgE) level between 30 IU/mL and 700 IU/mL

AND

2.1.7 The recipient's current weight must be recorded (document weight)

AND

2.1.8 The requested dose is appropriate for the recipient's pre-treatment serum IgE and body weight (see Table 1 (pharmacist review required))

OR

2.2 Diagnosis of chronic idiopathic urticaria (CIU) and all of the following:

2.2.1 The recipient is 12 years of age or older

AND

2.2.2 The recipient must have had an inadequate response, adverse reaction, or contraindication to two different oral second-generation antihistamines

AND

2.2.3 The recipient must have had an inadequate response, adverse reaction, or contraindication to an oral second-generation antihistamine in combination with a leukotriene receptor antagonist

AND

2.2.4 The prescriber must be one of the following, or there is documentation in the recipient's medical record that a consultation regarding diagnosis and treatment recommendations was done by one of the following:

- Allergist/immunologist
- Dermatologist
- Rheumatologist

AND

2.2.5 One of the following:

2.2.5.1 The request is for initiation of therapy and the dose will be 150 mg every four weeks

OR

2.2.5.2 The request is for initiation of therapy and the dose will be 300 mg every four weeks, and clinical rationale for starting therapy at 300 mg every four weeks has been provided (pharmacist review required)

OR

2.2.5.3 The request is for continuation of therapy and the dose will be 150 mg or 300 mg every four weeks

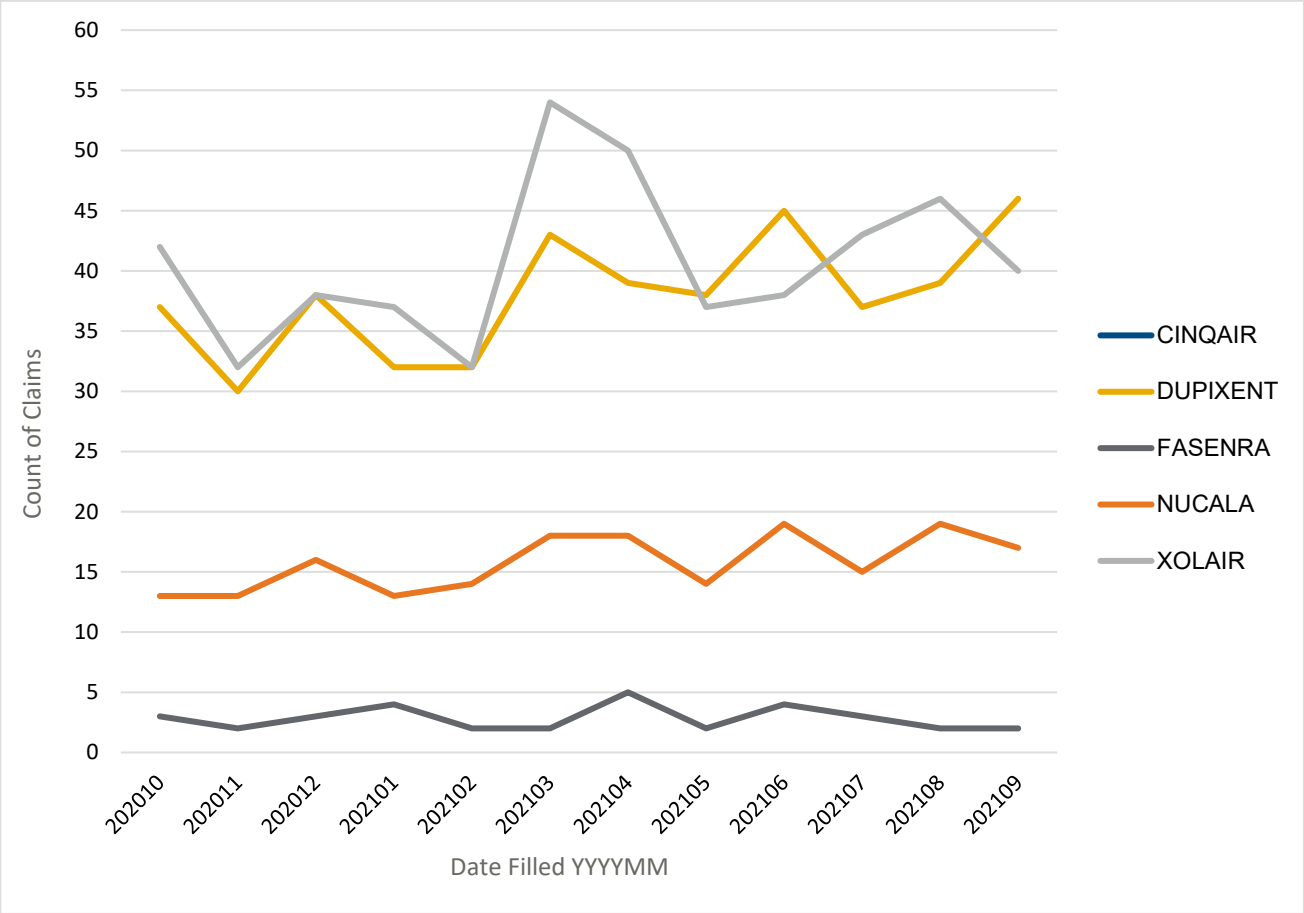
Nevada Medicaid

Utilization

Fee for Service

October 1, 2020 – September 30, 2021

Drug Name	Members	Claims	Total Day Supply	Total Quantity
CINQAIR	1	1	1	20
DUPIXENT	60	456	12,564	2,993
FASENRA	11	34	1,436	34
NUCALA	27	189	3,591	15,186
XOLAIR	62	489	10,877	5,483



Therapeutic Class Overview
Antiasthmatic – Monoclonal Antibodies

INTRODUCTION

- Asthma is a chronic lung disease that inflames and narrows the airways, making it difficult to breathe. Asthma causes recurring periods of wheezing, chest tightness, shortness of breath, and coughing. Asthma affects people of all ages, but most often starts during childhood. In 2019, asthma affected an estimated 20 million adults and 5.1 million children in the United States (U.S.). The exact cause(s) of asthma are unknown. A combination of factors such as genetics, certain respiratory infections during childhood, and contact with airborne allergens can contribute to its development. Most patients with asthma have allergies (*Centers for Disease Control and Prevention [CDC] 2021, National Heart, Lung, and Blood Institute [NHLBI] Web site*).
- Current pharmacologic options for asthma management are categorized as: (1) control medications to achieve and maintain control of persistent asthma or prevent exacerbations, and (2) quick-relief medications used to treat acute symptoms and exacerbations (*Cloutier et al 2020, NHLBI 2007, Global Initiative for Asthma [GINA] 2021*).
  - Control medications include:
    - Corticosteroids (inhaled corticosteroids [ICSs], or oral corticosteroids for severe exacerbations)
    - Long-acting beta$_2$-agonists (LABAs)
    - Leukotriene receptor antagonists (LTRAs) in select patients
    - Methylxanthines (ie, theophylline) in select patients
    - Add-on immunomodulators (ie, omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab) in patients with severe asthma
    - Add-on tiotropium in patients whose asthma is not well-controlled with ICS/LABA
    - Add-on azithromycin in patients whose asthma is not well-controlled with high dose ICS/LABA
  - Quick-relief/reliever medications include:
    - Short-acting beta$_2$-agonists (SABAs) for relief of acute symptoms and prevention of exercise-induced bronchospasm
    - ICS-formoterol for relief of acute symptoms and if needed before exercise
    - Anticholinergics (ie, ipratropium bromide) as an alternative bronchodilator for those not tolerating a SABA
    - Systemic corticosteroids, although not short-acting, are used for moderate and severe exacerbations as part of initial treatment.
- Approximately 3.7% of asthma patients have severe disease and 17% have difficult-to-treat asthma. Severe asthma is defined as asthma that is uncontrolled despite adherence to maximal optimized high dose ICS/LABA treatment or asthma that requires high doses of ICS/LABA to remain controlled (*GINA 2021*).
- While there are currently no widely accepted definitions of specific asthma phenotypes, several strategies have been proposed to categorize severe asthma phenotypes based on characteristics such as patient age, disease onset, corticosteroid resistance, chronic airflow obstruction, or type of cellular infiltrate in the airway lumen or lung tissue (*Walford et al 2014*). The most recent GINA guideline on severe or difficult-to-treat asthma recommends assessing for Type 2 inflammation through blood and sputum eosinophil levels, exhaled nitric oxide level, and allergic triggers to asthma (*GINA 2021*).
- Chronic idiopathic urticaria (CIU), also called chronic spontaneous urticaria, is defined by the presence of hives on most days of the week for 6 weeks or longer, with or without angioedema. The hives are circumscribed, raised, erythematous plaques, often with central pallor and variable in size. No external allergic cause or contributing disease process can be identified in 80 to 90% of adults and children with CIU (*Khan 2021, Saini 2021*).
- CIU affects up to 1% of the general population in the U.S., and the prevalence is believed to be similar in other countries. The condition is more common in adults than children and typically begins in the third to fifth decades of life. CIU is a self-limited disorder in most patients although the condition generally has a prolonged duration of 2 to 5 years (*Saini 2021*).
- Non-sedating H_1-antihistamines are the cornerstone of therapy for CIU. Limited courses of oral glucocorticoids are often used in combination with antihistamines for refractory symptoms. Other pharmacologic options for patients who do not

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

respond to H_1-antihistamines include the use of H_2-antihistamines, leukotriene modifiers, cyclosporine, tacrolimus, mycophenolate, hydroxychloroquine, sulfasalazine, dapsone, and omalizumab (*Khan 2021, Maurer et al 2013*).

- Eosinophilic granulomatosis with polyangiitis (EGPA), previously called Churg-Strauss syndrome, is a systemic necrotizing vasculitis that affects small-to-medium-sized vessels. It is typically associated with eosinophilia and severe asthma (*Groh et al 2015, Padmanabhan et al 2019).*
- EGPA is a rare condition with a prevalence of approximately 13 cases per 1 million persons and an annual incidence of approximately 7 new cases per 1 million persons. It has a higher incidence in patients with asthma (*Groh et al 2015*).
- Systemic glucocorticoids are the mainstay of treatment for EGPA. For refractory EGPA, the addition of cyclophosphamide, azathioprine, methotrexate, rituximab, or intravenous immunoglobulins (IVIG) can be considered *(Groh et al 2015).* In more than 85% of patients with EGPA, remission can be achieved with glucocorticoids with or without an immunosuppressant; however, relapses occur in more than 33% of patients (*Pagnoux and Groh 2016*).
- Chronic rhinosinusitis with nasal polyposis (CRSwNP) has a prevalence of approximately 2.7% in adults, and peaks in the sixth decade of life. Symptoms include nasal obstruction, reduced sense of smell, and sleep disturbance, all of which can substantially impact the quality of life. The majority of cases are idiopathic, but may be due to genetic, metabolic, or immunologic causes, resulting in inflammation characterized by eosinophilia and elevated levels of IL-4, IL-5, and IL-13 *(Hopkins 2019)*.
- Common treatment options for CRSwNP include saline irrigation and intranasal glucocorticoids in patients with mild symptoms, and short-term systemic glucocorticoids, surgery, and biologic agents in patients with severe symptoms *(Hopkins 2019)*.
- Hypereosinophilic syndromes (HES) are disorders characterized by overproduction of eosinophils which causes organ damage (*Roufosse et al 2020a*). Treatment for idiopathic HES may include systemic glucocorticoids, imatinib, hydroxyurea, interferon alfa, alemtuzumab, and Janus kinase inhibitors (eg, tofacitinib and ruxolitinib). Additionally, mepolizumab was Food and Drug Administration (FDA)-approved for HES in 2020.
- This monograph describes the use of Cinqair (reslizumab), Dupixent (dupilumab), Fasenra (benralizumab), Nucala (mepolizumab), and Xolair (omalizumab).
  - Cinqair, Fasenra, and Nucala are humanized monoclonal antibody interleukin-5 (IL-5) antagonists. The mechanism of action of Fasenra is slightly different, in that it binds to the IL-5 receptor on immune effector cells, whereas Cinqair and Nucala bind to the IL-5 cytokine. Eosinophils play a key role in the pathobiology of airway disorders by contributing to inflammation through the release of leukotrienes and pro-inflammatory cytokines. Increases in eosinophils are often correlated with greater asthma severity. IL-5, a cytokine critical to eosinophil differentiation and survival, has been isolated as a potential target in eosinophilic asthma.
    - Nucala is also approved for the treatment of adult patients with EGPA and patients ≥ 12 years of age with HES.
  - Xolair is a recombinant DNA-derived monoclonal antibody that selectively binds to human IgE. Xolair, which reduces the allergic response mediators, is useful in a subset of patients with allergic asthma. In addition, Xolair has been shown to improve symptoms in patients with CIU and is indicated for add-on maintenance treatment of nasal polyps in adult patients with inadequate response to nasal corticosteroids.
  - Dupixent is a human monoclonal antibody that inhibits signaling of IL-4 and IL-13. This results in a reduction of the release of inflammatory mediators including cytokines, chemokines, nitric oxide, and IgE. These actions are useful for eosinophilic asthma and add-on therapy for inadequately controlled CRSwNP. Dupixent is also approved to treat moderate to severe atopic dermatitis, but this indication is not discussed further in this review.
- Medispan class: Antiasthmatic – Monoclonal Antibodies

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Cinqair (reslizumab)	--
Dupixent (dupilumab)	--
Fasenra (benralizumab)	--
Nucala (mepolizumab)	--
Xolair (omalizumab)	--

(*Drugs@FDA 2021, Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations 2021*)

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

INDICATIONS

Table 2: Food and Drug Administration Approved Indications*

Indication	Cinqair† (reslizumab)	Dupixent (dupilumab)	Fasenra† (benralizumab)	Nucala (mepolizumab)	Xolair‡ (omalizumab)
Moderate to severe persistent asthma in patients ≥ 6 years of age with a positive skin test or in vitro reactivity to a perennial aeroallergen and symptoms that are inadequately controlled with ICS					✔
Add-on maintenance treatment for patients ≥ 12 years of age with severe asthma with an eosinophilic phenotype			✔		
Add-on maintenance treatment for patients ≥ 6 years of age with severe asthma with an eosinophilic phenotype				✔	
Add-on maintenance treatment for patients ≥ 12 years of age with moderate-to-severe asthma with an eosinophilic phenotype or with oral corticosteroid dependent asthma		✔			
Add-on maintenance treatment for patients ≥ 18 years of age with severe asthma with an eosinophilic phenotype	✔				
Treatment of adult patients with eosinophilic granulomatosis with polyangiitis (EGPA)				✔	
Add-on maintenance treatment of nasal polyps for patients ≥ 18 years of age with an inadequate response to nasal corticosteroids					✔
The treatment of adults and adolescents ≥ 12 years of age with chronic idiopathic urticaria (CIU) who remain symptomatic					✔

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Indication	Cinqair† (reslizumab)	Dupixent (dupilumab)	Fasenra† (benralizumab)	Nucala (mepolizumab)	Xolair‡ (omalizumab)
despite H_1-antihistamine treatment.					
Add-on maintenance treatment in adult patients with inadequately controlled chronic rhinosinusitis with nasal polyposis (CRSwNP)		✔			
Treatment of adult and pediatric patients ≥ 12 years of age with hypereosinophilic syndrome (HES) for ≥ 6 months without an identifiable non-hematologic secondary cause				✔	

* None of the agents are indicated for the relief of acute bronchospasm or status asthmaticus.
† Not indicated for the treatment of other eosinophilic conditions
‡ Not indicated for other allergic conditions or other forms of urticaria

(*Prescribing information: Cinqair 2020, Dupixent 2021, Fasenra 2021, Nucala 2020, Xolair 2021*)

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

CLINICAL EFFICACY SUMMARY

OMALIZUMAB

Asthma

- The original FDA approval of omalizumab was based on the results of 3 randomized, double-blind, placebo-controlled, multicenter trials conducted in patients ≥ 12 years of age with moderate to severe asthma for ≥ 1 year and a positive skin test reaction to a perennial aeroallergen. All patients were required to have a baseline IgE between 30 and 700 international unit (IU)/mL and body weight not more than 150 kg. Patients were treated according to a dosing table to administer at least 0.016 mg/kg/IU (IgE/mL) of omalizumab or placebo over each 4-week period.
  - Each study was comprised of a run-in period to achieve a stable conversion to a common ICS, followed by randomization to omalizumab or placebo. Patients received omalizumab for 16 weeks with an unchanged ICS dose unless an acute exacerbation necessitated an increase. Patients then entered an ICS reduction phase of 12 (*Busse et al 2001, Solèr et al 2001*) and 16 weeks (*Holgate et al 2004*) during which ICS dose reduction was attempted in a stepwise manner.
  - In the 28-week study by Busse et al (N = 525), during the steroid stable phase, patients treated with omalizumab had fewer mean exacerbations/subject (0.28 vs 0.54; p = 0.006) and decreased mean duration of exacerbations (7.8 vs 12.7 days; p < 0.001) compared with placebo-treated patients. Similarly, during the steroid reduction phase, omalizumab was associated with fewer exacerbations/subject (0.39 vs 0.66; p = 0.003), and a shorter mean duration of exacerbations (9.4 vs 12.6 days; p = 0.021) (*Busse et al 2001*).
  - In the 28-week study by Solèr et al (N = 546), asthma exacerbations/patient, the primary endpoint, decreased more in the omalizumab group compared to placebo during both the stable steroid (0.28 vs 0.66; p < 0.001) and steroid reduction phases (0.36 vs 0.75; p < 0.001) (*Solèr et al 2001*).
  - In the 32-week study by Holgate et al (N = 246), the percentage reduction in ICS dose, the primary endpoint, was greater among patients treated with omalizumab than among patients treated with placebo (median, 60 vs 50%; p = 0.003). The percentages of patients with ≥ 1 asthma exacerbation were similar between omalizumab and placebo groups during both the stable steroid and steroid reduction phases (p-value not reported). The absence of an

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

observed treatment effect may be related to differences in the patient population compared with the first 2 studies, study sample size, or other factors (*Holgate et al 2004*).

- A meta-analysis of 3 of the previously mentioned trials (*Busse et al 2001, Holgate et al 2004, Solèr et al 2001*) and their extension studies assessed the efficacy of omalizumab in a subgroup of 254 patients at high risk of serious asthma-related mortality and morbidity. Patients were defined as high-risk due to asthma histories that included the following: intubation history, emergency room visit within the last year, overnight hospitalization, or intensive care unit treatment. The primary outcome was an annualized rate of acute exacerbation episodes based on data from the initial 16-week stable steroid phase for high-risk patients. Two kinds of acute exacerbation episodes were considered as endpoints: significant acute exacerbation episodes and all acute exacerbation episodes (ie, all episodes recorded by the investigator). Significant acute exacerbation episodes were defined as those requiring a doubling of baseline ICS dose (*Busse et al 2001, Solèr et al 2001*) or use of systemic steroids (all 3 studies). During the stable steroid phase, mean significant acute exacerbation episode rates were 1.56 and 0.69/patient-year, respectively, a reduction of 56% with omalizumab (p = 0.007). Similar reductions in exacerbations in favor of omalizumab were observed for the whole study period and for all acute exacerbation episodes. The authors concluded that 113 significant acute exacerbation episodes were prevented for every 100 patients treated with omalizumab for 1 year (*Holgate et al 2001*).
- A Cochrane Review conducted in 2014 evaluated the efficacy of omalizumab in patients with allergic asthma. Treatment with omalizumab was associated with a significant reduction in the odds of a patient having an asthma exacerbation (odds ratio [OR], 0.55; 95% confidence interval [CI], 0.42 to 0.6; 10 studies; 3261 participants). This represents an absolute reduction from 26% for participants suffering an exacerbation on placebo to 16% on omalizumab, over 16 to 60 weeks. Additionally, in patients with moderate to severe asthma and in those who were receiving background ICS therapy, treatment with omalizumab resulted in a significant reduction in the odds of having an asthma exacerbation (OR, 0.50; 95% CI, 0.42 to 0.6; 7 studies; 1889 participants). A significant benefit was noted for subcutaneous (SC) omalizumab vs placebo with regard to reducing hospitalizations (OR, 0.16, 95% CI, 0.06 to 0.42; 4 studies; 1824 participants), representing an absolute reduction in risk from 3% with placebo to 0.5% with omalizumab over 28 to 60 weeks. The authors concluded that omalizumab was effective in reducing asthma exacerbations and hospitalizations as an adjunctive therapy to ICS and significantly more effective than placebo in increasing the numbers of participants who were able to reduce or withdraw their ICS. Omalizumab was generally well tolerated, although there were more injection site reactions with omalizumab. However, the clinical value of the reduction in steroid consumption has to be considered in light of the high cost of omalizumab (*Normansell et al 2014*).
- A systematic review of 8 randomized, placebo-controlled trials (N = 3429) evaluated the efficacy and safety of SC omalizumab as add-on therapy to corticosteroids in children and adults with moderate to severe allergic asthma. At the end of the steroid reduction phase, patients taking omalizumab were more likely to be able to withdraw corticosteroids completely compared with placebo (relative risk [RR], 1.8; 95% CI, 1.42 to 2.28; p = 0.00001). Omalizumab patients showed a decreased risk for asthma exacerbations at the end of the stable (RR, 0.57; 95% CI, 0.48 to 0.66; p = 0.0001) and adjustable-steroid phases (RR, 0.55; 95% CI, 0.47 to 0.64; p = 0.0001); post-hoc analysis suggests this effect was independent of duration of treatment, age, severity of asthma, and risk of bias. The frequency of serious adverse effects was similar between omalizumab (3.8%) and placebo (5.3%). However, injection site reactions were more frequent in the omalizumab patients (19.9 vs 13.2%). Omalizumab was not associated with an increased risk of hypersensitivity reactions, cardiovascular effects, or malignant neoplasms (*Rodrigo et al 2011*).
- In July 2016, the FDA expanded the indication of omalizumab to patients 6 to 11 years of age with moderate to severe persistent asthma. The approval was based primarily on a 52-week, randomized, double-blind, placebo-controlled, multicenter trial. The study evaluated the safety and efficacy of omalizumab as add-on therapy in 628 pediatric patients 6 to < 12 years of age with moderate to severe asthma inadequately controlled despite the use of an ICS (*Lanier et al 2009*).
  - Over the 24-week fixed-steroid phase, omalizumab reduced the rate of clinically significant asthma exacerbations (worsening symptoms requiring doubling of baseline ICS dose and/or systemic steroids) by 31% vs placebo (0.45 vs 0.64; RR, 0.69; p = 0.007). Over a period of 52 weeks, the exacerbation rate was reduced by 43% (p < 0.001). Other efficacy variables such as nocturnal symptom scores, beta-agonist use, and forced expiratory volume in 1 second (FEV_1) were not significantly different in omalizumab-treated patients compared to placebo.
- A 2017 systematic review of 3 randomized, placebo-controlled trials and 5 observational studies evaluated the safety and efficacy of omalizumab in children and adolescents. Omalizumab reduced exacerbations compared with placebo or baseline in all studies that included this outcome. The randomized controlled trials did not identify significant differences in FEV_1; however, 3 of the 4 observational studies that included this outcome did find significant FEV_1 improvement with

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

omalizumab. Generally, ICS and rescue medication use were reduced with omalizumab in the studies. The authors concluded that the evidence strongly supports omalizumab safety and efficacy in patients 6 to 11 years *(Corren et al 2017)*.

- The EXCELS study was a multicenter, observational cohort study to evaluate the clinical effectiveness and long-term safety of omalizumab in patients with moderate-to-severe allergic asthma. Patients were evaluated as part of 3 groups: non-omalizumab users, those newly starting omalizumab, and those who have established users at study initiation.
  - Interim efficacy results demonstrated that at month 24, the ACT score increased in all 3 patient groups: from 18.4 to 20 in non-omalizumab users, from 15.2 to 19.4 in those newly starting on omalizumab, and from 18.2 to 19.4 in established omalizumab users. For patients newly starting omalizumab treatment, 54% achieved at least a minimally important difference, defined as a ≥ 3 point increase from baseline in ACT. The study demonstrated that established users of omalizumab maintained asthma control during the study period (*Eisner et al 2012*).
  - To investigate the relationship between omalizumab and malignant neoplasms, safety information from the EXCELS trial was analyzed. Similar rates of primary malignancies in omalizumab- and non-omalizumab-treated patients were found. However, study limitations preclude definitively ruling out a malignancy risk with omalizumab (*Long et al 2014*).
  - A higher incidence of overall cardiovascular and cerebrovascular serious adverse events was observed in omalizumab-treated patients compared to non-omalizumab-treated patients (*Iribarren et al 2017*). To further evaluate the risk, a pooled analysis of 25 randomized controlled trials was conducted. An increased risk of cardiovascular and cerebrovascular serious adverse events was not noted, but the low number of events, the young patient population, and the short duration of follow-up prevent a definite conclusion about the absence of a risk (*FDA 2014*).
  - Patients from the EXCELS study were eligible for the XPORT trial, a 52-week, randomized, placebo-controlled trial evaluating the persistence of response to omalizumab in patients who discontinued omalizumab therapy after long-term use. Patients were randomized to continue their omalizumab therapy or to omalizumab discontinuation. More patients who continued omalizumab did not have an exacerbation compared to those who discontinued therapy (67.0% vs 47.7%; absolute difference, 19.3%; 95% CI, 5.0 to 33.6). The authors concluded that continuation of omalizumab after long-term use results in sustained benefit (*Ledford et al 2017*).

