Nevada Medicaid Drug Use Review Board Meeting

October 26, 2021

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Steve Sisolak
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Director

DEPARTMENT OF HEALTH AND HUMAN SERVICES
DIVISION OF HEALTH CARE FINANCING AND POLICY
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Suzanne Bierman, JD MPH
Administrator

NOTICE OF PUBLIC MEETING – DRUG USE REVIEW BOARD

Date of Publication: ~~August 25, 2021~~
First Amended: October 20, 2021

Date and Time of Meeting: October 26, 2021 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

OR

https://tinyurl.com/OCT2021DUR

Audio Only: (952) 222-7450
Event Number: 576 588 668#

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 e-mail 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 July 22, 2021.
b. Status Update by DHCFP.

~~. Informational Update from DHCFP Counsel: Board Requested information related to possible actions available to the Board relating to Opioid utilization reports.~~

~~6.~~4. **Clinical Presentations**

a. **For Possible Action:** Discussion and possible adoption of updated prior authorization criteria and/or quantity limits for sacubitril/valsartan (Entresto®).

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 Immunomodulator Drugs.

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 Growth Hormones.

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 Gastrointestinal Prokinetic 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.

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

f. **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.

~~7.~~5. DUR Board Requested Reports

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

i. Informational Update from DHCFP Counsel: Board Requested information related to possible actions available to the Board relating to Opioid utilization reports.
~~i.~~ii. Presentation of opioid criteria

~~ii.~~iii. Discussion by the Board and review of utilization data.

~~iii.~~iv. Requests for further evaluation or proposed clinical criteria to be presented at a later date.

~~8.~~6. Standard DUR Reports

a. Review of Prescribing/Program Trends.

i. Top 10 Therapeutic Classes for Q1 2021 and Q2 2022 (by Payment and by Claims).

b. Concurrent Drug Utilization Review (ProDUR).

i. Review of Q2 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.

~~9.~~7. 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 ~~http://dhcfp.nv.gov/ and~~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 e-mail.

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

Summary of 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

Netochi Adeolokun, Pharm.D., Vice Chair

Mark Canty, MD

Crystal Castaneda, MD

Jessica Cate, Pharm.D.

Dave England, Pharm.D.

Brian Le, DO

Michael Owens, MD

Rebecca Sparks, PA-C

Jim Tran, Pharm.D.

Drug Use Review (DUR) Board Meeting Schedule for 2021

Date	Time	Location
October 26, 2021	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

Draft Meeting Minutes

Date of Meeting: Thursday, July 22, 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	Chairwoman Wheeler called the meeting to order at 1:13 p.m. on July 22, 2021. Chairwoman Wheeler took the roll.			**The DHCFP Staff Present were as follows:** Woodrum, Homa, Senior Deputy Attorney General Gudino, Antonio, Social Services Program Specialist III Flowers, Ellen, Program Officer I Olsen, David, Chief, Pharmacy Services Capurro, Antonina, Deputy Administrator
		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.	☒	☐	
	Mohammad Khan, MD	☐	☒	
	Brian Le, DO	☒	☐	

Agenda Item	Record			Notes
	Michael Owens, MD	☒	☐	**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. Lee, Cara, Pharm.D. Whittington, Kevin, RPh **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.
	Jim Tran, Pharm.D.	☒	☐	
	A quorum was present.			

Agenda Item	Record	Notes
2. General Public Comment	It was announced the meeting is being recorded. Senior Deputy Attorney General Woodrum discussed changes to the Open Meeting Law. Telephonic and web comment was called for, and the phone lines were opened. No written comment was received. No public comment was offered.	
3. Administrative		
a. **For Possible Action**: Review and Approve Meeting Minutes from April 22, 2021	No corrections were offered. Board Member Canty moved to approve the minutes as presented, and Board Member Adeolokun seconded the motion. A vote was taken, and 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. ☐ Dave England, Pharm.D.: Yes ☒ No ☐ Abst. ☐ Brian Le, DO: Yes ☒ No ☐ Abst. ☐ Michael Owens, MD: Yes ☒ No ☐ Abst. ☐ Jim Tran, Pharm.D.: Yes ☒ No ☐ Abst. ☐	
b. Status Update by DHCFP	Chief Olsen announced Antonina Capurro as the DHCFP Deputy Administrator. Chief Olsen discussed Senate Bill 190 and Senate	

Agenda Item	Record	Notes
	Bill 325, highlighting the allowance of pharmacists to prescribe and dispense medications for self-administered birth control and HIV prevention. Passage of Senate Bill 380 allowed for increased drug price transparency. Chief Olsen reported the transition process began to the new pharmacy benefit manager. Chief Olsen expressed appreciation to Dr. Carl Jeffry for his service to the State of Nevada.	
4. Clinical Presentations		
a. **For Possible Action**: Discussion and possible adoption of prior authorization criteria and/or quantity limits for Antimigraine Medications-Miscellaneous.		
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 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 low utilization. Dr. Bitton was unable to present due to technical issues. Dr. LeCheminant noted Health Plan of Nevada agreed with the proposed criteria and highlighted low utilization. Mr. Beranek agreed with the proposed criteria and highlighted low utilization.	

Agenda Item	Record	Notes
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 Le moved to approve the proposed criteria as presented, and 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 ☒ ☐ ☐ Dave England, Pharm.D. ☒ ☐ ☐ Brian Le, DO ☒ ☐ ☐ Michael Owens, MD ☒ ☐ ☐ Jim Tran