Chronic idiopathic urticaria (CIU)

- The safety and efficacy of omalizumab for the treatment of CIU was assessed in 2 placebo-controlled, multiple-dose clinical studies. Patients received omalizumab 75, 150, or 300 mg or placebo by SC injection every 4 weeks in addition to their baseline level of H_1 antihistamine therapy for 24 or 12 weeks, followed by a 16-week washout observation period. In both studies, patients who received omalizumab 150 mg or 300 mg had greater decreases from baseline in weekly itch severity scores and weekly hive count scores than placebo at week 12. The 75 mg dose did not demonstrate consistent evidence of efficacy and is not approved for use (*Kaplan et al 2013, Maurer et al 2013*).
- Another randomized, double-blind, placebo-controlled study evaluated omalizumab as add-on therapy for 24 weeks in patients with CIU who remained symptomatic despite H_1 antihistamine therapy. Similar to previous studies, patients treated with omalizumab had significantly greater reductions in weekly itch severity score from baseline to week 12 compared to placebo ($p \leq 0.001$) (*Saini et al 2015*).
- A meta-analysis of randomized clinical trials evaluating omalizumab for the treatment of CIU was published in 2016. The analysis included 7 randomized, placebo-controlled studies with 1312 patients with CIU. Patients treated with omalizumab (75 to 600 mg every 4 weeks) had significantly reduced weekly itch and weekly wheal scores compared with the placebo group. The effects of omalizumab were dose-dependent, with the strongest reduction in weekly itch and weekly wheal scores observed with 300 mg. Rates of complete response were significantly higher in the omalizumab group ($p < 0.00001$) and dose-dependent, with the highest rates in the 300 mg group. Rates of patients with adverse events were similar in the omalizumab and placebo groups (*Zhao et al 2016*). Similar results were identified in a 2019 meta-analysis of 6 trials and a 2020 meta-analysis of 9 trials, both comparing omalizumab with placebo (*Jia and He 2020, Rubini et al 2019*).
- A Phase 4 randomized clinical trial evaluated the effect of omalizumab in 205 patients with antihistamine-resistant CIU/chronic spontaneous urticaria. After an initial 24-week period of open-label treatment with omalizumab 300 mg every 4 weeks, patients randomized to continue omalizumab for another 24 weeks of double-blind therapy experienced a significantly lower rate of clinical worsening compared with patients randomized to double-blind placebo (21.0% vs 60.4%; $p < 0.0001$). No new safety signals were detected over the 48-week omalizumab treatment period *(Maurer et al 2018)*.

Nasal Polyps

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- The efficacy and safety of omalizumab for the treatment of nasal polyps in adult patients with an inadequate response to intranasal corticosteroids were based on results from 2 randomized, multicenter, double-blind, placebo-controlled, Phase 3 studies, POLYP 1 (n = 138) and POLYP 2 (n = 127) (*Gevaert et al 2020*). Patients were randomly assigned to omalizumab 75 to 600 mg SC every 2 or 4 weeks (based upon pretreatment serum total IgE level and body weight) or placebo for 24 weeks. All patients received background intranasal mometasone therapy. Results from both studies revealed that omalizumab was associated with a significantly greater improvement from baseline at week 24 in Nasal Polyp Score (NPS) and weekly average Nasal Congestion Score (NCS) as compared to placebo. In POLYP 1 and POLYP 2, the mean changes in NPS from baseline to week 24 for omalizumab compared to placebo were -1.08 vs 0.06 ($p < 0.0001$) and -0.9 vs -0.31 ($p = 0.014$), respectively, and mean changed in NCS from baseline were -0.89 vs -0.35 ($p = 0.0004$) and -0.7 vs -0.2 ($p = 0.0017$), respectively. Adverse events were similar between treatment groups.

BENRALIZUMAB

Asthma

- The safety and efficacy of benralizumab were evaluated in a 52-week dose-ranging exacerbation trial, 4 confirmatory trials, and a 12-week lung function trial (*Bleecker et al 2016, Castro et al 2014, Ferguson et al 2017, Fitzgerald et al 2016, Nair et al 2017, Harrison et al 2021*).
  - In a randomized, controlled, double-blind, dose-ranging Phase 2b study, 324 adults with uncontrolled eosinophilic asthma were randomly assigned to placebo (n = 80), benralizumab 2 mg (n = 81), benralizumab 20 mg (n = 81), or benralizumab 100 mg (n = 82) and 285 adults with non-eosinophilic asthma were randomized to benralizumab 100 mg (n = 142) or placebo (n = 143) (*Castro et al 2014*). Treatments were given as 2 SC injections every 4 weeks for the first 3 doses, then every 8 weeks, for 1 year. Among adults with eosinophilic asthma, benralizumab 100 mg reduced exacerbation rates as compared to placebo (0.34 vs 0.57; rate reduction, 41%; 80% CI, 11 to 60; $p = 0.096$). A significant reduction in exacerbation rates was not seen with benralizumab 2 mg or 20 mg as compared to placebo in these patients. In patients with a baseline blood eosinophil count of ≥ 300 cells/µL, exacerbation rates were lower than in the placebo group for the benralizumab 20 mg (0.30 vs 0.68; rate reduction, 57%; 80% CI, 33 to 72; $p = 0.015$) and 100 mg (0.38 vs 0.68; rate reduction, 43%; 80% CI, 18 to 60; $p = 0.049$) groups.
  - SIROCCO was a randomized, multicenter, double-blind, placebo-controlled, 48-week, Phase 3 trial (N = 1205) involving patients with severe asthma with eosinophilia uncontrolled with high-dose ICS and LABAs (*Bleecker et al 2016*). Enrolled patients were randomly assigned to placebo (n = 407), benralizumab 30 mg every 4 weeks (n = 400), or benralizumab 30 mg every 8 weeks (n = 398). Compared with placebo, benralizumab reduced the annual asthma exacerbation rate over 48 weeks when administered every 4 weeks (RR, 0.55; 95% CI, 0.42 to 0.71; $p < 0.0001$) or every 8 weeks (RR, 0.49; 95% CI, 0.37 to 0.64; $p < 0.0001$). Both doses of benralizumab also significantly improved pre-bronchodilator FEV_1 in patients at week 48 vs placebo. Asthma symptoms were improved with benralizumab every 8 weeks, but not every 4 weeks, as compared to placebo.
  - CALIMA was a randomized, multicenter, double-blind, placebo-controlled, 56-week, Phase 3 trial that assessed benralizumab as add-on therapy (to high-dose ICS and LABA) for patients with severe, uncontrolled asthma and elevated blood eosinophil counts (*Fitzgerald et al 2016*). A total of 1306 patients were randomly assigned to benralizumab 30 mg every 4 weeks (n = 425), benralizumab 30 mg every 8 weeks (n = 441) or placebo (n = 440). When compared to placebo, significant reductions in annual exacerbation rates were seen with benralizumab every 4 weeks (RR, 0.64; 95% CI, 0.49 to 0.85; $p = 0.0018$) and every 8 weeks (RR, 0.72; 95% CI, 0.54 to 0.95; $p = 0.0188$). Benralizumab was also associated with significantly improved pre-bronchodilator FEV_1 and total asthma symptom scores vs placebo.
  - Patients enrolled in the SIROCCO and CALIMA trials who completed treatment were eligible for the BORA Phase 3 safety extension trial. This was a randomized, double-blind study that randomized patients to received benralizumab 30 mg every 4 or 8 weeks. Adult patients received treatment for 52 weeks and adolescents (12 to 17 years of age) were treated for 108 weeks. A total of 1576 patients were included in the full-analysis set with safety assessed at 56 weeks. Treatment discontinuation due to any adverse event occurred in approximately 2% of patients in each group. The most common adverse events were viral upper respiratory tract infections and worsening asthma. Serious adverse events included worsening asthma (3% in the every-8-week dosing group and 4% in the every-4-week dosing group), pneumonia (< 1% in both groups) and pneumonia caused by bacterial infection (< 1% in the every-4-week dosing group and 1% in the every-8-week dosing group). New malignancy occurred in 12 (1%) of the 1,576 patients. Hypersensitivity related to treatment occurred in 3 patients. For the secondary efficacy outcome, patients

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

with elevated blood eosinophil levels had similar exacerbation rates to that observed during the first year of treatment in the SIROCCO and CALIMA trials (*Busse et al 2019a*).
  - BISE was a randomized, multicenter, double-blind, placebo-controlled, 12-week, Phase 3 trial that evaluated benralizumab therapy for patients with mild to moderate persistent asthma (*Ferguson et al 2017*). Patients (N = 211) had been receiving either low- to medium-dose ICS or low-dose ICS plus LABA therapy and were randomized to benralizumab 30 mg every 4 weeks (n = 106) or placebo (n = 105). Benralizumab resulted in an 80 mL (95% CI, 0 to 150; p = 0.04) greater improvement in pre-bronchodilator FEV_1 after 12 weeks as compared to placebo. Despite this improvement, this lung function result does not warrant the use of benralizumab in mild to moderate asthma because it did not reach the minimum clinically important improvement of 10%.
  - ZONDA was a randomized, multicenter, double-blind, placebo-controlled, 28-week trial that primarily assessed whether or not benralizumab was effective as an oral glucocorticoid-sparing therapy in patients on oral steroids to manage severe asthma associated with eosinophilia (*Nair et al 2017*). Of the enrolled patients, 220 were randomly assigned to benralizumab 30 mg every 4 weeks (n = 72), benralizumab 30 mg every 8 weeks (n = 73), or placebo (n = 75). Results revealed that the 2 benralizumab dosing regimens significantly reduced the median final oral glucocorticoid doses from baseline by 75% vs a 25% reduction seen with placebo ($p < 0.001$ for both comparisons). Additionally, benralizumab administered every 4 weeks resulted in an annual exacerbation rate that was 55% lower than that seen with placebo (marginal rate, 0.83 vs 1.83; p = 0.003) and benralizumab administered every 8 weeks resulted in a 70% lower rate than that seen with placebo (marginal rate, 0.54 to 1.83; $p < 0.001$).
  - ANDHI was a randomized, multicenter, double-blind, placebo-controlled, Phase 3b study that assessed the effect of benralizumab in adults with severe eosinophilic asthma and at least 2 exacerbations in the previous year despite use of medium- to high-dose ICS plus another asthma controller (*Harrison et al 2021*). Patients were randomized to receive benralizumab 30 mg every 8 weeks (with the first 3 doses given 4 weeks apart; n = 427) or placebo (n = 229). Benralizumab significantly reduced annualized asthma exacerbation rate over the 24-week treatment period compared to placebo (RR, 0.51; 95% CI, 0.39 to 0.65; $p < 0.0001$).
- Fitzgerald et al conducted a study exploring the efficacy of benralizumab for patients with different baseline blood eosinophil thresholds and exacerbation histories. This study was a pooled analysis (n = 2295 patients) of the results from the SIROCCO and CALIMA Phase 3 studies. The annual exacerbation rate among patients with baseline blood eosinophil counts of ≥ 0 cells/μL was 1.16 (95% CI, 1.05 to 1.28) in patients who received placebo vs 0.75 (0.66 to 0.84) in patients who received benralizumab every 8 weeks (RR, 0.64; 0.55 to 0.75; $p < 0.0001$). In patients who received benralizumab every 4 weeks who had eosinophil counts of ≥ 0 cells/μL, the annual exacerbation rate was 0.73 (0.65 to 0.82); RR vs placebo was 0.63 (0.54 to 0.74; $p < 0.0001$). The extent to which exacerbation rates were reduced increased with increasing blood eosinophil thresholds and with greater exacerbation history in patients in the every-4-week and every-8-week benralizumab groups. Greater improvements in the annual exacerbation rate were seen with benralizumab compared with placebo for patients with a combination of high blood eosinophil thresholds and a history of more frequent exacerbations *(FitzGerald et al 2018).*
- A 2017 meta-analysis evaluated the therapeutic efficacy and safety of benralizumab in patients with eosinophilic asthma. A total of 7 articles (n = 2321) met the inclusion criteria of the systematic review. The pooled analysis found that benralizumab significantly reduced exacerbations (RR, 0.63; 95% CI, 0.52 to 0.76; $p < 0.00001$) compared to placebo. There was no statistical trend for improvement in FEV_1 or asthma control indices such as Quality of Life Assessment (AQLQ) and Asthma Control Questionnaire score in benralizumab-treated patients. In addition, safety data indicated that benralizumab administration did not result in an increased incidence of adverse events and was well tolerated (RR, 1.00; 95% CI, 0.95 to 1.05; p = 0.96) *(Tien et al 2017)*.

MEPOLIZUMAB

Asthma

- The safety and efficacy of mepolizumab were evaluated in 3 double-blind, placebo-controlled, multicenter, randomized controlled trials in adolescent and adult patients with severe refractory asthma and signs of eosinophilic inflammation. Generally, patients were eligible for enrollment in the trials if they had eosinophils ≥ 150 cells/μL in the peripheral blood at screening or ≥ 300 cells/μL at some time during the previous year. Patients also were required to be on a high-dose ICS as well as another controller medication (*Bel et al 2014, Ortega et al 2014, Pavord et al 2012*).
  - DREAM was a dose-ranging, 52-week, Phase 2b/3 study (N = 621) that compared annual asthma exacerbation frequency and improvements in clinical symptoms between patients receiving 75 mg, 250 mg, and 750 mg intravenous (IV) mepolizumab and placebo. Mepolizumab decreased clinically significant exacerbation rates across

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

all doses compared to placebo, at a rate of 2.40 per patient per year in the placebo group, 1.24 in the 75 mg mepolizumab group ($p < 0.0001$), 1.46 in the 250 mg mepolizumab group ($p = 0.0005$), and 1.15 in the 750 mg mepolizumab group ($p < 0.0001$). No significant improvements were found for secondary clinical symptom measures, which included change in pre-bronchodilator FEV_1 from baseline, or change in Asthma Control Questionnaire (ACQ) scores *(Pavord et al 2012)*.
  - MENSA was a 32-week Phase 3 trial (N = 576) that compared annual asthma exacerbation frequency and improvements in clinical symptoms between patients receiving SC and IV mepolizumab vs placebo. Patients were selected on the basis of frequent exacerbations, treatment with high doses of ICS, and a defined blood eosinophil count. Both SC and IV mepolizumab significantly decreased clinically significant exacerbation rates compared to placebo, at a rate of 1.74 per patient per year in the placebo group, 0.93 per patient per year in the IV mepolizumab group ($p < 0.001$), and 0.83 per patient per year in the SC mepolizumab group ($p < 0.001$). In both the SC and IV mepolizumab-treated groups, the ACQ scores met thresholds for minimal clinically important change and were significantly improved compared to placebo ($p < 0.001$) *(Ortega et al 2014)*.
  - SIRIUS was a 24-week Phase 3 trial (N = 135) that compared oral corticosteroid requirements between patients receiving SC mepolizumab and placebo. The likelihood of a reduction in the daily oral glucocorticoid dose was 2.39 times higher in the mepolizumab group (95% CI, 1.25 to 4.56; $p = 0.008$). The median reduction in daily oral corticosteroid dose was 50% (95% CI, 20 to 75) in the mepolizumab-treated group compared to 0% (95% CI, -20 to 33.3) in the placebo group ($p = 0.007$) *(Bel et al 2014)*.
- A post-hoc analysis of data from DREAM and MENSA was conducted to assess the relationship between baseline blood eosinophil counts and efficacy of mepolizumab. Of 1192 patients, 846 received mepolizumab and 346 received placebo. The overall rate of mean exacerbations per person per year was reduced from 1.91 with placebo to 1.01 with mepolizumab (47% reduction; RR, 0.53; 95% CI, 0.44 to 0.62; $p < 0.0001$). The exacerbation rate reduction with mepolizumab vs placebo increased progressively from 52% (RR, 0.48; 95% CI, 0.39 to 0.58) in patients with a baseline blood eosinophil count of ≥ 150 cells/μL to 70% (RR, 0.30; 95% CI, 0.23 to 0.40) in patients with a baseline count of ≥ 500 cells/μL. At a baseline count < 150 cells/μL, predicted efficacy of mepolizumab was reduced. The authors concluded that the use of a baseline blood eosinophil count will help to select patients who are likely to achieve important asthma outcomes with mepolizumab (*Ortega et al 2016*).
- COSMOS was a 52-week, open-label extension study in patients who received mepolizumab or placebo in MENSA or SIRIUS. Patients received SC mepolizumab regardless of prior treatment allocation and continued to receive appropriate standard-of-care asthma therapy throughout. In total, 558 (86%; previous mepolizumab: 358; previous placebo: 200) and 94 (14%; previous mepolizumab: 58; previous placebo: 36) patients experienced on-treatment adverse events and serious adverse events, respectively. No fatal adverse events or instances of mepolizumab-related anaphylaxis were reported. Mepolizumab treatment was shown to exert a durable response, with patients who previously received mepolizumab in MENSA or SIRIUS maintaining reductions in exacerbation rate and oral corticosteroid dosing throughout COSMOS. Patients who previously received placebo in MENSA or SIRIUS demonstrated improvements in these endpoints following treatment with mepolizumab (*Lugogo et al 2016*).
- COLUMBA was an open-label extension study of patients enrolled in the DREAM trial who received mepolizumab 100 mg every 4 weeks plus standard of care until criterion for discontinuation was met (safety profile not positive for patient, patient withdrawn by their physician, patient withdrew consent, or drug became commercially available). There were 347 patients enrolled who received treatment for a mean of 3.5 years. Adverse events most frequently reported were respiratory tract infection (67%), headache (29%), bronchitis (21%), and worsening asthma (27%). Although 6 deaths occurred, none were considered related to study treatment. No anaphylaxis reactions were reported. Malignancy was reported in 2% (n = 6) of patients. The exacerbation rate for patients on treatment for 156 weeks or longer was 0.74 events/year, which was a 56% reduction from the off-treatment period between the 2 studies (*Khatri et al 2018*).
- A pharmacokinetic study of SC mepolizumab 40 and 100 mg (for bodyweight < 40 and ≥ 40 kg, respectively) every 4 weeks in 36 children 6 to 11 years of age with severe eosinophilic asthma and ≥ 2 exacerbations in the prior year demonstrated reductions in blood eosinophil count by 89% at week 12 *(Gupta et al 2019a)*. A 52-week safety extension study of 30 children demonstrated no safety or immunogenicity concerns, as well as improvements in blood eosinophil counts and asthma control from baseline *(Gupta et al 2019b)*. Findings of these studies supported FDA approval of mepolizumab for the treatment of severe eosinophilic asthma in children (*GlaxoSmithKline 2019*).
- A systematic review and meta-analysis compared hospitalization or hospitalization and/or emergency room visit rates in patients with severe eosinophilic asthma treated with mepolizumab or placebo in addition to standard of care for ≥ 24 weeks. Four studies (N = 1388) were eligible for inclusion. Mepolizumab significantly reduced the rate of

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

exacerbations requiring hospitalization (relative rate, 0.49; 95% CI, 0.30 to 0.80; p = 0.004) and hospitalization/emergency room visit (relative rate, 0.49; 95% CI, 0.33 to 0.73; p < 0.001) vs placebo. Significant reductions of 45% and 38% were also observed for the proportion of patients experiencing 1 or more hospitalization and hospitalization and/or emergency room visit, respectively (*Yancey et al 2017*).

Eosinophilic granulomatosis with polyangiitis (EPGA)

- A 52-week, randomized, placebo-controlled, double-blind, parallel-group, multicenter, Phase 3 trial assessed the efficacy and safety of mepolizumab as add-on therapy (to glucocorticoid treatment, with or without immunosuppressive therapy) for patients with relapsing or refractory EGPA (*Wechsler et al 2017*). A total of 136 patients were randomly assigned to mepolizumab 300 mg every 4 weeks (n = 68) or placebo (n = 68). Results demonstrated the following for the mepolizumab and placebo groups, respectively:
  - Percentage of patients with ≥ 24 weeks of accrued remission: 28% vs 3% (OR, 5.91; 95% CI, 2.68 to 13.03; p < 0.001).
  - Percentage of patients in remission at both week 36 and week 48: 32% vs 3% (OR, 16.74; 95% CI, 3.61 to 77.56; p < 0.001).
  - Annualized relapse rate: 1.14 vs 2.27 (RR, 0.50; 95% CI, 0.36 to 0.70; p < 0.001).
  - Percentage of patients able to reduce their daily dose of concomitant prednisone or prednisolone to 4 mg or less (average of weeks 48 to 52): 44% vs 7% (OR, 0.20; 95% CI, 0.09 to 0.41; p < 0.001).

Hypereosinophilic syndrome (HES)

- A 32-week, double-blind, placebo-controlled, multicenter, randomized controlled trial evaluated the efficacy and safety of mepolizumab in patients ≥ 12 years with HES (without an identifiable nonhematologic secondary cause) for at least 6 months *(Nucala prescribing information 2020; Roufosse et al 2020b)*. A total of 108 patients were assigned to mepolizumab 300 mg every 4 weeks (n = 54) or placebo (n = 54). Results demonstrated the following for mepolizumab and placebo groups, respectively:
  - Proportion of patients with ≥ 1 HES flare or withdrew from the trial: 28% vs 56% (OR, 0.28; 95% CI, 0.12 to 0.64; p = 0.002)
  - Adjusted mean rate of HES flares per year: 0.50 vs 1.46 (rate ratio, 0.34; 95% CI, 0.19 to 0.63; p < 0.001)
  - Probability of first HES flare by week 32: 26.3% vs 52.7% (hazard ratio, 0.34; 95% CI, 0.18 to 0.67; p = 0.002)

RESLIZUMAB

Asthma

- The safety and efficacy of reslizumab were evaluated in 4 double-blind, placebo-controlled, multicenter, randomized controlled trials. In all 4 studies, patients were required to be on at least a medium-dose ICS with or without additional controller medications (*Bjermer et al 2016, Castro et al 2015, Corren et al 2016*).
  - Studies 3082 and 3083 were 52-week studies (N = 953) in patients with asthma who were required to have a blood eosinophil count ≥ 400 cells/μL, and ≥ 1 asthma exacerbation requiring systemic corticosteroid use over the past 12 months. These studies compared the asthma exacerbation rate and improvements in clinical symptoms between patients receiving reslizumab 3 mg/kg IV administered once every 4 weeks and placebo. In both studies, patients receiving reslizumab had a significant reduction in the frequency of asthma exacerbations (Study 3082: RR, 0.50; 95% CI, 0.37 to 0.67; Study 3083: RR, 0.41; 95% CI, 0.28 to 0.59; both p < 0.0001) compared with those receiving placebo. In both trials, an improvement in FEV_1 was evident for reslizumab vs placebo by the first on-treatment assessment at week 4, which was sustained through week 52. Reslizumab treatment also resulted in significant improvements compared with placebo in AQLQ total score, ACQ-7 score, and Asthma Symptom Utility Index (ASUI) score (*Castro et al 2015*).
  - Study 3081 was a 16-week study (N = 315) in patients who were required to have a blood eosinophil count ≥ 400 cells/μL. The study compared the change from baseline in FEV_1 and improvements in clinical symptoms between reslizumab 3 mg/kg vs placebo. Reslizumab 3 mg/kg significantly improved FEV_1 (difference vs placebo: 160 mL; 95% CI, 60 to 259; p = 0.0018). Reslizumab also statistically significantly improved ACQ and AQLQ; however, the minimally important difference was only reached for AQLQ (*Bjermer et al 2016*).
    - Study 3084 was a 16-week study in 496 patients unselected for baseline blood eosinophil levels (approximately 80% of patients had a screening blood eosinophil count < 400 cells/μL). Patients were not allowed to be on maintenance oral corticosteroids. The study compared the change from baseline in FEV_1 and improvements in clinical symptoms between reslizumab 3 mg/kg vs placebo. In the subgroup of patients with baseline eosinophils < 400 cells/μL, patients treated with reslizumab showed no significant improvement in FEV_1 compared with placebo.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

In the subgroup with eosinophils ≥ 400 cells/μL, however, treatment with reslizumab was associated with much larger improvements in FEV_1, ACQ, and rescue SABA use compared with placebo (*Corren et al 2016*).

- An open-label, non-randomized extension study of these placebo-controlled trials continued treatment of patients with eosinophilic asthma with reslizumab 3 mg/kg every 4 weeks for up to 24 months to assess the drug's safety. Patients initially randomized to placebo also received active drug. A total of 1051 patients were included (n = 480 reslizumab-naive and n = 571 reslizumab-treated patients). Of these, 740 patients received treatment for 12 months or longer, and 249 patients received treatment for 24 months or longer. Worsening asthma and nasopharyngitis were the most common adverse events. Serious adverse events occurred in 7% of patients and treatment discontinuation due to an adverse event occurred in 2% of patients. No deaths (n = 3) were related to treatment. Malignancy occurred in 15 (1%) patients. Patients previously on reslizumab maintained asthma control and those naive to treatment demonstrated improvement in asthma control and lung function. The authors concluded that reslizumab maintained asthma control for up to 2 years in patients with moderate-to-severe eosinophilic asthma (*Murphy et al 2017*).
- A post hoc analysis of pooled data from 2 randomized, placebo-controlled trials in patients with inadequately controlled asthma and elevated blood eosinophil levels compared the efficacy of reslizumab vs placebo among the subgroup of patients with oral corticosteroid dependent asthma. Reslizumab was associated with a significant improvement in overall asthma exacerbations (RR, 0.32; 95% CI, 0.18 to 0.55) *(Nair et al 2020)*.

- A 2017 meta-analysis of 5 randomized controlled trials comparing reslizumab to placebo (N = 1366) revealed improvements in exacerbations, FEV_1, and ACQ score with reslizumab. Asthma exacerbations occurred less frequently in reslizumab patients vs placebo (OR, 0.46; 95% CI, 0.35 to 0.59; $p < 0.00001$). FEV_1 also improved with reslizumab compared to placebo (mean difference, 0.16; 95% CI, 0.10 to 0.23; $p < 0.00001$). Finally, ACQ score improved with reslizumab compared to placebo (mean difference, -0.26; 95% CI, -0.36 to -0.16; $p < 0.00001$). All studies included in the meta-analysis were of limited duration of 15 or 16 weeks (*Li et al 2017*).
- A 2019 meta-analysis of 6 randomized controlled trials (5 placebo-controlled trials and 1 open-label extension) evaluated the safety of reslizumab (n = 1028) with placebo (n = 730) in adults with uncontrolled asthma. Compared with placebo, reslizumab was associated with lower proportions of patients with ≥ 1 adverse event (67% vs 81%; RR, 0.83; 95% CI, 0.79 to 0.89) and with ≥ 1 serious adverse event (7% vs 10%; RR, 0.65; 95% CI, 0.48 to 0.89) *(Virchow et al 2020)*.

DUPILUMAB

Asthma

- A 52-week randomized, double-blind, placebo-controlled study evaluated the efficacy of dupilumab in patients ≥ 12 years of age with moderate-to-severe asthma uncontrolled with a medium-to-high dose ICS plus up to 2 additional controller medications (LABA and/or leukotriene receptor antagonist). Approximately 1900 patients were randomized to add-on therapy with dupilumab (200 mg or 300 mg every 2 weeks) or matching placebo for 52 weeks. The annual rate of severe exacerbations during the 52-week study period and the absolute change in FEV_1 at week 12 were the primary endpoints. A subgroup analysis of patients with an elevated blood eosinophil count of 300/mm^3 was also planned. Both doses of dupilumab resulted in a reduced rate (46% and 47.7%, respectively) of asthma exacerbation compared to placebo ($p < 0.0001$). Patients with higher blood eosinophil levels had greater than 65% reduction in the annual exacerbation rate compared to placebo. The change in FEV_1 was also significantly improved with both doses of dupilumab compared to placebo and even more pronounced in patients with elevated blood eosinophil levels. Adverse events more common with dupilumab compared to placebo included injection-site reactions and eosinophilia (*Castro et al 2018*). In the subgroup of patients with baseline evidence of allergic asthma, dupilumab 200 mg and 300 mg every 2 weeks reduced severe asthma exacerbation rates by 36.9% and 45.5%, respectively (both $p < 0.01$) and improved FEV_1 at week 12 by 0.13 and 0.16 L, respectively (both $p < 0.001$) *(Corren et al 2020)*.
- A total of 210 patients ≥ 12 years of age with oral glucocorticoid-dependent severe asthma were randomized to receive add-on therapy with dupilumab 300 mg or placebo every other week for 24 weeks. Glucocorticoid doses were tapered from week 4 to week 20 and then maintained at a stable dose for 4 weeks. The percentage in glucocorticoid dose reduction at week 24 was the primary outcome. The percentage change in glucocorticoid dose was -70.1% with dupilumab vs -41.9% with placebo ($p < 0.001$). A dose reduction of ≥ 50% was observed in 80% of dupilumab-treated patients compared to 50% of placebo patients. Almost 70% of patients in the dupilumab group achieved a glucocorticoid dose of less than 5 mg compared to 33% in patients who received placebo. The exacerbation rate was 59% lower with dupilumab compared to placebo. Injection site reactions and eosinophilia were more common with dupilumab compared to placebo (*Rabe et al 2018*).

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- A meta-analysis and systematic review of 4 RCTs evaluated the safety and efficacy of dupilumab compared to placebo in approximately 3000 patients with uncontrolled asthma. The rate of severe asthma exacerbation was significantly reduced with dupilumab compared to placebo (RR, 0.44; 95% CI, 0.35 to 0.055; p < 0.01). FEV_1 was also significantly increased with dupilumab with a mean difference of 0.14 L (95% CI, 0.12 to 0.17; p < 0.01). With respect to adverse events, the risk of injection site reactions was higher with dupilumab compared to placebo (RR, 1.91; 95% CI, 1.14 to 2.59; p < 0.01) (*Zayed et al 2018*).

Chronic rhinosinusitis with nasal polyposis (CRSwNP)

- Two randomized, double-blind, placebo-controlled trials evaluated dupilumab added to standard of care in adults with severe bilateral CRSwNP (*Bachert et al 2019*). Patients had experienced symptoms despite receiving intranasal corticosteroids, systemic corticosteroids in the previous 2 years, or sinonasal surgery. In both the 24- and 52-week trials, dupilumab resulted in significant improvement as measured by least-squares mean differences in NPS (-2.06; 95% CI, -2.43 to -1.69 and -1.80; 95% CI, -2.10 to -1.51, respectively), nasal congestion or obstruction score (-0.89; 95% CI, -1.07 to -0.71 and -0.87; 95% CI, -1.03 to -0.71, respectively), and Lund-Mackay computed tomography score (-7.44; 95% CI, -8.35 to -6.53 and -5.13; 95% CI, -5.80 to -4.46, respectively). The risk of any adverse event, serious adverse events, and adverse events leading to treatment discontinuation were not significantly different between dupilumab and placebo.

COMPARATIVE REVIEWS

Asthma

- In 2017, Cockle et al conducted a systematic review and indirect treatment comparison to assess the comparative effectiveness and tolerability of mepolizumab and omalizumab, as add-on therapy to standard of care, in patients with severe asthma. Studies included in the primary analysis were double-blind, randomized controlled trials, ≥12 weeks' duration enrolling patients with severe asthma with a documented exacerbation history, and receiving a high-dose ICS plus ≥1 additional controller. Two populations were examined: patients potentially eligible for 1) both treatments (overlap population) and 2) either treatment (trial population) (*Cockle et al 2017*).
  - For the overlap population, no difference was found between mepolizumab and omalizumab. However, trends in favor of mepolizumab were observed, with median estimated RRs of 0.66 (95% CI, 0.37 to 1.19) for the rate of clinically significant exacerbations and 0.19 (95% CI, 0.02 to 2.32) for the rate of exacerbations requiring hospitalization.
  - Results of the trial population analysis showed that mepolizumab was associated with an estimated median RR of 0.63 (95% CI, 0.45 to 0.89) corresponding to a reduction of 37% in the rate of clinically significant exacerbations vs omalizumab. No difference between treatments was observed for the rate of exacerbations resulting in hospitalization; however, the median RR of 0.58 (95% CI, 0.16 to 2.13) demonstrated a trend for mepolizumab over omalizumab.
  - Both treatments had broadly comparable effects on lung function and similar tolerability profiles.
- Another 2017 systematic review was unable to detect differences in efficacy when comparing add-on therapy with mepolizumab or omalizumab in asthma patients who were not well controlled on ICS therapy. The analysis included both randomized controlled trials and cohort studies with duration of ≥12 weeks. A total of 18 omalizumab studies (N = 4854) and 4 mepolizumab studies (N = 1620) were included. Network meta-analysis did not find a significant difference in FEV_1 between groups (mean difference, 9.3 mL in favor of mepolizumab; 95% CI, -67.7 to 86.3). Both omalizumab and mepolizumab reduced the annualized rates of asthma exacerbations by approximately 50% compared with placebo. Although the authors were unable to identify significant differences in efficacy, there was high heterogeneity among the clinical trials and major differences in study inclusion criteria *(Nachef et al 2018)*.
- A systematic review of the IL-5 antagonists, mepolizumab, reslizumab, and benralizumab, included 13 studies (N = 6000) conducted in patients with asthma poorly controlled by ICS. The majority of patients had severe eosinophilic asthma. All of the IL-5 antagonists reduced asthma exacerbations by approximately 50% and improved FEV_1 by 0.08 L to 0.11 L. Overall, there was not an increase in serious adverse events with any IL-5 antagonist; however, more patients discontinued benralizumab (36/1599) than placebo (9/998) due to adverse events *(Farne et al 2017)*.
- A 2019 network meta-analysis of 11 studies aimed to indirectly compare the efficacy (n = 1855) and safety (n = 3462) of reslizumab with benralizumab in patients with eosinophilic asthma. The efficacy analysis compared a benralizumab subgroup with blood eosinophils ≥ 300 cells/µL (n = 1537) to a reslizumab subgroup in GINA step 4/5 with 2 or more previous exacerbations and blood eosinophils ≥ 400 cells/µL. Reslizumab was found to have significantly greater improvement in the ACQ and AQLQ scores compared to benralizumab. No significant difference between the groups was observed in clinical asthma exacerbation, but a sensitivity analysis with the overall study population suggested a

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

significantly greater reduction in exacerbations with reslizumab. There were fewer discontinuations due to adverse events with reslizumab; however, the frequency and types of adverse events were not significantly different between treatment groups (*Casale et al 2019).*

- A 2019 network meta-analysis of 11 studies compared efficacy of licensed doses of mepolizumab, benralizumab, and reslizumab in patients with severe eosinophilic asthma based on eosinophil levels. Mepolizumab reduced clinically significant exacerbations compared to benralizumab for patients with blood eosinophils ≥ 150 cells/μL (RR, 0.66; 95% CI, 0.49 to 0.89), ≥ 300 cells/μL (RR, 0.61; 95% CI, 0.37 to 0.99), and ≥ 400 cells/μL (RR, 0.55; 95% CI, 0.35 to 0.87) and with mepolizumab compared to reslizumab for patients with blood eosinophils ≥ 400 cells/μL (RR, 0.55; 95% CI, 0.36 to 0.85). Additionally, change from baseline in ACQ score was greater with mepolizumab compared to benralizumab in patients with baseline blood eosinophils ≥ 150 cells/μL (difference, -0.33; 95% CI, -0.54 to -0.11), ≥ 300 cells/μL (-0.40; 95% CI, -0.76 to -0.03), and ≥ 400 cells/μL (difference, -0.36; 95% CI, -0.66 to -0.05) and compared to reslizumab with blood eosinophils ≥ 400 cells/μL (difference, -0.39; 95% CI, -0.66 to -0.12). There was no difference between reslizumab and benralizumab in clinically significant exacerbations or ACQ scores in patients with blood eosinophils ≥ 400 cells/μL *(Busse et al 2019b)*.
- A 2019 systematic review and network meta-analysis of 30 randomized controlled trials compared biologic therapies for treatment of type 2 (ie, eosinophilic) asthma. Mepolizumab, reslizumab, and benralizumab significantly reduced the risk of exacerbations compared with placebo; however, network meta-analysis showed no superiority of any biologic therapy for this outcome among benralizumab, dupilumab, mepolizumab, reslizumab, and other biologics not available in the US (lebrikizumab, tralokinumab, and tezepelumab) *(Edris et al 2019)*.
- In a 2020 meta-analysis including data from 3 trials (n = 2640), dupilumab and benralizumab were compared in patients with inadequately controlled asthma. While there were no significant differences in the annual exacerbation rates between both drugs in the overall population (RR, 0.83; 95% CI, 0.62 to 1.09) and in the subgroup with the blood eosinophil count <150 cells/μL (RR, 1.57; 95% CI, 0.73 to 2.82), dupilumab was superior to benralizumab for the subgroup with a blood eosinophil count of ≥ 300 cells/μL (RR, 0.58; 95% CI, 0.39 to 0.84) and ≥ 150 but < 300 cells/μL (RR, 0.51; 95% CI, 0.29 to 0.92). The incidence of adverse events was similar between groups (OR, 1.023; 95% CI, 0.688 to 1.526) (*Ando et al 2020*).
- Additional meta-analyses have not found significant differences in asthma exacerbation rates between mepolizumab and reslizumab or between benralizumab and mepolizumab *(Bourdin et al 2018, Henriksen et al 2018, Yan et al 2019).*
- The magnitude of treatment effect of biologic agents (including benralizumab, reslizumab, dupilumab, mepolizumab, lebrikizumab [investigational], and tralokinumab [investigational]) in patients with eosinophilic asthma was evaluated in a network meta-analysis. The outcomes evaluated were change in FEV_1, ACQ score, and AQLQ score. Event rates for asthma exacerbation and associated RRs were determined for each drug. A total of 26 studies were included in the analysis (n = 7 benralizumab, n = 2 dupilumab, n = 4 lebrikizumab, n = 7 mepolizumab, n = 4 reslizumab, n = 2 tralokinumab) with a total of 8444 patients (n = 4406 on active treatment, n = 4038 in control groups). The duration of treatment ranged from 12 to 56 weeks. An increase in FEV_1, reduction in ACQ score, and increase in AQLQ score were observed with all treatments except tralokinumab. Compared to placebo, the greatest FEV_1 increase was with dupilumab (0.16 L; 95% CI, 0.08 to 0.24), followed by reslizumab (0.13 L; 95% CI, 0.10 to 0.17), and benralizumab (0.12 L; 95% CI, 0.08 to 0.17). Mepolizumab and lebrikizumab both had an increase of 0.09 L (95% CI, 0.03 to 0.15 with mepolizumab, 0.04 to 0.15 with lebrikizumab). Reduction in ACQ score (indicating better asthma control) in order of greatest to least reduction was mepolizumab, dupilumab, benralizumab, and reslizumab. The investigational agents had the least impact on the ACQ score. Quality of life scores were similarly increased with the 4 agents while the investigational agents had the least impact on quality of life. Compared to placebo, the calculated RR for annualized asthma exacerbation was significant only for dupilumab (RR, 0.37; 95% CI, 0.17 to 0.80) and reslizumab (RR, 0.64; 95% CI, 0.53 to 0.78). Comparisons between treatments did not show any significant difference for change in FEV_1, asthma control or quality of life except for superiority of mepolizumab to the 2 investigational agents in ACQ score reduction (*Iftikhar et al 2018*).
- In a 2020 network meta-analysis including 9 studies, treatment rankings estimated that dupilumab was most effective at reducing the risk of asthma exacerbation, followed by mepolizumab, reslizumab, and benralizumab. Similar to other indirect treatment comparisons, there were no within-group differences as related to the risk for asthma exacerbations (*Ramonell et al 2020*).

CLINICAL GUIDELINES

Asthma

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- According to guidelines from the NHLBI/National Asthma Education and Prevention Program, pharmacologic therapy is based on a stepwise approach in which medications are increased until asthma is controlled and then decreased when possible to minimize side effects of treatments. The level of asthma control is based on (*NHLBI 2007*):
  - Reported symptoms over the past 2 to 4 weeks
  - Current level of lung function (FEV_1 and FEV_1/forced vital capacity [FVC] values)
  - Number of exacerbations requiring oral corticosteroids per year.
- The NHLBI guidelines state that omalizumab is used as adjunctive therapy in patients ≥ 12 years of age who have allergies and severe persistent asthma that is not adequately controlled with the combination of high-dose ICS and LABA therapy (*NHLBI 2007*).
  - A 2020 focused update of the 2007 NHLBI guidelines provided updated recommendations on limited topics for the clinical management of adolescents and adults with asthma, including intermittent ICSs, add-on therapy with long-acting muscarinic antagonists, fractional exhaled nitric oxide, indoor allergen mitigation and immunotherapy. Addition of the asthma biologics (eg, anti-IgE, anti-IL5, anti-IL5R, or anti-IL4/IL13) to therapy could be considered in steps 5 and 6 in the stepwise approach for management of asthma. However, the systematic reviews that informed the update did not include studies examining the role of asthma biologics, and therefore, the report did not contain specific recommendations for use of biologics in asthma.
- In 2021, the Global Initiative for Asthma (GINA) published updated guidelines for asthma management and prevention. In April 2021, GINA updated a guideline on diagnosis and management of difficult-to-treat and severe asthma. Criteria for establishing a diagnosis of severe asthma were included, which requires multiple interventions before a diagnosis can be made. For patients with a diagnosis of severe asthma, uncontrolled on Step 4 treatment (eg, medium dose ICS/formoterol with as needed low dose ICS/formoterol as the reliever therapy), phenotyping for Type 2 inflammation into categories such as severe allergic, aspirin-exacerbated, allergic bronchopulmonary aspergillosis, chronic rhinosinusitis, nasal polyposis, atopic dermatitis, or eosinophilic asthma is recommended. Treatment with a biologic agent should be considered in patients who are uncontrolled despite a high-dose ICS/LABA, and who have allergic or eosinophilic biomarkers or need maintenance oral corticosteroids. Anti-IgE treatment with omalizumab is recommended for patients ≥ 6 years of age with severe allergic asthma. Similarly, add-on anti-IL-5 therapy (ie, benralizumab, mepolizumab) is recommended for patients ≥ 12 years of age or reslizumab for patients ≥ 18 years of age with severe eosinophilic asthma. Anti-IL4 receptor therapy (ie, dupilumab) is recommended for patients ≥ 12 years of age with severe eosinophilic/Type 2 asthma or patients taking oral corticosteroids. Prior to initiation of these agents, several factors are recommended to consider including cost, insurance eligibility criteria, evaluation of predictors of response, delivery route, dosing frequency, and patient preference (*GINA 2021*).
  - The 2021 GINA report provides interim guidance on the management of asthma in the context of the coronavirus disease 2019 (COVID-19) pandemic. Patients with asthma should continue their prescribed asthma medications, including ICS 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. Vaccination for COVID-19 is recommended for people with asthma (*GINA 2021*).
- A European Respiratory Society/American Thoracic Society guideline on the management of severe asthma suggests the use of anti-IL-5 therapy as an add-on in adults with severe uncontrolled eosinophilic asthma or severe corticosteroid-dependent asthma. A blood eosinophil count of 150 cells/mcL or greater is suggested as a cut-point to guide initiation of anti-IL-5 therapy in adults with severe asthma and prior exacerbations. A blood eosinophil count of 260 cells/mcL or greater or an exhaled nitric oxide level of 19.5 parts per billion or greater may be used to identify adolescents and adults with severe allergic asthma who are likely to benefit from anti-IgE treatment. Dupilumab is suggested for adults with severe eosinophilic asthma, and for those with severe corticosteroid-dependent asthma regardless of eosinophil levels (*Holguin et al 2020*).

Chronic idiopathic urticaria (CIU)

- Guidelines developed by the American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma & Immunology, and the Joint Council of Allergy, Asthma & Immunology recommend a stepwise treatment approach for CIU. Treatment with omalizumab is recommended in patients inadequately controlled with antihistamines and a leukotriene receptor antagonist (*Bernstein et al 2014*).
- Joint guidelines by the European Academy of Allergy and Clinical Immunology, the Global Allergy and Asthma European Network, the European Dermatology Forum, and the World Allergy Organization recommend treatment with omalizumab in patients with symptoms despite treatment with a 4-fold dose of modern second-generation

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

antihistamines. This is a change from previous guidelines in which use of either omalizumab or cyclosporine after failure of high-dose antihistamines was recommended. However, due to adverse effects and the lack of an approved indication, the new recommendation was that cyclosporine should only be considered if omalizumab does not provide an adequate response (*Zuberbier et al 2018*).
- Guidelines published by the British Society for Allergy and Clinical Immunology similarly recommend omalizumab as a potential second-line agent in patients inadequately controlled on a 4-fold dose of a non-sedating antihistamine (*Powell et al 2015*).

Eosinophilic granulomatosis with polyangiitis (EGPA)
- Both the EGPA (Churg-Strauss) Consensus Task Force recommendations and the American Society for Apheresis guideline recommend glucocorticoids alone for patients without life- and/or organ-threatening EGPA. For patients with life- and/or organ-threatening EGPA, both glucocorticoids and an immunosuppressant are recommended, as well as maintenance therapy with azathioprine or methotrexate. Guidelines from the American Society for Apheresis recognized mepolizumab as a future treatment option, and the EGPA Consensus Task Force recommendations noted that mepolizumab held promise for this condition based on the pilot studies available at the time of guideline development. IVIG can be considered for refractory EGPA or for treatment during pregnancy (*Groh et al 2015, Padmanabhan et al 2019*).

Chronic rhinosinusitis with nasal polyposis (CRSwNP)
- Treatment of CRSwNP is addressed in guidelines from the American Academy of Otolaryngology-Head and Neck Surgery; American Academy of Allergy, Asthma & Immunology, the American College of Allergy, Asthma & Immunology, and the Joint Council of Allergy, Asthma & Immunology; the International Forum of Allergy & Rhinology; and the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA).
- Routine treatment recommendations include saline irrigation and/or intranasal glucocorticoids in patients with mild symptoms, and short-term systemic glucocorticoids and surgery in patients with severe or refractory symptoms (*Orlandi et al 2016, Peters et al 2014, Rosenfeld et al 2015*). While not approved at the time of writing, some guidelines acknowledged the demonstration of benefit with IL-5 antagonists (*Orlandi et al 2016, Peters et al 2014*).
- In 2019, EUFOREA published an expert consensus focused on the use of biologics for CRSwNP with or without asthma. Per EUFOREA, biologics are indicated in patients with bilateral nasal polyps and previous sinus surgery who also meet 3 of the following criteria: evidence of type 2 inflammation (biological biomarkers); the need for systemic corticosteroids in the past 2 years; significant quality-of-life impairment; significant loss of smell; and diagnosis of comorbid asthma. In patients who have never had surgery, 4 of the aforementioned criteria need to be met before a biologic is indicated. Patients with previous sinus surgery plus severe asthma may also qualify for treatment in consultation with their pulmonologist. Lastly, biologics should not be initiated in the following situations: CRSwNP and lack of signs of type 2 inflammation; cystic fibrosis; unilateral nasal polyps; mucoceles; general contraindications for biological treatments, such as immunodeficiencies; and patient-related factors such as noncompliance to therapy (*Fokkens et al 2019*).

Hypereosinophilic syndrome (HES)
- The World Health Organization (WHO) guidance on eosinophilic disorders have stated that identification of rearranged *PDGFRA* or *PDGFRB* is important in the management of eosinophilic disorders as those variants respond to imatinib (*Shomali and Gotlib 2019*). For patients with idiopathic HES (without imatinib-sensitive variants), corticosteroids are first-line therapy; second-line options include hydroxyurea, interferon-alfa, other cytotoxic chemotherapy agents, and hematopoietic stem cell transplantation. The WHO listed use of mepolizumab or benralizumab as an area of active investigation. The WHO guidance was published prior to the FDA approval of mepolizumab for HES.

SAFETY SUMMARY
- All of the antiasthmatic monoclonal antibodies are contraindicated in patients with a history of hypersensitivity to the specific agent or excipients of the formulation.
- Abrupt discontinuation of systemic, topical or inhaled corticosteroids is not recommended when treatment with any of these agents are initiated. If appropriate, the corticosteroid dosage should be reduced gradually.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Cinqair

- Boxed warning: Anaphylaxis has been observed with Cinqair infusion in 0.3% of patients in placebo-controlled clinical studies. Anaphylaxis was reported as early as the second dose of Cinqair. Patients should be observed for an appropriate period of time after Cinqair administration by a healthcare professional prepared to manage anaphylaxis.
- Key warnings and precautions:
  - In placebo-controlled clinical studies, 6/1028 (0.6%) patients receiving 3 mg/kg Cinqair had ≥1 malignant neoplasm reported compared to 2/730 (0.3%) patients in the placebo group. The observed malignancies in Cinqair-treated patients were diverse in nature and without clustering of any particular tissue type.
  - Pre-existing helminth infections should be treated before therapy with Cinqair. If patients become infected while receiving Cinqair and do not respond to anti-helminth treatment, Cinqair should be discontinued until the parasitic infection resolves.
- The most common adverse reaction (≥ 2%) included oropharyngeal pain.

Dupixent

- Key warnings and precautions:
  - Hypersensitivity reactions (eg, anaphylaxis, erythema nodosum, serum sickness, urticaria, and rash) have occurred after administration of Dupixent. Dupixent should be discontinued in the event of a hypersensitivity reaction.
  - For patients with asthma, cases of eosinophilic pneumonia and vasculitis consistent with EGPA have been reported. Occurrence of vasculitic rash, worsening pulmonary symptoms, and/or neuropathy, especially upon reduction of oral corticosteroids should be monitored.
  - Pre-existing helminth infections should be treated before therapy with Dupixent. If a patient becomes infected while receiving Dupixent and does not respond to anti-helminth treatment, Dupixent should be discontinued until the parasitic infection resolves.
- Adverse reactions:
  - Asthma: the most common adverse reactions included injection site reactions, oropharyngeal pain, and eosinophilia.
  - CRSwNP: the most common adverse reactions included injection site reactions, eosinophilia, insomnia, toothache, gastritis, arthralgia, and conjunctivitis.

Fasenra

- Key warnings and precautions:
  - Hypersensitivity reactions (eg, anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of Fasenra. Fasenra should be discontinued in the event of a hypersensitivity reaction.
  - Pre-existing helminth infections should be treated before therapy with Fasenra. If patients become infected while receiving Fasenra and do not respond to anti-helminth treatment, Fasenra should be discontinued until the parasitic infection resolves.
- The most common adverse reactions (≥ 5%) included headache and pharyngitis.

Nucala

- Key warnings and precautions:
  - Hypersensitivity reactions (eg, anaphylaxis, angioedema, bronchospasm, hypotension, urticaria, rash) have occurred after administration of Nucala.
  - Herpes zoster infections have occurred in patients receiving Nucala. Vaccination should be considered if clinically appropriate.
  - Pre-existing helminth infections should be treated before therapy with Nucala. If patients become infected while receiving Nucala and do not respond to anti-helminth treatment, Nucala should be discontinued until the parasitic infection resolves.
- The most common adverse reactions (≥ 5%) included headache, injection site reaction, back pain, and fatigue.

Xolair

- Boxed warning: Anaphylaxis, presenting as bronchospasm, hypotension, syncope, urticaria, and/or angioedema of the throat or tongue, has been reported. Initiate Xolair in a healthcare setting and closely observe patients for an appropriate period of time after administration. Health care providers administering Xolair should be prepared to

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

manage anaphylaxis that can be life-threatening. Selection of patients for self-administration of Xolair should be based on criteria to mitigate risk from anaphylaxis.
  - Patients with a prior history of anaphylactic reactions to other causes may be at an increased risk for anaphylaxis. The frequency of anaphylaxis is reported to be between 0.1 to 0.2% and may occur immediately or up to a year post-treatment. Approximately 60 to 70% of anaphylaxis cases have been reported to occur within the first 3 doses.
- Key warnings and precautions:
  - Malignant neoplasms were observed in a higher rate of Xolair-treated patients (0.5%) than control patients (0.2%) in clinical trials. A subsequent 5-year observational cohort study found similar rates of primary malignancies in Xolair- and non-Xolair-treated patients. However, study limitations preclude definitively ruling out a malignancy risk with Xolair (*Long et al 2014*).
  - Rarely, patients on therapy with Xolair may present with serious systemic eosinophilia, which may present with features of vasculitis consistent with Churg-Strauss syndrome. These events usually have been associated with the reduction of oral corticosteroid therapy.
  - Systemic or inhaled corticosteroids should not be abruptly discontinued upon initiation of Xolair therapy for asthma or nasal polyps.
  - Some patients have reported signs and symptoms similar to serum sickness, including arthritis/arthralgia, rash, fever, and lymphadenopathy.
- Adverse reactions:
  - Asthma: In patients ≥ 12 years of age, the most commonly observed adverse reactions in clinical studies (≥ 1% in Xolair-treated patients and more frequently than reported with placebo) were arthralgia, pain (general), leg pain, fatigue, dizziness, fracture, arm pain, pruritus, dermatitis, and earache. In clinical studies with pediatric patients 6 to < 12 years of age, the most common adverse reactions were nasopharyngitis, headache, pyrexia, upper abdominal pain, streptococcal pharyngitis, otitis media, viral gastroenteritis, arthropod bites, and epistaxis.
    - Cardiovascular and cerebrovascular events in asthma studies: In a 5-year observational cohort study, a higher incidence of overall cardiovascular and cerebrovascular serious adverse events was observed in Xolair-treated patients compared to non-Xolair-treated patients. To further evaluate the risk, a pooled analysis of 25 randomized, controlled, clinical trials was conducted. An increased risk of cardiovascular and cerebrovascular serious adverse events was not noted, but the low number of events, the young patient population, and the short duration of follow-up prevent a definite conclusion about the absence of a risk (*FDA 2014*).
  - CIU: Adverse reactions from 3 placebo-controlled, multiple-dose CIU studies that occurred in ≥ 2% of patients receiving Xolair and more frequently than in those receiving placebo included arthralgia, cough, headache, nasopharyngitis, nausea, sinusitis, upper respiratory tract infection, and viral upper respiratory tract infection.
  - Nasal polyps: The most common adverse reactions (≥ 3% of patients) in clinical studies included headache, injection site reaction, arthralgia, upper abdominal pain, and dizziness.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Cinqair (reslizumab)	Single-use vials	IV	Every 4 weeks	• Safety and effectiveness in pediatric patients ≤ 17 years of age have not been established. • Cinqair should be administered by a healthcare professional by IV infusion over 20 to 50 minutes.
Dupixent (dupilumab)	Single-dose pre-filled syringe, single-dose pre-filled pen	SC	Asthma: every other week Chronic rhinosinusitis with nasal polyposis: every other week	• Safety and efficacy in patients < 12 years of age (asthma) and < 18 years of age (chronic rhinosinusitis with nasal polyposis) have not been established. • Dupixent may be administered by a healthcare professional or self-

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				administered via pre-filled syringe or pen.
Fasenra (benralizumab)	Single-dose pre-filled syringe, single-dose pre-filled pen (autoinjector)	SC	Every 4 weeks for first 3 doses, followed by every 8 weeks	• Safety and efficacy in pediatric patients < 12 years of age have not been established. • Fasenra may be administered by a healthcare professional or self-administered via an autoinjector.
Nucala (mepolizumab)	Single-dose vial for reconstitution, single-dose pre-filled pen (autoinjector), single-dose prefilled syringe	SC	Asthma: every 4 weeks EGPA: every 4 weeks HES: every 4 weeks	• Safety and efficacy in pediatric patients < 6 years (asthma), < 18 years (EGPA) and < 12 years (HES) of age have not been established. • Nucala may be administered by a healthcare professional or self-administered via an autoinjector or pre-filled syringe.
Xolair (omalizumab)	Single-dose vial for reconstitution, single-dose prefilled syringe	SC	Allergic asthma: Every 2 or 4 weeks CIU: Every 4 weeks Nasal polyps: Every 2 or 4 weeks	• Safety and efficacy in pediatric patients < 6 years of age (asthma), < 12 years of age (CIU), < 18 years of age (nasal polyps) have not been established. • Xolair should be initiated in a healthcare setting: once therapy has been safely established, Xolair may be administered by a healthcare professional or self-administered via a pre-filled syringe. • For allergic asthma and nasal polyps, dose and frequency are determined by serum total IgE level (measured before the start of treatment) and body weight. • Dosing in CIU is not dependent on serum IgE level or body weight.

See the current prescribing information for full details.

CONCLUSION

- Xolair is a humanized monoclonal antibody that is FDA-approved for patients ≥ 6 years of age with moderate to severe persistent asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and whose symptoms are inadequately controlled with an ICS. Xolair has been shown to decrease the incidence of asthma exacerbations in these patients.
  - Although clinical trial results have been mixed and several trials had an open-label design, there is some evidence to indicate that Xolair may decrease asthma-related emergency visits and hospitalizations, as well as decreasing the dose of ICS and rescue medication and increasing symptom-free days (*Buhl et al 2002, Busse et al 2011, Holgate et al 2004, Lanier et al 2003, Solèr et al 2011*).
  - Xolair carries a boxed warning due to the risk of anaphylaxis, and thus must be initiated in a healthcare setting. Once therapy has been safely established, select patients may be able to self-administer Xolair using a pre-filled syringe.
  - Although Xolair therapy is generally safe, analysis of a 5-year, observational cohort, epidemiological study (EXCELS) showed an increased number of cardiovascular and cerebrovascular adverse events in patients receiving Xolair compared to placebo (*Iribarren et al 2017*). However, a pooled analysis of 25 randomized, double-blind, placebo-controlled clinical trials did not find notable imbalances in the rates of cardiovascular and cerebrovascular serious adverse events (*FDA 2014*).

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Asthma guidelines generally recommend Xolair therapy in patients with severe allergic asthma that is inadequately controlled with a combination of high-dose ICS and LABA (*Cloutier et al 2020, GINA 2021, NHLBI 2007*). Based on a limited place in therapy, Xolair is appropriate for a small percentage of patients with asthma.

- Xolair received FDA approval for the treatment of adults and adolescents (≥ 12 years of age) with CIU who remain symptomatic despite H_1-antihistamine treatment. Two randomized, placebo-controlled trials demonstrated its efficacy in reducing weekly itch severity scores and weekly hive count scores significantly greater than placebo at week 12. Xolair was well-tolerated, with a safety profile similar to that observed in asthma patients.
  - In patients with CIU, Xolair is administered at 150 or 300 mg SC every 4 weeks.
  - Guidelines for the treatment of CIU recommend treatment with Xolair in patients who are inadequately controlled with a 4-fold dose of modern second-generation antihistamines. Although previous guidelines suggested the use of omalizumab after a leukotriene receptor antagonist, the most recent guideline from the European Academy of Allergy and Clinical Immunology, the Global Allergy and Asthma European Network, the European Dermatology Forum, and the World Allergy Organization state that a recommendation regarding use of a leukotriene receptor antagonist cannot be made due to a low level of evidence. Additionally, use of Xolair is recommended before treatment with cyclosporine (*Bernstein et al 2014, Zuberbier et al 2018, Powell et al 2015*).
- Xolair was approved as add-on maintenance treatment for nasal polyps in adult patients with an inadequate response to nasal corticosteroids, based on results from 2 identical, randomized, multicenter, double-blind, placebo-controlled, Phase 3 studies [POLYP 1 and POLYP 2] (*Gevaert et al 2020*). Results from both studies revealed that Xolair was associated with a significantly greater improvement from baseline at week 24 in NPS and weekly average NCS as compared to placebo. Adverse events were similar between groups.
- Cinqair, Fasenra, and Nucala are IL-5 antagonists approved as add-on treatment options for patients with severe eosinophilic asthma, and have demonstrated effectiveness in reducing asthma exacerbations (*Bel et al 2014, Bjermer et al 2016, Castro et al 2015, Corren et al 2016, Pavord et al 2012, Ortega et al 2014, Bleecker et al 2016, Fitzgerald et al 2016*).
  - The mechanism of action of Fasenra is slightly different, in that it binds to the IL-5 receptor on immune effector cells, whereas Cinqair and Nucala bind to the IL-5 cytokine. All of these agents provide a more targeted treatment option for patients with severe asthma and should be considered in patients who are uncontrolled despite a high-dose ICS/LABA, and who have allergic or eosinophilic biomarkers or need maintenance oral corticosteroids (*GINA 2021*).
- Dupixent is an IL-4/IL-13 antagonist approved for the treatment of patients ≥ 12 years of age with severe asthma of the eosinophilic type or dependent on oral corticosteroids, and as an add-on treatment in adults with inadequately controlled CRSwNP.
  - According to GINA guidelines, the use of Dupixent for severe asthma with an eosinophilic phenotype can be considered for patients with severe eosinophilic/Type 2 asthma or patients taking oral corticosteroids.
- Dupixent was approved for CRSwNP after the publication of several guidelines, although some acknowledged the potential role for biologic therapies (*Orlandi et al 2016, Peters et al 2014).*
  - In a 2019 EUFOREA expert consensus publication focused on the use of biologics for CRSwNP with or without asthma, biologics were indicated in patients with bilateral nasal polyps and previous sinus surgery who also meet 3 of the following criteria: evidence of type 2 inflammation (biological biomarkers); need for systemic corticosteroids in the past 2 years; significant quality-of-life impairment; significant loss of smell; and diagnosis of comorbid asthma. In patients who have never had surgery, 4 of the aforementioned criteria need to be met before a biologic is indicated. Patients with previous sinus surgery plus severe asthma may also qualify for treatment in consultation with their pulmonologist. Lastly, biologics should not be initiated in the following situations: CRSwNP and lack of signs of type 2 inflammation; cystic fibrosis; unilateral nasal polyps; mucoceles; general contraindications for biological treatments, such as immunodeficiencies; and patient-related factors such as noncompliance to therapy (*Fokkens et al 2019*).
- Nucala is the only antiasthmatic monoclonal antibody approved for the treatment of adult patients with EGPA and patients ≥ 12 years of age with HES.
- There are no head-to-head trials comparing Cinqair, Fasenra, Dupixent and Nucala.
  - A systematic review of the IL-5 antagonists conducted in patients with asthma poorly controlled by ICS revealed that all of the IL-5 antagonists reduced asthma exacerbations by approximately 50% and improved FEV_1 by 0.08 L to 0.11 L. Overall, there was not an increase in serious adverse events with any IL-5 antagonist; however, more patients discontinued benralizumab (36/1599) than placebo (9/998) due to adverse events (*Farne et al 2017*).
  - One network meta-analysis of IL-4, IL-5 and IL-13 antagonists demonstrated that all agents reduced FEV_1 and improved ACQ and AQLQ scores, except for the investigational agent, tralokinumab; other analyses found that

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

dupilumab, mepolizumab, reslizumab, and benralizumab significantly reduced the risk of exacerbations compared with placebo (*Iftikhar et al 2018, Edris et al 2019, Ando et al 2020, Ramonell et al 2020*).
  - Treatment rankings in a 2020 network meta-analysis estimate that dupilumab is most effective at reducing the risk of asthma exacerbation, followed by mepolizumab, reslizumab, and benralizumab (*Ramonell et al 2020*).
- Compared to Nucala and Fasenra, Cinqair has various limitations, including an indication for patients ≥ 18 years of age (vs ≥ 6 and 12 years of age with Nucala and Fasenra, respectively), IV administration (SC for Nucala and Fasenra), and a boxed warning for anaphylaxis. Dupixent is indicated for treatment of patients ≥ 12 years of age with severe asthma.
- Subcutaneous autoinjector formulations are available for Dupixent, Fasenra, and Nucala.

REFERENCES

- Ando K, Tanaka A, Sagara H. Comparative efficacy and safety of dupilumab and benralizumab in patients with inadequately controlled asthma: a systematic review. *Int J Mol Sci*. 2020;21(3):889. doi:10.3390/ijms21030889
- Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials *Lancet*. 2019;394(10209):1638-1650. doi: 10.1016/s0140-6736(19)31881-1.
- Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014;371:1189-1197.
- Bernstein JA, Lang DM, Khan DA, et al. The diagnosis and management of acute and chronic urticaria: 2014 update. *J Allergy Clin Immunol*. 2014;133:1270-1277.
- Bjermer L, Lemiere C, Maspero J, Weiss S, Zangrilli J, Germinaro M. Reslizumab for inadequately controlled asthma with elevated blood eosinophil levels: a randomized phase 3 study. *Chest*. 2016;150(4):789-798.
- Bleecker ER, Fitzgerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomized, multicenter, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2115-2127.
- Bourdin A, Husereau D, Molinari N, et al. Matching-adjusted indirect comparison of benralizumab versus interleukin-5 inhibitors for the treatment of severe asthma: a systematic review. *Eur Respir J*. 2018;52(5). doi: 10.1183/13993003.01393-2018.
- Buhl R, Solèr M, Matz J, et al. Omalizumab provides long-term control in patients with moderate-to-severe allergic asthma. *Eur Respir J*. 2002;20(1):73-78.
- Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol*. 2001;108(2):184-90.
- Busse WW, Bleecker ER, FitzGerald JM, et al; BORA study investigators. Long-term safety and efficacy of benralizumab in patients with severe, uncontrolled asthma: 1-year results from the BORA phase 3 extension trial. *Lancet Respir Med*. 2019a;7(1):46-59. doi: 10.1016/S2213-2600(18)30406-5.
- Busse W, Chupp G, Nagase H, et al. Anti-IL-5 treatments in patients with severe asthma by blood eosinophil thresholds: Indirect treatment comparison. *J Allergy Clin Immunol*. 2019b;143(1):190-200.e20. doi: 10.1016/j.jaci.2018.08.031.
- Casale TB, Pacou M, Mesana L, et al. Reslizumab compared with benralizumab in patients with eosinophilic asthma: a systematic literature review and network meta-analysis. *J Allergy Clin Immunol Pract*. 2019;7(1):122-130.e1. doi: 10.1016/j.jaip.2018.08.036.
- Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med*. 2018;378(26):2486-2496. doi: 10.1056/NEJMoa1804092.
- Castro M, Wenzel SE, Bleecker ER, et al. Benralizumab, an anti-interleukin 5 receptor α monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomized dose-ranging study. *Lancet Respir Med*. 2014;2(11):879-890.
- Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med*. 2015;3(5):355-366.
- Centers for Disease Control and Prevention. Asthma: Most Recent National Asthma Data. 2019. Updated March 2021. https://www.cdc.gov/asthma/most_recent_national_asthma_data.htm. Accessed May 26, 2021.
- Cinqair [package insert], information. Frazer, PA: Teva Pharmaceutical Industries Ltd.; June 2020.
- Cloutier MM, Dixon AE, Krishnan JA, et al. Managing asthma in adolescents and adults: 2020 asthma guideline update from the National Asthma Education and Prevention Program. *JAMA*. 2020;324(22):2301-2317. doi: 10.1001/jama.2020.21974.
- Cockle SM, Stynes G, Gunsoy NB, et al. Comparative effectiveness of mepolizumab and omalizumab in severe asthma: An indirect treatment comparison. *Respir Med*. 2017;123:140-148.
- Corren J, Castro M, O'Riordan T, et al. Dupilumab efficacy in patients with uncontrolled, moderate-to-severe allergic asthma. *J Allergy Clin Immunol Pract*. 2020;8(2):516-526. doi: 10.1016/j.jaip.2019.08.050.
- Corren J, Kavati A, Ortiz B, et al. Efficacy and safety of omalizumab in children and adolescents with moderate-to-severe asthma: a systematic literature review. *Allergy Asthma Proc*. 2017;38(4):250-263.
- Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts. *Chest*. 2016;150(4):799-810.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed May 25, 2021.
- Dupixent [package insert], Bridgewater, NJ: Sanofi-Aventis US, LLC and Tarrytown, NY: Regeneron Pharmaceuticals, Inc.; January 2021.
- Edris A, De Feyter S, Maes T, Joos G, Lahousse L. Monoclonal antibodies in type 2 asthma: a systematic review and network meta-analysis. *Respir Res*. 2019;20(1):179. doi: 10.1186/s12931-019-1138-3.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Eisner MD, Zazzali JL, Miller MK, et al. Longitudinal changes in asthma control with omalizumab: 2-year interim data from the EXCELS study. *J Asthma*. 2012;49:642-648.
- Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. *Cochrane Database Syst Rev*. 2017 Sep 21;9:CD010834.
- Fasenra [package insert], Wilmington, DE: AstraZeneca Pharmaceuticals.; February 2021.
- Ferguson GT, Fitzgerald JM, Beecker ER, et al. Benralizumab for patients with mild to moderate, persistent asthma (BISE): a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Respir Med*. 2017;5(7):568-576.
- FitzGerald JM, Bleecker ER, Menzies-Gow A, et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. *Lancet Respir Med*. 2018;6(1):51-64.
- Fitzgerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomized, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2128-2141.
- Fokkens WJ, Lund V, Bachert C, et al. EUFOREA consensus on biologics for CRSwNP with or without asthma. *Allergy*. 2019;74(12):2312-2319. doi:10.1111/all.13875
- Food and Drug Administration press release. FDA Drug Safety Communication: FDA approves label changes for asthma drug Xolair, including describing slightly higher risk of heart and brain adverse events. September 26, 2014. FDA Web site. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-approves-label-changes-asthma-drug-xolair-omalizumab-including. Accessed May 26, 2021.
- Gevaert P, Omachi TA, Corren J, et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. *J Allergy Clin Immunol*. 2020;146(3):595-605. doi: 10.1016/j.jaci.2020.05.032.
- GlaxoSmithKline. Nucala is the first biologic approved in the US for six to 11-year-old children with severe eosinophilic asthma. September 12, 2019. GlaxoSmithKline Web site. https://www.gsk.com/en-gb/media/press-releases/nucala-is-the-first-biologic-approved-in-the-us-for-six-to-11-year-old-children-with-severe-eosinophilic-asthma/. Accessed May 26, 2021.
- Global Initiative for Asthma (GINA). Global strategy for asthma management and prevention. 2021. www.ginasthma.org. Accessed May 26, 2021.
- Groh M, Pagnoux C, Baldini C, et al. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA) Consensus Task Force recommendations for evaluation and management. *Eur J Intern Med.* 2015;26(7):545-553.
- Gupta A, Ikeda M, Geng B, et al. Long-term safety and pharmacodynamics of mepolizumab in children with severe asthma with an eosinophilic phenotype. *J Allergy Clin Immunol*. 2019b;144(5):1336-1342.e7. doi: 10.1016/j.jaci.2019.08.005.
- Gupta A, Pouliquen I, Austin D, et al. Subcutaneous mepolizumab in children aged 6 to 11 years with severe eosinophilic asthma. *Pediatr Pulmonol.* 2019a;54(12):1957-1967. doi: 10.1002/ppul.24508.
- Harrison TW, Chanez P, Menzella F, et al. Onset of effect and impact on health-related quality of life, exacerbation rate, lung function, and nasal polyposis symptoms for patients with severe eosinophilic asthma treated with benralizumab (ANDHI): a randomised, controlled, phase 3b trial. *Lancet Respir Med.* 2021;9(3):260-274. doi: 10.1016/S2213-2600(20)30414-8.
- Henriksen DP, Bodtger U, Sidenius K, et al. Efficacy, adverse events, and inter-drug comparison of mepolizumab and reslizumab anti-IL-5 treatments of severe asthma - a systematic review and meta-analysis. *Eur Clin Respir J*. 2018;5(1):1536097. doi: 10.1080/20018525.2018.1536097.
- Holgate S, Bousquet J, Wenzel S, et al. Efficacy of omalizumab, an antiimmunoglobulin E antibody, in patients with allergic asthma at high risk of serious asthma-related morbidity and mortality. *Curr Med Res Opin*. 2001;17(4):233-240.
- Holgate ST, Chuchalin AG, Hébert J, et al. Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. *Clin Exp Allergy*. 2004;34(4):632-8.
- Holguin F, Cardet JC, Chung KF, et al. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J*. 2020;55(1). pii: 1900588. doi: 10.1183/13993003.00588-2019.
- Hopkins C. Chronic Rhinosinusitis with Nasal Polyps. *N Engl J Med*. 2019;381(1):55-63. doi: 10.1056/NEJMcp1800215.
- Iftikhar IH, Schimmel M, Bender W, et al. Comparative efficacy of anti IL-4, IL-5 and IL-13 drugs for treatment of eosinophilic asthma: a network meta-analysis. *Lung.* 2018;196(5):517-530. doi: 10.1007/s00408-018-0151-5.
- Iribarren C, Rahmaoui A, Long AA, et al. Cardiovascular and cerebrovascular events among patients receiving omalizumab: Results from EXCELS, a prospective cohort study of moderate-to-severe asthma. *J Allergy Clin Immunol*. 2017;139(5):1489-1495.e5.
- Jia HX, He YL. Efficacy and safety of omalizumab for chronic spontaneous urticaria: a systematic review and meta-analysis of randomized controlled trials. *Am J Ther*. 2020. doi:10.1097/MJT.0000000000000912
- Kaplan A, Ledford D, Ashby M, et al. Omalizumab in patients with symptomatic chronic idiopathic/spontaneous urticaria despite standard combination therapy. *J Allergy Clin Immunol*. 2013;132:101-9.
- Khan DA. Chronic spontaneous urticaria: treatment of refractory symptoms. UpToDate Web site. https://www.uptodate.com. Updated January 21, 2021. Accessed May 26, 2021.
- Khatri S, Moore W, Gibson PG, et al. Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma. *J Allergy Clin Immunol*. 2018;143(5):1742-1751. doi: 10.1016/j.jaci.2018.09.033.
- Lanier B, Bridges T, Kulus M, Taylor AF, Berhane I, Vidaurre CF. Omalizumab for the treatment of exacerbations in children with inadequately controlled allergic (IgE-mediated) asthma. *J Allergy Clin Immunol*. 2009;124(6):1210-6.
- Lanier BQ, Corren J, Lumry W, et al. Omalizumab is effective in the long-term control of severe allergic asthma. *Ann Allergy Asthma Immunol*. 2003;91(2):154-9.
- Ledford D, Busse W, Trzaskoma B, et al. A randomized multicenter study evaluating Xolair persistence of response after long-term therapy. *J Allergy Clin Immunol*. 2017;140(1):162-169.e2.
- Li J, Wang F, Lin C, et al. The efficacy and safety of reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: a systematic review and meta-analysis. *J Asthma.* 2017;54(3):300-307.
- Long A, Rahmaoui A, Rothman KJ, et al. Incidence of malignancy in patients with moderate-to-severe asthma treated with or without omalizumab. *J Allergy Clin Immunol*. 2014;134:560-567.
- Lugogo N, Domingo C, Chanez P, et al. Long-term efficacy and safety of mepolizumab in patients with severe eosinophilic asthma: a multi-center, open-label, phase IIIb study. *Clin Ther*. 2016;38(9):2058-2070.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Maurer M, Kaplan A, Rosen K, et al. The XTEND-CIU study: long term use of omalizumab in chronic idiopathic urticaria. *J Allergy Clin Immunol.* 2018;141(3):1138-1139.e7.
- Maurer M, Rosen K, Hsieh HJ, et al. Omalizumab for the treatment of chronic idiopathic or spontaneous urticaria. *N Engl J Med*. 2013;368:924-935.
- Murphy K, Jacobs J, Bjermer L, et al. Long-term safety and efficacy of reslizumab in patients with eosinophilic asthma. *J Allergy Clin Immunol Pract.* 2017;5(6):1572-1581.e3. doi: 10.1016/j.jaip.2017.08.024.
- Nachef Z, Krishnan A, Mashtare T, Zhuang T, Mador MJ. Omalizumab versus mepolizumab as add-on therapy in asthma patients not well controlled on at least an inhaled corticosteroid: a network meta-analysis. *J Asthma*. 2018;55(1):89-100.
- Nair P, Bardin P, Humbert M, et al. Efficacy of intravenous reslizumab in oral corticosteroid-dependent asthma. *J Allergy Clin Immunol Pract.* 2020;8(2):555-564. doi: 10.1016/j.jaip.2019.09.036.
- Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med*. 2017;376(25):2448-2458.
- National Heart, Lung, and Blood Institute: Asthma. NHLBI Web site. https://www.nhlbi.nih.gov/health-topics/asthma. Accessed May 26, 2021.
- National Heart, Lung, and Blood Institute. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma (guideline on the Internet). 2007. http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed May 26, 2021.
- Normansell R, Walker S, Milan SJ, et al. Omalizumab for asthma in adults and children. Cochrane Database Syst Rev. 2014 Jan 13;(1):CD003559.
- Nucala [package insert], Philadelphia, PA: GlaxoSmithKline LLC; September 2020.
- Orlandi RR, Kingdom TT, Hwang PH, et al. International Consensus Statement on Allergy and Rhinology: Rhinosinusitis. *Int Forum Allergy Rhinol.* 2016;6 Suppl 1:S22-209. doi: 10.1002/alr.21695.
- Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med. 2014;371(13):1198-1207.
- Ortega HG, Yancey SW, Mayer B, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. *Lancet Respir Med*. 2016;4(7):549-556.
- Padmanabhan A, Connelly-smith L, Aqui N, et al. Guidelines on the use of therapeutic apheresis in clinical practice - evidence-based approach from the Writing Committee of the American Society for Apheresis: The Eighth Special Issue. *J Clin Apher*. 2019;34(3):171-354. doi: 10.1002/jca.21705.
- Pagnoux C, Groh M. Optimal therapy and prospects for new medicines in eosinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome). *Expert Rev Clin Immunol;*2016;12(10):1059-1067.
- Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet.* 2012;380:651-659.
- Peters AT, Spector S, Hsu J, et al. Diagnosis and management of rhinosinusitis: a practice parameter update. *Ann Allergy Asthma Immunol.* 2014;113(4):347-85. doi: 10.1016/j.anai.2014.07.025.
- Powell RJ, Leech SC, Till S, et al. BSACI guideline for the management of chronic urticaria and angioedema. *Clin Exp Allergy*. 2015;45(3):547-565.
- Purple Book: Lists of licensed biological products with reference product exclusivity and biosimilarity or interchangeability evaluations. Food and Drug Administration Web site. https://www.fda.gov/drugs/biosimilars/purple-book-lists-licensed-biological-products-reference-product-exclusivity-and-biosimilarity-or. Accessed May 26, 2021.
- Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med*. 2018;378(26):2475-2485. doi: 10.1056/NEJMoa1804093.
- Ramonell RP, Iftikhar IH. Effect of anti-IL5, anti-IL5r, anti-IL13 therapy on asthma exacerbations: a network meta-analysis. *Lung*. 2020;198(1):95-103. doi:10.1007/s00408-019-00310-8
- Rodrigo GJ, Neffen H, Castro-Rodriguez JA. Efficacy and safety of subcutaneous omalizumab vs placebo as add-on therapy to corticosteroids for children and adults with asthma: a systematic review. *Chest*. 2011;139(1):28-35.
- Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): adult sinusitis. *Otolaryngol Head Neck Surg*. 2015;152(2 Suppl):S1-S39. doi: 10.1177/0194599815572097.
- Roufosse F, Kahn JE, Rothenberg ME, et al; HES Mepolizumab study group. Efficacy and safety of mepolizumab in hypereosinophilic syndrome: A phase III, randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2020b;146(6):1397-1405. doi: 10.1016/j.jaci.2020.08.037.
- Roufosse F, Klion AD, Weller PF. Hypereosinophilic syndromes: treatment. UpToDate Web site. www.uptodate.com. Updated November 24, 2020a. Accessed May 26, 2021.
- Rubini NPM, Ensina LFC, Silva EMK, Sano F, Sole D. Effectiveness and safety of omalizumab in the treatment of chronic spontaneous urticaria: Systematic review and meta-analysis. *Allergol Immunopathol (Madr)*. 2019;47(6):515-522. doi: 10.1016/j.aller.2019.05.003.
- Saini S. Chronic spontaneous urticaria: clinical manifestations, diagnosis, pathogenesis, and natural history. UpToDate Web site. https://www.uptodate.com. Updated January 25, 2021. Accessed May 26, 2021.
- Saini SS, Bindslev-Jensen C, Maurer M, et al. Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. *J Invest Derm*. 2015;135:67-75.
- Shomali W, Gotlib J. World Health Organization-defined eosinophilic disorders: 2019 update on diagnosis, risk stratification, and management. *Am J Hematol.* 2019;94(10):1149-1167. doi: 10.1002/ajh.25617.
- Solèr M, Matz J, Townley R, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J*. 2001;18(2):254-61.
- Virchow JC, Katial R, Brusselle GG, et al. Safety of reslizumab in uncontrolled asthma with eosinophilia: a pooled analysis from 6 trials. *J Allergy Clin Immunol Pract.* 2020;8(2):540-548. doi: 10.1016/j.jaip.2019.07.038.
- Walford HH, Doherty TA. Diagnosis and management of eosinophilic asthma: a US perspective. J Asthma and Allergy. 2014;7:53-65.
- Wechsler ME, Akuthota P, Jayne D, et al. Mepolizumab or placebo for eosinophilic granulomatosis with polyangiitis. *N Engl J Med*. 2017;376(20):1921-1932.
- Xolair [package insert], South San Francisco, CA: Genentech, Inc. and East Hanover, NJ: Novartis Pharmaceuticals; April 2021.
- Yancey SW, Ortega HG, Keene ON, et al. Meta-analysis of asthma-related hospitalization in mepolizumab studies of severe eosinophilic asthma. *J Allergy Clin Immunol*. 2017;139(4):1167-1175.
- Zayed Y, Kheiri B, Banifadel M, et al. Dupilumab safety and efficacy in uncontrolled asthma: a systematic review and meta-analysis of randomized clinical trials. *J Asthma.* 2018:1-10. doi: 10.1080/02770903.2018.1520865.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Zhao ZT, Ji CM, Yu WJ, et al. Omalizumab for the treatment of chronic spontaneous urticaria: A meta-analysis of randomized clinical trials. *J Allergy Clin Immunol*. 2016;137(6):1742-1750.
- Zuberbier T, Aberer W, Asero R, et al. The EAACI/GA/LEN/EDF/WAO guideline for the definition, classification, diagnosis, and management of urticaria. *Allergy*. 2018;73(7):1393-1414.doi: 10.1111/all.13397.

Publication Date: June 30, 2021

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Prior Authorization Guideline

Guideline Name: Qutenza (capsaicin)

1. Criteria

Product Name: **Qutenza (capsaicin)**	
Diagnosis	Neuropathic pain associated with postherpetic neuralgia (PHN)
Approval Length	3 month(s)
Therapy Stage	Initial Authorization
Approval Criteria **1** - Diagnosis of neuropathic pain associated with postherpetic neuralgia (PHN) **AND** **2** - Trial and failure, contraindication, or intolerance to over-the-counter capsaicin.	

Product Name: **Qutenza (capsaicin)**	
Diagnosis	Neuropathic pain associated with diabetic peripheral neuropathy (DPN) of the feet
Approval Length	3 month(s)
Therapy Stage	Initial Authorization
Approval Criteria **1** - Diagnosis of neuropathic pain associated with diabetic peripheral neuropathy (DPN) of the feet **AND** **2** - Trial and failure, contraindication, or intolerance to over-the-counter capsaicin.	

Product Name: **Qutenza (capsaicin)**	
Diagnosis	All indications
Approval Length	3 month(s)
Therapy Stage	Reauthorization

Approval Criteria

1 - It has been at least 3 months since the last application/administration

AND

2 - Patient experienced pain relief with a prior course of therapy

AND

3 - Patient is experiencing a return of neuropathic pain

Nevada Medicaid

Utilization

Fee for Service

October 1, 2020 – September 30, 2021

Drug Name	Members	Claims	Total Day Supply	Total Quantity
QUTENZA	0	0	0	0

Therapeutic Class Overview
Neuropathic Pain and Fibromyalgia Agents

INTRODUCTION

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

Diabetic Neuropathy

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

Fibromyalgia

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

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

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

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

PHN

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

Table 1. Medications Included Within Class Review

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

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

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

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

INDICATIONS

Table 2. FDA-Approved Indications

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

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

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

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

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

CLINICAL EFFICACY SUMMARY

Neuropathic Pain

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

Fibromyalgia

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

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

PHN

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

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

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

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

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

CLINICAL GUIDELINES

Diabetic Neuropathy

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

PHN

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

Fibromyalgia

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

SAFETY SUMMARY

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

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

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

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

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

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

See the current prescribing information for full details.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

CONCLUSION

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

REFERENCES

- Albrecht MA. Treatment of herpes zoster in the immunocompetent host. UpToDate Web site. Updated March 11, 2020. www.uptodate.com. Accessed August 4, 2021.
- American Diabetes Association (ADA). Microvascular complications and foot care: standards of medical care in diabetes-2021. *Diabetes Care.* 2021;44(Suppl 1):S151-S167. doi: 10.2337/dc21-S011.
- Armstrong DG, Chappell AS, Le TK, et al. Duloxetine for the management of diabetic peripheral neuropathic pain: evaluation of functional outcomes. *Pain Med.* 2007;8(5):410-418.
- Arnold LM, Goldenberg DL, Stanford SB, et al. Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. *Arthritis Rheum.* 2007;56(4):1336-1344.
- Arnold LM, Hudson JI, Wang F, et al. Comparisons of the efficacy and safety of duloxetine for the treatment of fibromyalgia in patients with vs without major depressive disorder. *Clin J Pain*. 2009;25:461-468.
- Arnold LM, Russell IJ, Diri EW, et al. A 14-week, randomized, double-blinded, placebo-controlled monotherapy trial of pregabalin in patients with fibromyalgia. *J Pain*. 2008;9(9):792-805.
- Attal N, Cruccu G, Baron R, et al. EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision. *Eur J Neurol*. 2010;17(9):1113-e88.
- Backonja MM, Canafax DM, Cundy KC. Efficacy of gabapentin enacarbil vs placebo in patients with postherpetic neuralgia and a pharmacokinetic comparison with oral gabapentin. *Pain Medicine.* 2011;12:1098-1108.
- Backonja MM, Wallace MS, et al. NGX-4010, a high-concentration capsaicin patch, for the treatment of postherpetic neuralgia: a randomised, double-blind study. *Lancet Neurol*. 2008;7(12):1106-1112.
- Bajwa ZH, Ortega E. Postherpetic neuralgia. UpToDate Web site. Updated July 31, 2019. http://www.uptodate.com/contents/postherpetic-neuralgia. Accessed August 4, 2021.
- Bril V, England J, Franklin GM, et al. Evidence-based guideline: treatment of painful diabetic neuropathy: report of the American Academy of Neurology, the American Association of Neuromuscular and Electrodiagnostic Medicine, and the American Academy of Physical Medicine and Rehabilitation. *Neurology.* 2011;76(20):1758-1765.
- Chou R, Carson S, Chan BK. Gabapentin vs tricyclic antidepressants for diabetic neuropathy and post-herpetic neuralgia: discrepancies between direct and indirect meta-analyses of randomized controlled trials. *J Gen Intern Med*. 2009;24(2):178-188.
- Clauw DJ, Mease P, Palmer RH, et al. Milnacipran for the treatment of fibromyalgia in adults: a 15-week, multicenter, randomized, double-blind, placebo-controlled, multiple-dose clinical trial. *Clin Ther*. 2008;30(11):1988-2004.
- Clauw DJ. Fibromyalgia: an overview. *Am J Med*. 2009;122(12 Suppl):S3-S13.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Crofford LJ, Rowbotham MC, Mease PJ, et al. Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double-blind, placebo-controlled trial. *Arthritis Rheum.* 2005;52(4):1264-1273.
- Crofford LJ. Fibromyalgia. In: Jameson J, Fauci AS, Kasper DL, Hauser SL, Longo DL, Loscalzo J., eds. *Harrison's Principles of Internal Medicine, 20th ed*. McGraw-Hill. https://accessmedicine.mhmedical.com/content.aspx?sectionid=192286180&bookid=2129. 2018. Accessed August 4, 2021.
- Cymbalta [package insert]. Eli Lilly and Company. Indianapolis, IN. May 2020.
- Derry S, Bell RF, Straube S, Wiffen PJ, Aldington D, Moore, RA. Pregabalin for neuropathic pain in adults. *Cochrane Database Syst Rev*. 2019;1:CD007076.
- Derry S, Sven-Rice A, Cole P, Tan T, Moore RA. Topical capsaicin (high concentration) for chronic neuropathic pain in adults. *Cochrane Database Syst Rev*. 2017;13(1):CD007393.pub4.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed August 4, 2021.
- Dworkin RH, Corbin AE, Young JP Jr, et al. Pregabalin for the treatment of postherpetic neuralgia: a randomized, placebo-controlled trial. *Neurology.* 2003;60:1274-1283.
- Dworkin RH, O'Connor AB, Backonja M, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. *Pain.* 2007;132(3):237-251.
- Edelsberg JS, Lord C, Oster G. Systematic review and meta-analysis of efficacy, safety, and tolerability data from randomized controlled trials of drugs used to treat postherpetic neuralgia. *Ann Pharmacother*. 2011;45:1483-1490.
- FDA Approved Risk Evaluation and Mitigation Strategies (REMS). Opioid analgesic REMS program. Food and Drug Administration Web site. Updated September 2018. https://www.fda.gov/drugs/information-drug-class/opioid-analgesic-risk-evaluation-and-mitigation-strategy-rems. Accessed August 4, 2021.
- Feldman EL. Management of diabetic neuropathy. UpToDate Web site. Updated June 21, 2021[a]. https://www.uptodate.com/contents/management-of-diabetic-neuropathy. Accessed August 4, 2021.
- Feldman EL. Epidemiology and classification of diabetic neuropathy. UpToDate Web site. Updated January 27, 2021[b]. https://www.uptodate.com/contents/epidemiology-and-classification-of-diabetic-neuropathy. Accessed August 4, 2021.
- Fitzcharles MA, Ste-Marie PA, Goldenberg DL, et al; National Fibromyalgia Guideline Advisory Panel. 2012 Canadian Guidelines for the diagnosis and management of fibromyalgia syndrome: executive summary. *Pain Res Manag.* 2013;18(3):119-126.
- Freynhagen R, Strojek K, Griesing T, et al. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomized, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. *Pain.* 2005;115:254-263.
- Galer B, Jensen M, Ma T, et al. The lidocaine patch 5% effectively treats all neuropathic pain qualities: results of a randomized, double-blind, vehicle-controlled, three-week efficacy study with use of the neuropathic pain scale. *Clin J Pain*. 2002;18(5):297-301.
- Galer B, Rowbotham M, Perander J, et al. Topical lidocaine patch relieves postherpetic neuralgia more effectively than a vehicle topical patch: results of an enriched enrollment study. *Pain.* 1999;80:533-538.
- Gilron I, Bailey RN, Tu D, et al. Morphine, gabapentin, or their combination for neuropathic pain. *N Engl J Med*. 2005;352:1324-1334.
- Goldenberg DL. Clinical manifestations and diagnosis of fibromyalgia in adults. UpToDate Web site. Updated August 26, 2020[a]. www.uptodate.com. Accessed August 4, 2021.
- Goldenberg DL. Initial treatment of fibromyalgia in adults. UpToDate Web site. Updated January 23, 2020[b]. www.uptodate.com. Accessed August 4, 2021.
- Gralise [package insert]. Almatica Pharma LLC. Morristown, NJ. April 2020.
- Guan Y, Ding X, Cheng Y, et al. Efficacy of pregabalin for peripheral neuropathic pain: results of an eight-week, flexible-dose, double-blind, placebo-controlled study conducted in China. *Clin Ther*. 2011;33:159-166.
- Handelsman Y, Bloomgarden ZT, Grunberger G, et al. American Association of Clinical Endocrinologists and American College of Endocrinology clinical practice guideline for developing a diabetes mellitus comprehensive care plan- 2015. *Endocr Pract.* 2015;21(Suppl 1):39-44.
- Hauser W, Bernardy K, Uceyler N, et al. Treatment of fibromyalgia syndrome with antidepressants: a meta-analysis. *JAMA*. 2009[a];301(2):198-209.
- Hauser W, Bernardy K, Uceyler N, et al. Treatment of fibromyalgia syndrome with gabapentin and pregabalin - a meta-analysis of randomized controlled trials. *Pain.* 2009[b];145(1-2):69-81.
- Hauser W, Petzke F, Sommer C. Comparative efficacy and harms of duloxetine, milnacipran, and pregabalin in fibromyalgia syndrome (abstract). *J Pain*. 2010;11(6):505-521.
- Herndon CM, Strickland JM, Ray JB. Pain management. In: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey L, eds. *Pharmacotherapy: A Pathophysiologic Approach, 10th ed*. McGraw-Hill. . https://accesspharmacy-mhmedical-com.proxy.cc.uic.edu/content.aspx?bookid=1861&sectionid=146063604. Accessed August 4, 2021.
- Horizant [package insert]. Arbor Pharmaceuticals, LLC. Atlanta, GA. April 2020.
- Huffman CL, Goldenberg JN, Weintraub J, et al. Efficacy and safety of once-daily controlled-release pregabalin for the treatment of patients with postherpetic neuralgia: a double-blind, enriched enrollment randomized withdrawal, placebo-controlled trial. *Clin J Pain*. 2017;33(7):569-578. doi: 10.1097/AJP.0000000000000445.
- Ifuku M, Iseki M, Hidaka I, et al. Replacement of gabapentin with pregabalin in postherpetic neuralgia therapy. *Pain Medicine.* 2011;12:1112-1126.
- Irving G, Backonja M, Rauck R, et al. NGX-4010, a capsaicin 8% dermal patch, administered alone or in combination with systemic neuropathic pain medications, reduces pain in patients with postherpetic neuralgia. *Clin J Pain*. 2012;28(2):101-107.
- Irving G, Jensen M, Cramer M, et al. Efficacy and tolerability of gastric-retentive gabapentin for the treatment of postherpetic neuralgia: results of a double-blind, randomized, placebo-controlled clinical trial (abstract). *Clin J Pain*. 2009;25(3):185-192.
- Jensen MP, Chiang YK, Wu J. Assessment of pain quality in a clinical trial of gabapentin extended release for postherpetic neuralgia. *Clin J Pain*. 2009;25(4):286-292.
- Kajdasz DK, Iyengar S, Desaiah D, et al. Duloxetine for the management of diabetic peripheral neuropathic pain: evidence-based findings from post hoc analysis of three multicenter, randomized, double-blind, placebo-controlled, parallel-group studies. *Clin Ther*. 2007;29:2536-2546.
- Katz N, Gammaitoni A, Davis MW, et al; Lidoderm Patch Study. Lidocaine patch 5% reduces pain intensity and interference with quality of life in patients with postherpetic neuralgia: an effectiveness trial. *Pain Medicine.* 2002;3(4):324-332.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Lee YH, Song GG. Comparative efficacy and tolerability of duloxetine, pregabalin, and milnacipran for the treatment of fibromyalgia: a Bayesian network meta-analysis of randomized controlled trials. *Rheumatol Int*. 2016;36(5):663-672.
- Lesser H, Sharma U, LaMoreaux L, et al. Pregabalin relieves symptoms of painful diabetic neuropathy. *Neurology*. 2004;63:2104-2110.
- Liampas A, Rekatsina M, Vadalouca A, Paladini A, Varrassi G, Zis P. Pharmacological management of painful peripheral neuropathies: a systematic review. *Pain Ther*. 2021;10(1):55-68. doi: 10.1007/s40122-020-00210-3
- Lidoderm [package insert]. Endo Pharmaceuticals Inc. Malvern, PA. November 2018.
- Lunn MPT, Hughes RAC, Wiffen PJ. Duloxetine for treating painful neuropathy, chronic pain or fibromyalgia. *Cochrane Database Syst Rev* 2014;(1):CD007115.pub3.
- Lyrica [package insert]. Pfizer Inc. New York, NY. June 2020.
- Lyrica CR [package insert]. Pfizer Inc. New York, NY. June 2020.
- Macfarlane GJ, Kronisch C, Dean LE, et al. EULAR revised recommendations for the management of fibromyalgia. *Ann Rheum Dis*. 2017 Feb;76(2):318-328. doi: 10.1136/annrheumdis-2016-209724.
- Mease PJ, Clauw DJ, Gendreau RM, et al. The efficacy and safety of milnacipran for treatment of fibromyalgia: a randomized, double-blind, placebo-controlled trial. *J Rheumatol*. 2009;36:398-409.
- Mease PJ, Russell IJ, Kajdasz DK, et al. Long-term safety, tolerability, and efficacy of duloxetine in the treatment of fibromyalgia. *Semin Arthritis Rheum.* 2010;39:454-464.
- Meier T, Wasner G, Faust M, et al. Efficacy of lidocaine patch 5% in the treatment of focal peripheral neuropathic pain syndromes: a randomized, double-blind, placebo-controlled study. *Pain*. 2003;106:151-158.
- Meng FY, Zhang LC, Liu Y, et al. Efficacy and safety of gabapentin for treatment of postherpetic neuralgia: a meta-analysis of randomized controlled trials. *Minerva Anesthesiol*. 2014;80(5):556-567.
- Moon DE, Lee DI, Lee SC, et al. Efficacy and tolerability of pregabalin using a flexible, optimized dose schedule in Korean patients with peripheral neuropathic pain: a 10-week, randomized, double-blind, placebo-controlled, multicenter study. *Clin Ther*. 2010;32:2370-2385.
- Neurontin [package insert]. Pfizer Inc. New York, NY. December 2020.
- Nucynta ER [package insert]. Collegium Pharmaceutical, Inc. Stoughton, MA. March 2021.
- Ogawa S, Suzuki M, Arakawa A, et al. Long-term efficacy and safety of pregabalin in patients with postherpetic neuralgia: results of a 52-week, open-label, flexible-dose study (abstract). *Masui*. 2010;59(8):961-970.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed August 4, 2021.
- Parsons B, Li C. The efficacy of pregabalin in patients with moderate and severe pain due to diabetic peripheral neuropathy. *Curr Med Res Opin*. 2016;32(5):929-937.
- Pop-Busui R, Coulton A JM, Feldman EL, et al. Diabetic neuropathy: a position statement by the American Diabetes Association. *Diabetes Care.* 2017;40(1):136-154.
- Quilici S, Chancellor J, Lothgren M, et al. Meta-analysis of duloxetine vs pregabalin and gabapentin in the treatment of diabetic peripheral neuropathic pain. *BMC Neurol.* 2009;9:6-19.
- Qutenza [package insert]. Averitas Pharma, Inc. Morristown, NJ. August 2021.
- Raskin J, Smith TR, Wong K, et al. Duloxetine vs routine care in the long-term management of diabetic peripheral neuropathic pain. *J Palliative Med*. 2006;9(1):29-40.
- Rice ASC, Maton S; Postherpetic Neuralgia Study Group. Gabapentin in postherpetic neuralgia: a randomized, double blind, placebo controlled study. *Pain.* 2001;94:215-24.
- Rosenstock J, Tuchman M, LaMoreaux L, et al. Pregabalin for the treatment of painful diabetic peripheral neuropathy: a double-blind, placebo-controlled trial. *Pain.* 2004;110:628-638.
- Roth T, van Seventer R, Murphy TK. The effect of pregabalin on pain-related sleep interference in diabetic peripheral neuropathy or postherpetic neuralgia: a review of nine clinical trials. *Clin Med Res & Opin*. 2010;26(10):2411-2419.
- Rowbotham M, Harden N, Stacey B, et al; Gabapentin Postherpetic Neuralgia Study Group. Gabapentin for the treatment of postherpetic neuralgia. A randomized controlled trial. *JAMA*. 1998;280:1837-1842.
- Russell IJ, Mease PJ, Smith TR, et al. Efficacy and safety of duloxetine for treatment of fibromyalgia in patients with or without major depressive disorder: Results from a six-month, randomized, double-blind, placebo-controlled, fixed-dose trial. *Pain.* 2008;136:432-444.
- Sabatowski R, Galvez R, Cherry DA, et al. Pregabalin reduces pain and improves sleep and mood disturbances in patients with post-herpetic neuralgia: results of a randomized, placebo-controlled clinical trial. *Pain.* 2004;109:26-35.
- Savella [package insert]. Allergan USA, Inc. Irvine, CA. December 2017.
- Schwartz S, Etropolski M, Shapiro DY, et al. Safety and efficacy of tapentadol ER in patients with painful diabetic peripheral neuropathy: results of a randomized-withdrawal, placebo-controlled trial. *Curr Med Res Opin*. 2011;27(1):151-162.
- Semel D, Murphy TK, Zlateva G, et al. Evaluation of the safety and efficacy of pregabalin in older patients with neuropathic pain: results from a pooled analysis of 11 clinical studies. *BMC Family Practice*. 2010;11:85.
- Sharma U, Griesing T, Emir B, et al. Time to onset of neuropathic pain reduction: a retrospective analysis of data from nine controlled trials of pregabalin for painful diabetic peripheral neuropathy and postherpetic neuralgia. *Am J Ther*. 2010;17:577-585.
- Siddall PJ, Cousins MJ, Otte A, et al. Pregabalin in central neuropathic pain associated with spinal cord injury: a placebo-controlled trial. *Neurology*. 2006 Nov 28;67(10):1792-1800.
- Simpson DM, Robinson-Papp J, Van J, et al. Capsaicin 8% patch in painful diabetic peripheral neuropathy: a randomized, double-blind, placebo-controlled study. *J Pain.* 2017;18(1):42-53. doi:10.1016/j.jpain.2016.09.008
- Skvarc NK, Kamenik M. Effects of pregabalin on acute herpetic pain and postherpetic neuralgia incidence. *Wien Klin Wochenschr*. 2010;122(Suppl 2):49-53.
- Tanenberg RJ, Clemow DB, Giaconia JM, et al. Duloxetine compared with pregabalin for diabetic peripheral neuropathic pain management in patients with suboptimal pain response to gabapentin and treated with or without antidepressants: a post hoc analysis. *Pain Pract.* 2014;14(7):640-648.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Tanenberg RJ, Irving GA, Risser RC, et al. Duloxetine, pregabalin, and duloxetine plus gabapentin for diabetic peripheral neuropathic pain management in patients with inadequate pain response to gabapentin: an open-label, randomized, noninferiority comparison. *Mayo Clin Proc*. 2011;86(7):615-24.
- Tesfaye S, Wilhelm S, Lledo A, et al. Duloxetine and pregabalin: High-dose monotherapy or their combination? The "COMBO-DN study" – a multinational, randomized, double-blind, parallel-group study in patients with diabetic peripheral neuropathic pain. *Pain.* Dec 2013;154(12):2616-2625.
- Upadhyaya HP, Arnold LM, Alaka K, Qiao M, Williams D, Mehta R. Efficacy and safety of duloxetine versus placebo in adolescents with juvenile fibromyalgia: results from a randomized controlled trial. *Pediatr Rheumatol Online J.* 2019;17(1):27. doi:10.1186/s12969-019-0325-6
- Vinik AL, Perrot S, Vinik EJ, et al. Capsaicin 8% patch repeat treatment plus standard of care (SOC) versus SOC alone in painful diabetic peripheral neuropathy: a randomised, 52-week, open-label, safety study. *BMC Neurol*. 2016;16(1):1-14.
- Vitton O, Gendreau M, Gendreau J, et al. A double-blind placebo-controlled trial of milnacipran in the treatment of fibromyalgia. *Hum Psychopharmacol Clin Exp*. 2004;19:S27-S35.
- Vranken JH, Kijkgraaf MG, Kruis MR, et al. Pregabalin in patients with central neuropathic pain: a randomized, double-blind, placebo-controlled trial of a flexible-dose regimen. *Pain.* 2008;136(1-2):150-157.
- Wallace MS, Irving G, Crowles VE. Gabapentin extended-release tablets for the treatment of patients with postherpetic neuralgia: a randomized, double-blind, placebo-controlled, multicentre study. *Clin Drug Investig*. 2010;30(11):765-776.
- Welsch P, Uceyler N, Klose P, Walitt B, Hauser W. Serotonin and noradrenaline reuptake inhibitors (SNRIs) for fibromyalgia. *Cochrane Database Syst Rev*. 2018;2:CD010292.
- Wernicke J, Lledo A, Raskin J, et al. An evaluation of the cardiovascular safety profile of duloxetine. *Drug Safety*. 2007[a];30(5):437-455.
- Wernicke J, Wang F, Pritchett YL, et al. An open-label 52-week clinical extension comparing duloxetine with routine care in patients with diabetic peripheral neuropathic pain. *Pain Medicine*. 2007[b];8(6):503-513.
- Wiffen PJ, Derry S, Bell RF, et al. Gabapentin for chronic neuropathic pain in adults. *Cochrane Database Syst Rev*. 2017;6:CD007938.
- Xochilcal-Morales M, Castro EM, Guajardo-Rosas J, et al. A prospective, open-label, multicentre study of pregabalin in the treatment of neuropathic pain in Latin America. *Int J Clin Pract*. 2010;64(9):1301-1309.
- Yan G, Guang N, Wei-ping J, et al. Duloxetine vs placebo in the treatment of patients with diabetic neuropathic pain in China. *Chin Med J*. 2010;123(22):3184-3192.
- Zhang L, Rainka M, Freeman R, et al. A randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of gabapentin enacarbil in subjects with neuropathic pain associated with postherpetic neuralgia (PXN110748). *J Pain*. 2013;14(6):590-603.
- ZTlido [package insert]. Scilex Pharmaceuticals Inc. San Diego, CA. April 2021.

Publication Date: September 24, 2021

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Prior Authorization Guideline

Guideline Name Amondys 45 (casimersen)

1. Indications

Drug Name: Amondys 45
Duchenne muscular dystrophy (DMD) Indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 45 skipping.

2. Criteria

Product Name: Amondys 45	
Approval Length	6 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Submission of medical records (e.g., chart notes, laboratory values) documenting both of the following:

1.1 Diagnosis of Duchenne muscular dystrophy (DMD)

AND

1.2 Documentation of a confirmed mutation of the dystrophin gene amenable to exon 45 skipping

AND

2 - Prescribed by or in consultation with a neurologist who has experience treating children

AND

3 - Dose will not exceed 30 milligrams per kilogram of body weight infused once weekly

Product Name: Amondys 45	
Approval Length	12 month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - All of the following:

1.1 Patient is tolerating therapy

AND

1.2 Dose will not exceed 30 milligrams per kilogram of body weight infused once weekly

AND

1.3 Prescribed by or in consultation with a neurologist who has experience treating children

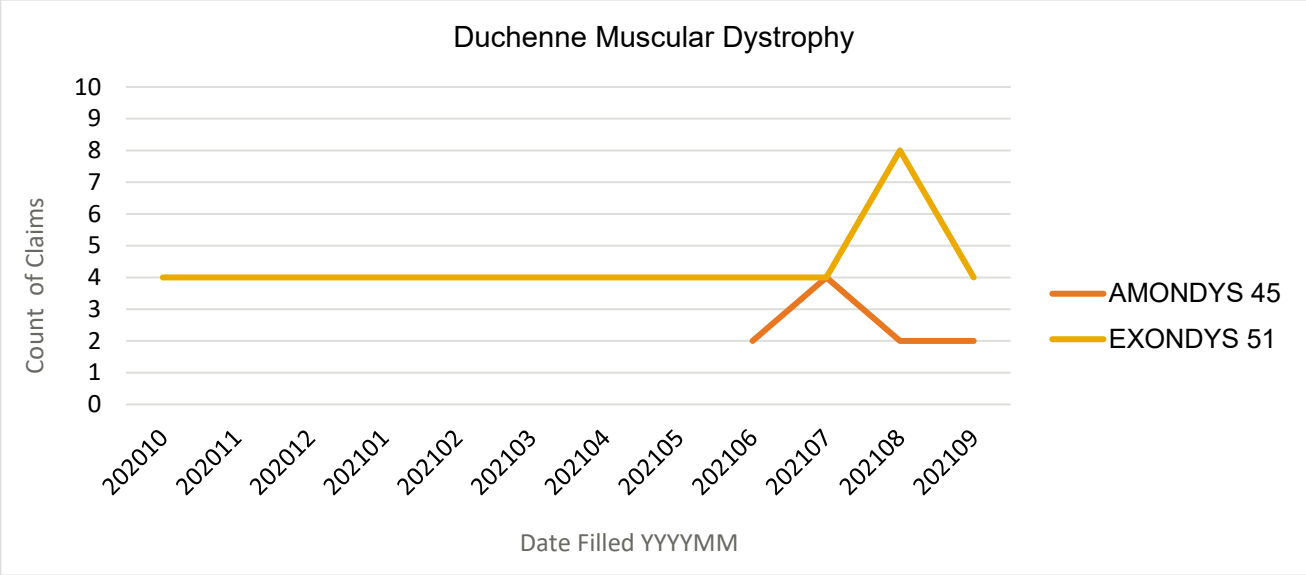
Nevada Medicaid

Utilization

Fee for Service

October 1, 2020 – September 30, 2021

Drug Name	Members	Claims	Total Day Supply	Total Quantity
AMONDYS 45	2	10	280	760
EXONDYS 51	2	48	1,456	2,368



Therapeutic Class Overview
Duchenne muscular dystrophy (DMD) Agents

INTRODUCTION

- Duchenne muscular dystrophy (DMD) is a fatal, X-linked neuromuscular disorder caused by *DMD* gene mutations that result in the absence or near-absence of functional dystrophin protein in muscle cells and progressive loss of skeletal and cardiac function (*Institute for Clinical and Economic Review [ICER] 2019*).
  - DMD is the most common pediatric muscular dystrophy, with an incidence of about 400 to 600 cases per year and a prevalence of approximately 6000 males in the US (*ICER 2019*).
- Diagnosis of DMD typically occurs in early childhood, with symptoms beginning around 3 to 5 years of age. Early symptoms include muscle weakness, clumsiness, difficulty with rising from a squatted position (Gower's sign), and difficulty going up and down stairs (*ICER 2019*).
  - DMD patients may also have developmental delay, behavioral issues, impaired growth, delayed puberty, adrenal insufficiency, and gastrointestinal complications (eg, dysphagia and gastroparesis) (*ICER 2019*).
  - Osteoporosis with resultant fractures may occur from the disease itself and as an AE of glucocorticoid therapy (*ICER 2019*).
  - Loss of ambulation typically occurs by 12 years of age. Fatal respiratory or cardiac complications frequently develop in the second or third decade of life, and many deaths occur in the setting of an acute infection (*Food and Drug Administration [FDA] Vyondys 53 summary review 2020, ICER 2019*).
- Dystrophin forms an important part of the glycoprotein complex, strengthening and connecting muscle fibers in skeletal and cardiac muscle. Lack of dystrophin results in degeneration of muscle fibers, inflammation, and ultimately replacement of muscle by fibrotic and adipose tissue (*ICER 2019*).
- DMD may be caused by more than 2000 mutations in the *DMD* gene that result in loss of expression or expression of nonfunctional dystrophin protein. An estimated 70% of DMD patients have single- or multi-exon deletions or duplications that are amenable to detection via genetic testing. Disease severity appears to vary by mutation, resulting in a heterogeneous population with differing rates of progression (*ICER 2019*).
- Becker muscular dystrophy (BMD) has a similar presentation to DMD, but typically has a later onset (5 to 60 years of age) and a milder clinical course. BMD patients typically remain ambulatory into adult life and survive beyond the age of 30 years (*Darras 2020*).

Table 1. Clinical features of DMD vs BMD (*Darras 2020*)

	Duchenne muscular dystrophy	Becker muscular dystrophy
Clinical course	Severe	Mild
Age of onset	3 to 5 years	5 to 60 years
Loss of ambulation	Early teens	Adulthood
Common *DMD* gene mutations	Out-of-frame exon deletion/ duplication, nonsense mutation	In-frame exon deletion/ duplication, missense mutation
Dystrophin expression by immunohistochemistry	Absent	Reduced
Dystrophin expression by western blot	< 5% of normal	> 20% of normal

- There are currently no therapies available to cure DMD or halt disease progression (*Messina and Vita 2018*).
- Corticosteroids are the mainstay of pharmacologic therapy for DMD. Early initiation of corticosteroids has been associated with prolonged ambulation, decreased contractures and deformities, and prolonged function and participation in activities of daily living. Steroids are usually begun early in the disease course, prior to substantial physical decline. AEs of corticosteroids include weight gain, hirsutism, decreased bone density with increased risk of fracture, and cataracts (*ICER 2019, Messina and Vita 2018*).
  - In 2017, Emflaza (deflazacort) was the first corticosteroid FDA approved specifically for DMD. In clinical trials of DMD patients, treatment with deflazacort offered similar benefits to prednisone and was associated with less weight gain; however, deflazacort may be associated with an increased risk of cataracts compared with prednisone (*ICER 2019*).

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Many patients with DMD carry mutations in the *DMD* gene that cause misalignments in the transcription reading frame, leading to nonfunctional or absent dystrophin. As part of RNA synthesis, exons are connected to generate mRNA that encodes dystrophin, and mutations in a single exon can disrupt all downstream synthesis of protein if the reading frame is disrupted (*ICER 2019*).
  - Exon-skipping therapies are antisense oligonucleotides that prevent mutated exons from being transcribed, allowing for downstream exons to be transcribed in the correct reading frame. The remaining exons form a shortened mRNA that encodes a truncated, partially functional dystrophin protein. Animal models and anecdotal data suggest that restoration of small amounts of dystrophin (between 2 to 4% of normal) may be beneficial in slowing DMD progression; however, clinical correlation has yet to be established (*ICER 2019*).
- There are 4 exon-skipping therapies with FDA approval for DMD. Each therapy received biomarker-based accelerated approval based on increases in dystrophin protein expression in muscle biopsy tissue. There is no consensus on the threshold of dystrophin expression in skeletal muscle fibers required to increase or to normalize muscle function in patients with DMD. The clinical benefit of exon-skipping therapies has not been established and will be evaluated in ongoing confirmatory studies (*FDA Amondys 45 summary review 2021*).
  - Exondys 51 (eteplirsen) was the first exon-skipping therapy to receive FDA approval for DMD in 2016. It remains the only therapy indicated for DMD patients with mutations amenable to exon 51 skipping (approximately 13% of the DMD population) (*FDA Exondys 51 summary review 2016*).
    - Prior to approval, the FDA's Peripheral and Central Nervous System Drugs Advisory Committee voted against the efficacy of eteplirsen for DMD based on a single historically-controlled study and against the availability of substantial evidence from adequate and well controlled studies that eteplirsen induced dystrophin production to a level that was reasonably likely to predict clinical benefit (*FDA Exondys 51 summary review 2016*).
    - An appeal of the decision to approve eteplirsen convened the Agency Scientific Dispute Process Review Board, whose Chair ultimately agreed with the conclusions of the Director of the Office of Drug Evaluation I (ODE-1) that the overall evidence derived from the limited clinical development program did not support that the levels of dystrophin produced by eteplirsen were reasonably likely to provide clinical benefit (*FDA Vyondys 53 clinical review 2020*).
  - Vyondys 53 (golodirsen) and Viltepso (viltolarsen) were approved in 2019 and 2020, respectively, for DMD patients with mutations amenable to exon 53 skipping (approximately 9% of the DMD population) (*FDA Viltepso clinical review 2020, FDA Vyondys 53 summary review 2020*).
    - Golodirsen was initially issued a complete response letter issued based on the determination that the small, unverified benefit with golodirsen did not outweigh the risks for renal toxicity and serious infections related to drug delivery. FDA approval of golodirsen was granted upon appeal (*FDA Vyondys 53 clinical review 2020*).
  - Amondys 45 (casimersen) was approved in 2021 as the only therapy for DMD patients with mutations amenable to exon 45 skipping (approximately 8% of the DMD population) (*FDA Amondys 45 summary review 2021*).
- Ataluren is an oral therapy that promotes ribosomal read-through of nonsense (stop) mutations, which are present in 10 to 15% of patients with DMD. Although not approved by the FDA, ataluren is available to patients in 23 countries through either expanded access programs or commercial sales (*Darras 2021*).
- Clinical trials for investigational DMD therapies are ongoing, including gene transfer by intravascular administration of recombinant adeno-associated viral vectors that carry microdystrophin or minidystrophin genes (*Darras 2021*).
- Medispan classes: Neuromuscular agents, muscular dystrophy agents; Corticosteroids, glucocorticosteroids

Table 2. Medications Included Within Class Review

Drug	Generic Availability
Amondys 45 (casimersen)	-
Emflaza (deflazacort)	-
Exondys 51 (eteplirsen)	-
Vyondys 53 (golodirsen)	-
Viltepso (viltolarsen)	-

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

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

INDICATIONS

Table 3. FDA-Approved Indications

Indication	Amondys 45 (casimersen)	Emflaza (deflazacort)	Exondys 51 (eteplirsen)	Vyondys 53 (golodirsen)	Viltepso (viltolarsen)
Treatment of DMD in patients ≥ 2 years of age		✔			
Treatment of DMD in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 45 skipping	✔				
Treatment of DMD in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 51 skipping			✔		
Treatment of DMD in patients who have a confirmed mutation of the *DMD* gene that is amenable to exon 53 skipping				✔	✔

(*Prescribing information: Amondys 45 2021, Emflaza 2021, Exondys 51 2020, Viltepso 2021, Vyondys 53 2021*)

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

CLINICAL EFFICACY SUMMARY

Corticosteroids (deflazacort)

- There is considerable experience with the use of Emflaza (deflazacort) and other corticosteroids for the management of patients with DMD. Several observational studies have assessed the long-term effects of corticosteroid use on muscle strength, ambulation, weight gain, and other outcomes. Overall, these studies concluded that patients taking steroids performed better on functional outcome testing and experienced prolonged ambulation vs untreated patients (*Balaban et al 2005, Bello et al 2015, Kim et al 2015*).
- A Cochrane systematic review of 12 randomized controlled trials (RCTs) (N = 667) found moderate quality evidence supporting treatment with corticosteroids in patients with DMD. Compared to placebo, corticosteroids improved muscle strength and function (including respiratory muscle strength and function) for 6 months, with continued evidence of benefit at 1 year. There was no evidence other than from non-randomized trials to establish the effect of corticosteroids on prolongation of ambulation (*Matthews et al 2016*).
- The safety and efficacy of deflazacort for the treatment of DMD were demonstrated in 2 pivotal trials conducted in the 1980s and 1990s (*Angelini et al 1994, Griggs et al 2016*).
  - A 52-week, Phase 3, double-blind (DB), placebo-controlled (PC), multi-center (MC), RCT (N = 196) was conducted to assess the safety and efficacy of deflazacort and prednisone vs placebo in boys aged 5 to 15 years old with DMD. For the first 12 weeks of the study (ie, Phase 1), patients were randomized to 1 of 4 groups (deflazacort 0.9 mg/kg/day, deflazacort 1.2 kg/mg/day, prednisone 0.75 mg/kg/day, or placebo). For the remainder of the study through week 52 (ie, Phase 2), patients initially randomized to placebo were re-randomized to 1 of the 3 active treatments (deflazacort 0.9 mg/kg/day, deflazacort 1.2 kg/mg/day, or prednisone 0.75 mg/kg/day). For the primary efficacy endpoint, all treatment groups demonstrated statistically significant improvements in muscle strength vs placebo from baseline to week 12. During Phase 2, only the deflazacort 0.9 mg/kg/day group maintained a statistically significant improvement in muscle strength vs prednisone-treated patients; however, both deflazacort groups outperformed the prednisone group by week 52 (secondary efficacy endpoint) (*Griggs et al 2016*).
    - In the opinion of the FDA, the results for the change from week 12 to week 52 were not interpretable. The larger increase in muscle strength score from week 12 to week 52 in the deflazacort 0.9 mg/kg/day group was mostly due to a lower score at week 12 in this group. Because the groups were not comparable at week 12, the comparisons of the treatment effect from weeks 12 to 52 were not considered meaningful (*FDA Emflaza summary review 2017).*

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- At week 52, patients taking prednisone had significantly more weight gain than both deflazacort groups. The most frequent adverse effects (AEs) reported were: Cushingoid appearance, erythema, hirsutism, increased weight, headache, and nasopharyngitis.

- A 2-year, Phase 3, DB, PC, MC, RCT (N = 29) was conducted to evaluate the change in muscle strength from baseline to 2 years or loss of ambulation, whichever occurred first, in boys aged 5 to 11 years old with DMD and symptom onset before age 5. By year 2, the study failed to show a statistically significant result for change in muscle strength, possibly because of a limited number of patients remaining in the placebo arm (12 patients vs 3 patients). The median time to loss of ambulation was significantly longer in patients treated with deflazacort vs placebo (63.0 months [95% CI, 35.1 to not estimable] vs 31.9 months [95% CI, 13.6 to 54.6]; p = 0.0052) (*Angelini et al 1994*).

Exon-skipping therapies (casimersen, eteplirsen, golodirsen, viltolarsen)

- Exondys 51 (eteplirsen) was evaluated in 3 clinical studies in patients with a confirmed mutation of the DMD gene that is amenable to exon 51 skipping (*Exondys 51 prescribing information 2020*).
  - Study 201 was a 24-week, Phase 2b, DB, PC, RCT (N = 12) that evaluated the surrogate outcome of dystrophin production and the clinical efficacy outcome of 6-minute walk test (6MWT) distance in boys aged 7 to 13 years of age that were stable on corticosteroid treatment for at least 6 months. Patients were randomized to weekly intravenous (IV) infusions of eteplirsen 30 or 50 mg/kg/wk or placebo for 24 weeks (n = 4 for each group). Patients in the placebo group were switched to 30 or 50 mg/kg of eteplirsen (n = 2 for each group) at week 25. Study 202 was a 212-week, Phase 2, open-label (OL), MC extension study; all 12 patients who participated in Study 201 continued treatment in Study 202 (*Mendell et al 2013*).
    - The Study 201 authors concluded that at week 24, dystrophin-positive fibers increased by 23% from baseline in patients treated with 30 mg/kg eteplirsen, with no significant increases in the placebo group (p ≤ 0.002). Greater increases continued to occur by week 48 (52% and 43% in the 30 and 50 mg/kg groups, respectively). The authors also concluded that 6 ambulation-evaluable patients taking eteplirsen demonstrated an increase in the 6MWT (67.3 meters, p ≤ 0.001) vs placebo (*Mendell et al 2013*).
    - The mean dystrophin protein expression after 180 weeks of treatment with eteplirsen was 0.93% of the normal dystrophin level in healthy subjects (*Exondys 51 prescribing information 2020*).
      - The FDA noted that for the week 180 analysis, archived pre-treatment muscle biopsy samples were available for re-analysis from only 3 patients in Studies 201/202, and samples from controls were also obtained from different muscle groups than the eteplirsen-treated patients; therefore, the true change in dystrophin was difficult to estimate (*FDA Exondys 51 summary review 2016*).
      - In contrast to the conclusions of Mendell et al, the FDA found no significant difference in the change in 6MWT distance between patients treated with eteplirsen and those treated with placebo in Study 201. Additionally, Study 202 failed to provide evidence of a clinical benefit when compared to the external control group (primary endpoint, week 48) (*FDA Exondys 51 summary review 2016*).
    - Long-term results from Study 201/202 demonstrated attenuation in pulmonary function decline (p < 0.001) and fewer patients with loss of ambulation at 4 years (17% vs 88%; p = 0.007) with eteplirsen (n = 12) compared with an untreated natural history control group (n = 20) of DMD patients amenable to exon 51 skipping from the Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (DNHS) matched for baseline characteristics (*McDonald et al 2020*).
  - The Phase 3, OL PROMOVI trial (Study 301) was designed to evaluate the primary endpoint of 6MWT distance in 79 DMD patients treated with eteplirsen for 96 weeks compared with 30 patients in an untreated control group of DMD patients with mutations that were not amenable to exon 51 skipping (*ClinicalTrials.gov Web site*).
    - Accelerated approval of eteplirsen was based on western blot analyses of 13 patients enrolled in PROMOVI, which was ongoing at the time of FDA review. Among the 12 patients with evaluable results, mean dystrophin expression increased from 0.157% of normal at baseline to 0.440% of normal at Week 48 (mean change from baseline, 0.283%; p = 0.008). Overall, 8 (67%) patients experienced a change in dystrophin of ≤ 0.25%; only 1 patient (8%) experienced an increase > 1% of normal (*FDA Exondys 51 medical review 2016*).
    - The primary efficacy analysis was performed in all patients with a baseline 6MWT distance of 300 to 450 meters and ≥ 1 post-baseline functional assessment. The mean change from baseline to week 96 in 6MWT distance was −117.91 meters in 65 evaluable patients treated with eteplirsen and −133.56 meters in 9 evaluable patients in the untreated control group. The proportion of patients with loss of ambulation at week 96 was 17.9% in 67 evaluable

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

eteplirsen-treated patients, compared to 5.0% in 20 evaluable patients in the untreated control group (*ClinicalTrials.gov Web site*).
    - According to a poster presented at the World Muscle Society Virtual Congress, PROMOVI included a flawed comparison of eteplirsen-treated patients with a mismatched control arm that consisted entirely of patients with mutations not amenable to exon 51 skipping. Inadequate choice of control group became clear after study initiation, as emerging natural history data demonstrated patients with different mutations have different disease trajectories. Additionally, the control arm did not retain enough patients (15 of 30 completed the study) to allow for statistically and clinically meaningful comparisons (*McDonald et al 2020*).
  - The confirmatory study for eteplirsen (MIS51ON; NCT03992430) was initiated in 2020 with an estimated completion date in 2026. The randomized, DB phase will evaluate the safety and efficacy of a high dose of eteplirsen compared to the FDA-approved dose of 30 mg/kg IV weekly (*ClinicalTrials.gov Web site*).
- Vyondys 53 (golodirsen) was evaluated in SKIP-NMD, a 2-part, Phase 1/2 trial that enrolled ambulatory boys aged 6 to 15 years with DMD caused by out-of-frame deletions amenable to exon 53 skipping. Part 1 (n = 12) was a 12-week, Phase 1, DB, PC, dose-escalation RCT that established the safety of golodirsen. Part 2 of SKIP-NMD was a 168-week, Phase 2, OL evaluation of efficacy with golodirsen (*Frank et al 2020*).
  - Accelerated approval of golodirsen was based on the surrogate endpoint of dystrophin expression assessed by western blot. At interim analysis (n = 25), mean dystrophin expression increased from 0.095% of normal at baseline to 1.019% of normal at Week 48 (mean change from baseline, 0.924%; p < 0.001) (*Frank et al 2020*).
  - For the primary efficacy outcome of 6MWT distance, the mean change from baseline to 144 weeks was −99.0 meters in 22 evaluable patients treated with golodirsen and −160.8 meters in 6 evaluable patients who were not amenable to exon 53 skipping and did not receive treatment (*ClinicalTrials.gov Web site*).
  - The confirmatory study for golodirsen (ESSENCE; NCT02500381) is an ongoing Phase 3 trial with a 96-week, DB, PC phase followed by a 48-week OL phase with an estimated completion date in 2023. The primary endpoint will be the change in 6MWT distance from baseline to Week 96 (*ClinicalTrials.gov Web site*).
- Viltepso (viltolarsen) was evaluated in a 2-part, Phase 2, MC trial that enrolled 16 ambulatory boys aged 4 to 9 years with DMD amenable to exon 53 skipping. Two doses of viltolarsen (40 mg/kg/week [unapproved dose] and 80 mg/kg/week [approved dose]) were evaluated as add-on therapy to a stable dose of glucocorticoids. Part 1 was a 4-week, randomized, DB, PC period that established the safety of viltolarsen. Part 2 was a 20-week, OL treatment period that evaluated the efficacy and safety of low-dose and high-dose viltolarsen (*Clemens et al 2020*).
  - Accelerated approval of viltolarsen was based on an increase in dystrophin from 0.3% of normal at baseline to 5.7% of normal at week 25 with low-dose viltolarsen (mean change, 5.4%; p < 0.001), and from 0.6% of normal at baseline to 5.9% of normal at week 25 with high-dose viltolarsen (mean change, 5.3%; p = 0.01). Assessment of functional outcomes demonstrated improvement or stabilization of motor function with viltolarsen (n = 16) compared to an external natural history control group (n = 65) from the CINRG DNHS matched for age and treatment (*Clemens et al 2020*).
  - The confirmatory RACER53 trial (NCT04060199) for viltolarsen is an ongoing Phase 3, DB, PC, MC, RCT with an estimated completion date in 2024. The primary outcome will be the change from baseline to Week 48 in the time to stand test. Other functional outcomes include the time to run/walk 10 meters test, 6MWT, North Star Ambulatory Assessment (NSAA), and time to climb 4 steps test (*ClinicalTrials.gov Web site*).
- Amondys 45 (casimersen) was evaluated in the ongoing 96-week, Phase 3, randomized, DB, PC, MC ESSENCE trial that will serve as the confirmatory trial for both casimersen and golodirsen (*FDA Amondys 45 clinical review 2021*).
  - The casimersen arm of the ESSENCE study enrolled boys 7 to 13 years of age with a clinical diagnosis of DMD and a documented mutation amenable to exon 45 skipping. Key inclusion criteria included a mean 6MWT distance ≥ 300 and ≤ 450 meters, stable pulmonary and cardiac function, and stable corticosteroid therapy for ≥ 24 weeks (*FDA Amondys 45 clinical review 2021*).
  - Accelerated approval of casimersen was based on an interim analysis of the ESSENCE trial in 43 patients randomized to receive casimersen (n = 27) or placebo (n = 16) once weekly via IV infusion for 48 weeks. Mean dystrophin protein expression increased from 0.93% of normal levels at baseline to 1.74% at week 48 in the casimersen group (mean change from baseline, 0.81%; p < 0.001), as compared to 0.54% of normal at baseline to 0.76% at week 48 in the placebo group (mean change from baseline, 0.22%; p = 0.089). The between-group difference in dystrophin expression with casimersen vs placebo was 0.59% (p = 0.004) (*FDA Amondys 45 clinical review 2021*).

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

Table 4. FDA-approved exon-skipping therapies for DMD (*ClinicalTrials.gov Web site, Exondys 51 prescribing information 2020, FDA Amondys 45 clinical review 2021, ICER 2019, Viltepso prescribing information 2021, Vyondys 53 prescribing information 2021*)

Exon skipped	Amenable DMD Population	Drug	Manufacturer	Accelerated Approval	Dystrophin*	Confirmatory trial (Estimated completion date)
45	8%	**Amondys 45** (casimersen)	Sarepta	2021	0.81%	ESSENCE (2023)
51	13%	**Exondys 51** (eteplirsen)		2016	0.28%	MIS51ON (2026)
53	9%	**Vyondys 53** (golodirsen)		2019	0.92%	ESSENCE (2023)
		Viltepso (viltolarsen)	NS Pharma	2020	5.3%†	RACER53 (2024)

* Mean change from baseline in dystrophin measured by western blot as reported in the prescribing information
† Differences in the western blot assay methodology may prevent meaningful comparisons across studies

CLINICAL GUIDELINES

- **DMD Care Considerations Working Group: Diagnosis and management of DMD, part 1: Diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management** (*Birnkrant et al 2018*)
  - The DMD Care Considerations Working Group was supported by the CDC with involvement of the TREAT-NMD network for neuromuscular diseases, the Muscular Dystrophy Association, and Parent Project Muscular Dystrophy.
    - The guidance was not conventionally evidence based, as few large-scale RCTs have been completed for DMD, with the exception of corticosteroid studies.
    - No recommendations were provided to inform the place in therapy for eteplirsen, golodirsen, viltolarsen, or casimersen.
  - Consistent and reproducible clinical assessments of neuromuscular function performed by trained practitioners underpin the management of DMD.
    - The NSAA and timed function tests should be assessed every 6 months. They have high validity and reliability, as well as correlation between tests across time, minimum clinically important differences, and predictive capabilities regarding functional motor changes that are important in monitoring clinical progression and assessing new and emerging therapies.
    - Before 7 years of age, gains might occur in the 6MWT and timed function tests. After 7 years of age, a 6MWT distance < 325 meters and a mean linearized NSAA of 34 or less (raw score of 9) have been associated with greater functional decline in ambulation over the subsequent 12 months.
  - Physiotherapy and glucocorticoids are the mainstays of DMD treatment and should continue after loss of ambulation.
    - The benefits of long-term glucocorticoid therapy include loss of ambulation at a later age, preserved upper limb and respiratory function, and avoidance of scoliosis surgery.
    - Although the benefits of glucocorticoid therapy are well established, uncertainty remains about which glucocorticoids are best and at what doses.
  - Although the DMD Care Considerations Working Group acknowledged the FDA approval of eteplirsen, no specific recommendations were provided.

- **American Academy of Neurology (AAN) − Practice guideline update summary: Corticosteroid treatment of DMD** (*Gloss et al 2016, reaffirmed 2019*)
  - The AAN recommendations are focused on corticosteroid therapy; no recommendations are provided regarding exon-skipping therapies.
  - In children with DMD, prednisone should be offered to improve strength (Level B) and pulmonary function (Level B).
  - Prednisone may be offered to improve timed motor function (Level C), reducing the need for scoliosis surgery (Level C), and delaying cardiomyopathy onset by 18 years of age (Level C).

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Deflazacort may be offered to improve strength and timed motor function and delay age at loss of ambulation by 1.4 to 2.5 years (Level C). Deflazacort may be offered to improve pulmonary function, reduce the need for scoliosis surgery, delay cardiomyopathy onset, and increase survival at 5 to 15 years of follow-up (Level C for each).
- Deflazacort and prednisone may be equivalent in improving motor function (Level C).
- Prednisone may be associated with greater weight gain in the first years of treatment than deflazacort (Level C).
- Deflazacort may be associated with a greater risk of cataracts than prednisone (Level C).

SAFETY SUMMARY

Corticosteroids (deflazacort)

- Deflazacort is contraindicated in patients with known hypersensitivity to deflazacort or to any of the inactive ingredients.
- Warnings and precautions for deflazacort are similar to those of other corticosteroids (eg, prednisone) and include alterations in endocrine function, immunosuppression and increased risk of infection, alterations in cardiovascular/renal function, gastrointestinal perforation, behavioral and mood disturbances, effects on bones, ophthalmic effects, avoiding certain vaccinations, serious skin rashes, effects on growth and development, myopathy, Kaposi's sarcoma, risk of serious AEs in infants because of the benzyl alcohol preservative, thromboembolic events, and anaphylaxis.
- The most common AEs (≥ 10% and greater than placebo) with deflazacort use were Cushingoid appearance (33% with deflazacort vs 12% with placebo), increased weight (20% vs 6%), increased appetite (14% vs 2%), upper respiratory tract infection (12% vs 10%), cough (12% vs 6%), pollakiuria (12% vs 2%), hirsutism (10% vs 2%), central obesity (10% vs 4%), and nasopharyngitis (10% vs 6%).

Exon-skipping therapies (casimersen, eteplirsen, golodirsen, viltolarsen)

- There are no labeled contraindications to any of the exon-skipping therapies.
- Eteplirsen and golodirsen have a labeled warning for hypersensitivity reactions.
- Casimersen, golodirsen, and viltolarsen have warnings for kidney toxicity.
  - Although kidney toxicity was not reported in clinical trials with casimersen, golodirsen, or viltolarsen, it was observed in animal studies with these agents and in human studies with other antisense oligonucleotides.
- The most common AEs with exon-skipping therapies included:
  - Casimersen (incidence ≥ 20% and ≥ 5% higher than placebo): Upper respiratory tract infection, cough, pyrexia, headache, arthralgia, and oropharyngeal pain.
  - Eteplirsen (incidence ≥ 35% and higher than placebo): Balance disorder and vomiting.
  - Golodirsen (incidence ≥ 20% and higher than placebo): Headache, pyrexia, fall, abdominal pain, nasopharyngitis, cough, vomiting, and nausea.
  - Viltolarsen (incidence ≥ 15%): Upper respiratory tract infection, injection site reaction, cough, and pyrexia.

DOSING AND ADMINISTRATION

Table 5. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Amondys 45 (casimersen)	Injection	IV infusion	Once weekly	Monitor renal function
Emflaza (deflazacort)	Tablets, suspension	Oral	Once daily	
Exondys 51 (eteplirsen)	Injection	IV infusion	Once weekly	
Vyondys 53 (golodirsen)	Injection	IV infusion	Once weekly	Monitor renal function
Viltepso (viltolarsen)	Injection	IV infusion	Once weekly	Monitor renal function

See the current prescribing information for full details

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

CONCLUSION

- DMD is a rare, genetic neuromuscular disease characterized by progressive loss of muscle function, resulting in early death due to respiratory or cardiac failure.
- No currently available therapies cure DMD or halt disease progression. Corticosteroids are the mainstay of pharmacologic therapy for DMD and may prolong ambulation and participation in activities of daily living.
- Emflaza (deflazacort) is the only corticosteroid indicated specifically for the treatment of DMD. Deflazacort is available as oral tablets or suspension and is administered once daily.
  - Other corticosteroids such as prednisone have been used off-label for decades to treat DMD. RCTs and clinical practice guidelines do not support the superiority of one corticosteroid over the others for DMD.
- The FDA granted biomarker-based accelerated approvals to 4 antisense oligonucleotides that demonstrated increases in dystrophin protein expression in muscle biopsy tissue. There is no consensus on the threshold of dystrophin expression in skeletal muscle fibers required to increase or to normalize muscle function in patients with DMD. The exon-skipping therapies are administered once weekly via IV infusion.
  - Amondys 45 (casimersen) is the only exon-skipping therapy indicated for DMD patients with mutations amenable to exon 45 skipping (approximately 8% of the DMD population).
  - Exondys 51 (eteplirsen) is the only exon-skipping therapy indicated for DMD patients with mutations amenable to exon 51 skipping (approximately 13% of the DMD population).
  - Vyondys 53 (golodirsen) and Viltepso (viltolarsen) are both indicated for DMD patients with mutations amenable to exon 53 skipping (approximately 9% of the DMD population).
- The clinical benefit of exon-skipping therapies has not been established and will be evaluated in ongoing confirmatory studies, which are expected to conclude between 2023 and 2026.

REFERENCES

- Amondys 45 [package insert], Cambridge, MA: Sarepta Therapeutics, Inc.; February 2021.
- Angelini C, Pegoraro E, Turella E, Intino MT, Pini A, Costa C. Deflazacort in Duchenne dystrophy: study of long-term effect. *Muscle Nerve*. 1994;17(4):386-391.
- Balaban B, Matthews DJ, Clayton GH, Carry T. Corticosteroid treatment and functional improvement in Duchenne muscular dystrophy: long-term effect. *Am J Phys Med Rehabil*. 2005;84(11):843-850.
- Bello L, Gordish-Dressman H, Morgenroth LP, et al; CINRG Investigators. Prednisone/prednisolone and deflazacort regimens in the CINRG Duchenne Natural History Study. *Neurology*. 2015;85(12):1048-1055.
- Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. *Lancet Neurol*. 2018;17(3):251-267. doi: 10.1016/S1474-4422(18)30024-3.
- Clemens PR, Rao VK, Connolly AM, et al. Safety, tolerability, and efficacy of viltolarsen in boys with Duchenne muscular dystrophy amenable to exon 53 skipping: A Phase 2 randomized clinical trial. *JAMA Neurol*. 2020;77(8):982-991. doi: 10.1001/jamaneurol.2020.1264.
- ClinicalTrials.gov Web site. https://clinicaltrials.gov. Accessed April 19, 2021.
- Darras BT. Duchenne and Becker muscular dystrophy: Clinical features and diagnosis. UpToDate Web site. Updated July 24, 2020. https://www.uptodate.com/contents/duchenne-and-becker-muscular-dystrophy-clinical-features-and-diagnosis. Accessed April 19, 2021.
- Darras BT. Duchenne and Becker muscular dystrophy: Glucocorticoid and disease-modifying treatment. UpToDate Web site. Updated March 16, 2021. https://www.uptodate.com/contents/duchenne-and-becker-muscular-dystrophy-glucocorticoid-and-disease-modifying-treatment. Accessed April 19, 2021.
- Drugs@FDA: FDA approved drug products. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed April 19, 2021.
- Emflaza [package insert], South Plainfield, NJ: PTC Therapeutics, Inc.; February 2021.
- Exondys 51 [package insert], Cambridge, MA: Sarepta Therapeutics, Inc; July 2020.
- Food and Drug Administration (FDA). Amondys 45 clinical review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/213026Orig1s000SumR.pdf. March 18, 2021. Accessed April 19, 2021.
- Food and Drug Administration (FDA). Amondys 45 summary review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/213026Orig1s000SumR.pdf. March 18, 2021. Accessed April 19, 2021.
- Food and Drug Administration (FDA). Emflaza summary review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/208684,208685Orig1s000SumR.pdf. March 9, 2017. Accessed April 19, 2021.
- Food and Drug Administration (FDA). Exondys 51 medical review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488Orig1s000MedR.pdf. October 26, 2016. Accessed April 19, 2021.
- Food and Drug Administration (FDA). Exondys 51 summary review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2016/206488_summary%20review_Redacted.pdf. October 26, 2016. Accessed April 19, 2021.
- Food and Drug Administration (FDA). Viltepso clinical review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2020/212154Orig1s000MedR.pdf. August 31, 2020. Accessed April 19, 2021.
- Food and Drug Administration (FDA). Vyondys 53 clinical review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211970Orig1s000MedR.pdf. January 21, 2020. Accessed April 19, 2021.

This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

- Food and Drug Administration (FDA). Vyondys 53 summary review. https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/211970Orig1s000SumR.pdf. January 21, 2020. Accessed April 19, 2021.
- Frank DE, Schnell FJ, Akana C, et al. Increased dystrophin production with golodirsen in patients with Duchenne muscular dystrophy. *Neurology*. 2020;94(21):e2270-e2282. doi: 10.1212/WNL.0000000000009233.
- Gloss D, Moxley RT, Ashwal S, Oskoui M. Practice guideline update summary: Corticosteroid treatment of Duchenne muscular dystrophy: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology*. 2016;86(5):465-472. doi: 10.1212/WNL.0000000000002337.
- Griggs RC, Miller JP, Greenberg CR, et al. Efficacy and safety of deflazacort vs prednisone and placebo for Duchenne muscular dystrophy. *Neurology*. 2016;87(20):2123-2131.
- Institute for Clinical and Economic Review (ICER). Deflazacort, eteplirsen, and golodirsen for Duchenne muscular dystrophy: Effectiveness and value: Final evidence report. https://icer-review.org/material/dmd-final-evidence-report/. August 15, 2019. Accessed April 19, 2021.
- Kim S, Campbell KA, Fox DJ, Matthews DJ, Valdez R; MD STARnet. Corticosteroid treatments in males with Duchenne muscular dystrophy: treatment duration and time to loss of ambulation. *J Child Neurol*. 2015;30(10):1275-1280.
- Matthews E, Brassington R, Kuntzer T, Jichi F, Manzur AY. Corticosteroids for the treatment of Duchenne muscular dystrophy. *Cochrane Database Syst Rev*. 2016;(5):CD003725.
- McDonald C, Shieh P, Abdel-Hamid HZ, et al. Open-label evaluation of eteplirsen in patients with Duchenne muscular dystrophy amenable to exon 51 skipping: PROMOVI trial. Poster presented at: World Muscle Society Virtual Congress; September 28-October 2, 2020.
- Mendell JR, Rodino-Klapac LR, Sahenk Z et al. Eteplirsen for the treatment of Duchenne muscular dystrophy. *Ann Neurol*. 2013 Nov;74(5):637-47.
- Messina S, Vita GL. Clinical management of Duchenne muscular dystrophy: the state of the art. *Neurol Sci*. 2018;39(11):1837-1845. doi: 10.1007/s10072-018-3555-3.
- Orange Book: Approved drug products with therapeutic equivalence evaluations. Food and Drug Administration Web site. https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed April 19, 2021.
- Viltepso [package insert], Paramus, NJ: NS Pharma, Inc.; March 2021.
- Vyondys 53 [package insert], Cambridge, MA: Sarepta Therapeutics, Inc.; February 2021.

Publication Date: May 21, 2021

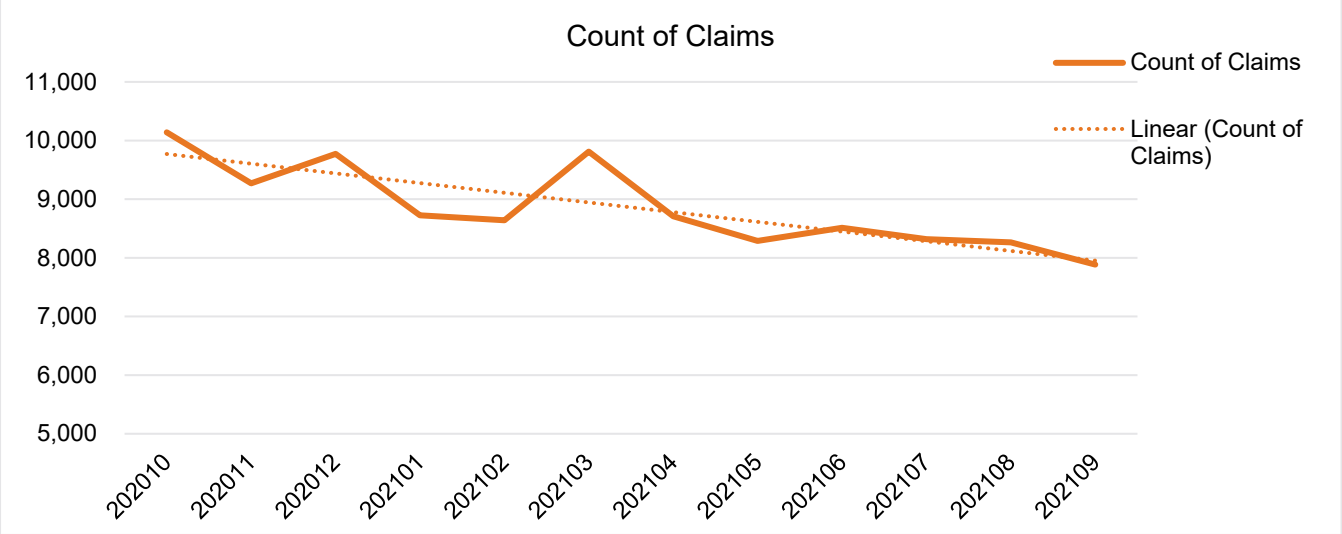
This information is considered confidential and proprietary to OptumRx. It is intended for internal use only and should be disseminated only to authorized recipients. The contents of the therapeutic class overviews on this website ("Content") are for informational purposes only. The Content is not intended to be a substitute for professional medical advice, diagnosis, or treatment. Patients should always seek the advice of a physician or other qualified health provider with any questions regarding a medical condition. Clinicians should refer to the full prescribing information and published resources when making medical decisions.

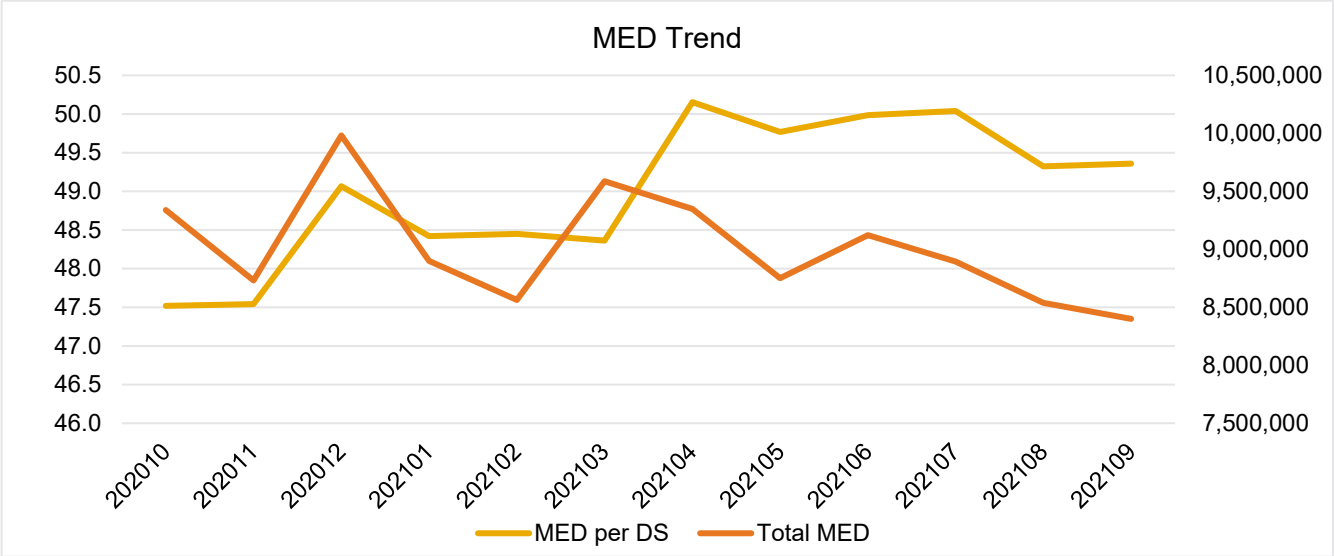
Board Requested Reports

Nevada Medicaid

Opioid Trends
Fee for Service
October 1, 2020 – September 30,2021

Date Filled	Count of Claims	Days Supply	Count of Members	Total Qty	Total MED	MED per DS
202010	10,140	196,519	8,836	656,699	9,338,370	47.5
202011	9,271	183,657	8,225	614,818	8,731,258	47.5
202012	9,773	203,436	8,400	685,502	9,981,963	49.1
202101	8,726	183,800	7,860	622,999	8,899,862	48.4
202102	8,641	176,744	7,776	593,816	8,563,078	48.4
202103	9,810	198,235	8,470	668,665	9,587,333	48.4
202104	8,708	186,404	7,708	630,228	9,348,850	50.2
202105	8,289	175,838	7,437	593,115	8,750,997	49.8
202106	8,513	182,492	7,505	619,603	9,122,032	50.0
202107	8,319	177,747	7,304	602,263	8,894,309	50.0
202108	8,263	173,105	7,259	585,982	8,538,198	49.3
202109	7,885	170,190	7,023	574,890	8,400,255	49.4





Nevada Medicaid

Opioid Trends

Fee for Service

October 1, 2020 – September 30,2021

Member ID Encrypted	Count of Claims	Days Supply	Quantity	MED per DS	Total MED
38F2770CD7C1B94	8	240	1,440	640	76,800
38E297CC6761590	6	170	720	617	52,200
78A2875CF741397	6	176	968	540	47,520
38F2477CF7C1090	6	180	1,260	525	47,250
78A2875CF741394	7	193	1,160	451	44,100
68D2975CF741397	6	180	630	480	43,200
38C2470C77D1191	3	90	390	990	37,800
38E2175CA731794	7	83	920	843	37,050
38F2170C674149F	6	180	720	390	35,100
38F2276CA731A91	4	120	555	630	35,100

Member ID Encrypted	Drug Label Name	Count of Claims	Days Supply	Total Quantity
78A2875CF741394		7	193	1,160
	MORPHINE SULFATE ER	3	90	540
	OXYCODONE HYDROCHLORIDE	4	103	620
78A2875CF741397		6	176	968
	MORPHINE SULFATE ER	3	88	264
	OXYCODONE HYDROCHLORIDE	3	88	704
68D2975CF741397		6	180	630
	MORPHINE SULFATE ER	3	90	270
	OXYCODONE HYDROCHLORIDE	3	90	360
38C2470C77D1191		3	90	390
	FENTANYL	1	30	30
	OXYCODONE HYDROCHLORIDE	2	60	360
38E2175CA731794		7	83	920
	OXYCODONE HYDROCHLORIDE	7	83	920
38E297CC6761590		6	170	720
	MORPHINE SULFATE ER	3	84	360
	OXYCODONE HYDROCHLORIDE	3	86	360
38F2170C674149F		6	180	720
	MORPHINE SULFATE	3	90	180
	MORPHINE SULFATE ER	3	90	540
38F2276CA731A91		4	120	555
	FENTANYL	1	30	15
	OXYCODONE HYDROCHLORIDE	3	90	540
38F2477CF7C1090		6	180	1,260
	HYDROCODONE BITARTRATE/ACETAMINOPHEN	3	90	270
	OXYCODONE HYDROCHLORIDE	3	90	990
38F2770CD7C1B94		8	240	1,440
	MORPHINE SULFATE ER	4	120	480
	OXYCODONE HYDROCHLORIDE	4	120	960

Nevada Medicaid

Fee for Service - Opioid Trends - Top Ten Prescribers

By Morphine Equivalent Dose (MED)

Quarter filled	Prescriber ID	City	State	Specialty	Count of Members	Count of Claims	Total Days Supply	Total Qty	Total MED	MED/DS	MED/DS/ Member
2021 Q2	Pres 4	LAS VEGAS	NV	- Hospitalist	183	399	11,117	36,382	875,507	78.75	0.43
2021 Q2	Pres 13	LAS VEGAS	NV	-	157	346	9,630	32,714	577,715	59.99	0.38
2021 Q2	Pres 10	LAS VEGAS	NV	- Physician Assistant	120	266	7,578	25,834	534,835	70.58	0.59
2021 Q2	Pres 34	LAS VEGAS	NV	-	159	342	9,717	34,423	521,985	53.72	0.34
2021 Q2	Pres 31	SPARKS	NV	- Anesthesiology	84	210	6,083	19,713	511,833	84.14	1.00
2021 Q2	Pres 18	SPARKS	NV	Allopathic & Osteopathic Physic	106	273	7,891	31,197	479,133	60.72	0.57
2021 Q2	Pres 23	LAS VEGAS	NV	- Physical Medicine & Rehabilit	115	250	7,306	22,837	472,132	64.62	0.56
2021 Q2	Pres 14	LAS VEGAS	NV	-	158	310	8,023	27,383	416,380	51.90	0.33
2021 Q2	Pres 20	LAS VEGAS	NV	-	135	288	8,356	28,032	374,603	44.83	0.33
2021 Q2	Pres 39	LAS VEGAS	NV	-	89	159	4,731	17,149	373,868	79.03	0.89
2021 Q3	Pres 4	LAS VEGAS	NV	- Hospitalist	170	321	9,008	28,848	718,938	79.81	0.47
2021 Q3	Pres 10	LAS VEGAS	NV	Physician Assistants & Advanced	142	324	9,231	31,835	614,700	66.59	0.47
2021 Q3	Pres 13	LAS VEGAS	NV	-	158	350	9,716	34,144	601,250	61.88	0.39
2021 Q3	Pres 20	LAS VEGAS	NV	-	161	376	10,918	36,716	492,415	45.10	0.28
2021 Q3	Pres 18	SPARKS	NV	Allopathic & Osteopathic Physicians -	126	272	7,912	31,412	464,850	58.75	0.47
2021 Q3	Pres 31	RENO	NV	Allopathic & Osteopathic Physicians -	81	189	5,546	17,694	431,321	77.77	0.96
2021 Q3	Pres 34	LAS VEGAS	NV	-	126	259	7,170	25,995	401,280	55.97	0.44
2021 Q3	Pres 41	LAS VEGAS	NV	Physician Assistants & Advanced	117	201	5,974	25,100	371,993	62.27	0.53
2021 Q3	Pres 16	LAS VEGAS	NV	-	102	210	6,258	21,500	354,703	56.68	0.56
2021 Q3	Pres 45	LAS VEGAS	NV	- Specialist	49	131	3,841	15,183	332,130	86.47	1.76

By Morphine Equivalent Dose (MED) Per Day Supply Per Member

Quarter filled	Prescriber ID	City	State	Specialty	Count of Members	Count of Claims	Total Days Supply	Total Qty	Total MED	MED/DS	MED/DS/ Member
2021 Q2	Pres 3	LAS VEGAS	NV	-	1	3	90	360	16,200	180.00	180.00
2021 Q2	Pres 17	SALT LAKE CITY	UT	- Student in an Organized Healt	1	1	30	10	5,400	180.00	180.00
2021 Q2	Pres 6	LAS VEGAS	NV	-	1	1	30	120	5,400	180.00	180.00
2021 Q2	Pres 8	LAS VEGAS	NV	- Internal Medicine	1	1	30	90	4,050	135.00	135.00
2021 Q2	Pres 12	LAS VEGAS	NV	- Specialist	2	4	97	577	25,703	264.97	132.49
2021 Q2	Pres 29	PAHRUMP	NV	- Internal Medicine	1	3	90	360	10,800	120.00	120.00
2021 Q2	Pres 15	LAS VEGAS	NV	-	1	1	30	160	3,600	120.00	120.00
2021 Q2	Pres 2	LAS VEGAS	NV	Allopathic & Osteopathic Physic	1	1	30	240	3,600	120.00	120.00
2021 Q2	Pres 23	RENO	NV	- Specialist	1	1	30	60	3,600	120.00	120.00
2021 Q2	Pres 5	RENO	NV	- Physician Assistant	1	1	5	40	600	120.00	120.00
2021 Q3	Pres 1	ELKO	NV	- Pediatrics	1	5	72	25	18,000	250.00	250.00
2021 Q3	Pres 9	LAS VEGAS	NV	-	2	3	45	250	18,000	400.00	200.00
2021 Q3	Pres 30	SPARKS	NV	- Family Medicine	1	1	30	60	6,000	200.00	200.00
2021 Q3	Pres 21	LAS VEGAS	NV	- Family Medicine	1	4	105	420	18,900	180.00	180.00
2021 Q3	Pres 37	WEST JORDAN	UT	- Internal Medicine	1	3	90	30	16,200	180.00	180.00
2021 Q3	Pres 28	LAS VEGAS	NV	- Internal Medicine	1	3	60	360	10,800	180.00	180.00
2021 Q3	Pres 2	LAS VEGAS	NV	- Internal Medicine	1	1	29	114	5,130	176.90	176.90
2021 Q3	Pres 15	LAS VEGAS	NV	-	1	1	30	90	4,050	135.00	135.00
2021 Q3	Pres 7	HOUSTON	TX	- Internal Medicine	1	1	30	180	4,050	135.00	135.00
2021 Q3	Pres 22	DAYTON	OH	- Internal Medicine	1	1	7	42	945	135.00	135.00

Standard DUR Reports

Nevada Medicaid

Top Ten Therapeutic Classes Fee for Service

April 1, 2021 - September 30, 2021

Top 10 Classes by Claim Count

2021 Q3

Drug Class Name	Count of Claims	Amt Paid
ANTICONVULSANTS - MISC.	26,812	$2,953,866.87
SYMPATHOMIMETICS	19,755	$3,141,806.54
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)	16,604	$212,635.23
OPIOID COMBINATIONS	14,019	$433,201.22
NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)	12,442	$265,428.79
CENTRAL MUSCLE RELAXANTS	12,408	$202,372.98
VIRAL VACCINES	11,899	$500,009.45
HMG COA REDUCTASE INHIBITORS	11,630	$163,822.89
ANTIANXIETY AGENTS - MISC.	10,244	$150,428.02
DIBENZAPINES	10,139	$342,501.06

2021 Q2

Drug Class Name	Count of Claims	Amt Paid
ANTICONVULSANTS - MISC.	27,153	$2,886,723.32
SYMPATHOMIMETICS	17,900	$2,947,120.94
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)	16,800	$212,631.41
OPIOID COMBINATIONS	14,339	$446,662.76
VIRAL VACCINES	13,191	$554,314.45
CENTRAL MUSCLE RELAXANTS	12,617	$205,247.38
NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)	12,336	$300,688.89
HMG COA REDUCTASE INHIBITORS	11,577	$160,301.86
DIBENZAPINES	10,128	$345,659.92
ANTIANXIETY AGENTS - MISC.	9,913	$148,482.21

Top 10 Classes by Amount Paid

2021 Q3

Drug Class Name	Count of Claims	Amt Paid
ANTIHEMOPHILIC PRODUCTS	133	$14,856,720.46
ANTIRETROVIRALS	1,774	$4,149,649.60
INSULIN	15	$3,306,133.29
SYMPATHOMIMETICS	4,813	$3,254,544.57
ANTIPSYCHOTICS - MISC.	3,177	$2,926,168.01
ANTICONVULSANTS - MISC.	27,010	$2,782,581.05
BENZISOXAZOLES	17,148	$2,776,809.02
ANTI-TNF-ALPHA - MONOCLONAL ANTIBODIES	5,843	$2,657,143.75
INCRETIN MIMETIC AGENTS (GLP-1 RECEPTOR AGONISTS)	288	$2,112,511.84
CYSTIC FIBROSIS AGENTS	175	$2,032,524.70

2021 Q2

Drug Class Name	Count of Claims	Amt Paid
ANTIHEMOPHILIC PRODUCTS	128	$12,297,696.07
ANTIRETROVIRALS	1,763	$4,079,643.17
INSULIN	4,812	$3,183,755.09
ANTIPSYCHOTICS - MISC.	3,199	$3,023,300.35
SYMPATHOMIMETICS	17,900	$2,947,120.94
ANTICONVULSANTS - MISC.	27,153	$2,886,723.32
BENZISOXAZOLES	5,852	$2,613,456.74
ANTI-TNF-ALPHA - MONOCLONAL ANTIBODIES	349	$2,583,810.52
INCRETIN MIMETIC AGENTS (GLP-1 RECEPTOR AGONISTS)	1,364	$2,068,333.57
CYSTIC FIBROSIS AGENTS	213	$1,907,945.75

cDUR Quarterly Report

Client(s): 'NVM'
Carrier ID: NVM
Account(s): All
Group(s): All
Primary Start Date: April 1, 2021
Primary End Date: June 30, 2021

Claims Summary:

Claim Status	Total Rxs	Total Interventions	% Total Rxs with Interventions
Paid	643,875	145,800	22.6%
Rejected	563,870	177,628	31.5%
Reversed	108,710	33,848	31.1%
Total	***1,316,455***	***357,276***	***27.1%***

cDUR Savings Outcomes Analysis Summary:

Current		Accruing		Total		Total Year to Date	
Successes	Savings	Successes	Savings	Successes	Savings	Successes	Savings
46,855	**$5,276,162**	**24,906**	**$9,984,396**	**71,761**	**$15,260,558**	**119,955**	**$30,445,208**

© 2021 OptumRx.
Produced by, and proprietary to, OptumRx's Clinical Analytics. This confidential information may not be distributed to or disseminated to any third party without the expressed written prior consent of OptumRx.

cDUR Detailed Activity Summary:

Intervention Type	Total	Paid Rxs		Rejected Rxs		Reversed Rxs	
	Interventions	Interventions	% Total Interventions	Interventions	% Total Interventions	Interventions	% Total Interventions
Dosing/Duration (DOSECHEK)	44,217	35,179	79.6%	1,004	2.3%	8,034	18.2%
Drug-Drug Interaction (DDI-DTMS)	117,995	53,762	45.6%	56,617	48.0%	7,616	6.5%
Duplicate Therapy (DUPTHER)	105,216	46,977	44.6%	49,283	46.8%	8,956	8.5%
Drug Safety Screening (CDSAFETY)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Multiple Drug Screening (OVERLAP)	26	12	46.2%	N/A	N/A	14	53.8%
Duplicate Rx (DUPRX)	89,335	9,862	11.0%	70,249	78.6%	9,224	10.3%
Drug Inferred Health State (DINFERRD)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Drug Sex Caution (DRUG_SEX)	2	1	50.0%	N/A	N/A	1	50.0%
Drug/Diagnosis Caution (DIAGCAUT)	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Drug Age Caution (DRUG_AGE)	10	7	70.0%	N/A	N/A	3	30.0%
Refill Too Soon	475	N/A	N/A	475	100.0%	N/A	N/A
Morphine Equivalent Dose Limit Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Therapeutic Dose Limits Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Allergy Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Acute/Maintenance Dose Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total All cDURs	***357,276***	***145,800***	***40.8%***	***177,628***	***49.7%***	***33,848***	***9.5%***

© 2021 OptumRx. ** The Count and % of cDUR Type for Paid, Rejected and Reversed Rxs are based on cDUR Type totals for each row*
Produced by, and proprietary to, OptumRx's Clinical Analytics. This confidential information may not be distributed to or disseminated to any third party without the expressed written prior consent of OptumRx.

cDUR Detailed Saving Outcomes Summary:

Intervention Type	Current		Accruing		Total		Total Year to Date	
	Successes	Savings	Successes	Savings	Successes	Savings	Successes	Savings
Dosing/Duration (DOSECHEK)	1,250	$958,966	1,867	$2,907,149	3,117	$3,866,115	4,525	$8,944,794
Drug-Drug Interaction (DDI-DTMS)	4,049	$358,403	3,891	$802,331	7,940	$1,160,734	11,318	$2,389,809
Duplicate Therapy (DUPTHER)	5,044	$1,027,667	9,543	$3,066,211	14,587	$4,093,878	19,549	$8,019,138
Drug Safety Screening (CDSAFETY)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Multiple Drug Screening (OVERLAP)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Duplicate Rx (DUPRX)	36,120	$2,902,359	9,499	$3,204,992	45,619	$6,107,352	83,691	$11,011,460
Drug Inferred Health State (DINFERRD)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Drug Sex Caution (DRUG_SEX)	1	$23	45	$846	46	$869	47	$2,234
Drug/Diagnosis Caution (DIAGCAUT)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Drug Age Caution (DRUG_AGE)	2	$40	N/A	N/A	2	$40	4	$188
Refill Too Soon	389	$28,704	61	$2,866	450	$31,571	821	$77,585
Morphine Equivalent Dose Limit Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Therapeutic Dose Limits Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Allergy Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Acute/Maintenance Dose Screening	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Total All cDURs	***46,855***	***$5,276,162***	***24,906***	***$9,984,396***	***71,761***	***$15,260,558***	***119,955***	***$30,445,208***

© 2021 OptumRx. ** The Count and % of cDUR Type for Paid, Rejected and Reversed Rxs are based on cDUR Type totals for each row*
Produced by, and proprietary to, OptumRx's Clinical Analytics. This confidential information may not be distributed to or disseminated to any third party without the expressed written prior consent of OptumRx.

Claims Summary:

Column Name	Description
Claim Status	The claims status associated with the RxCLAIM transaction: Paid, Reversed, Rejected •Paid Claims with CDUR edit(s) are those which had an override by a pharmacist •Rejected claims with CDUR edit(s) include both hard and soft rejects •Reversed claims with CDUR edit(s) include Paid claims which were reversed, originating with a message and an override by a pharmacist
Total Rxs	The total number of pharmacy claims with or without a cDUR edit
Total Interventions	The total number of pharmacy claims with at least one cDUR edit
% Total Rxs w/ Interventions	Percentage of all pharmacy claims which had a cDUR edit

cDUR Savings Outcomes Summary:

Column Name	Description
Current	Savings from CDUR interventions which occurred in the current period
Accruing	Savings from CDUR interventions which succeeded prior to the current reporting period, where savings continue to accrue in the current reporting period
Total	Total CDUR savings recognized in the current period (Current + Accruing)
Year To Date	Total CDUR savings recognized since the start of the current year
Successes	cDUR Interventions which resulted in Pharmacy Savings in the Current Period

Edit Type	Short Description	Long Description
ACTMAINT	Acute/Maintenance Dose Screening	Member is taking a medication at a higher dose than recommended based on acute daily use versus maintenance daily use.
ALLERCHK	Drug-Allergy Interaction Screening	Member is taking a medication to which he/she may be allergic.
DDI-DTMS	Drug-Drug Interaction Screening	Member is taking 2 interacting medications and/or medication classes.
DIAGCAUT	Drug-Disease screening using actual member disease profile	Member has a certain diagnosis (as determined by member disease profile) and is taking a medication that worsens the diagnosis.
DINFERRD	Drug-Disease screening using medication history as proxy for determining existing disease states	Member has a certain diagnosis (as determined by drug proxy) and is taking a medication that may worsen the member diagnosis.
DOSECHEK	Identifies if incoming claim exceeds recommended daily dose and/or recommended duration	Member is taking a medication for longer and/or at a higher dose than recommended.
DRUG_AGE	Drug-Age contraindication screening	Member is taking a medication that is not recommended for people of certain ages (pediatric and geriatric).
DRUG_SEX	Drug-sex contraindication screening	Member is taking a medication that is not recommended for his/her gender.
DUPRX	Exact GPI duplication screening	Member is taking 2 medications with the same ingredient.
DUPTHER	Drug class duplication screening	Member is taking 2 medications in the same drug class.
MEDLIMIT	Morphine Equivalent Dose Limit Screening	Member is taking opioids where the total cumulative daily dose exceeds the suggested morphine equivalent dose (MED).
REFILL	Refill Too Soon	Member tried refilling with medicagtion still left of hand from prior fill
THERDOSE	Therapeutic Dose Limits Screening	Member is taking medications where the total cumulative daily dose exceeds the FDA approved maximum dose for the medication.

© 2021 OptumRx.
Produced by, and proprietary to, OptumRx's Clinical Analytics. This confidential information may not be distributed to or disseminated to any third party without the expressed written prior consent of OptumRx.

Nevada Medicaid

RetroDUR

Fee for Service

Second Quarter 2021 and Third Quarter 2021

Q2 2021

Initiative	Sent	Responses	Prescribers	Recipients	Response Rate
Gabapentin Utilization	94	12	85	94	12.77%

Q3 2021

Initiative	Sent	Responses	Prescribers	Recipients	Response Rate
Opioid, Antiphsychotic and Benzodiazepine Utlization	235	11	126	235	4.68%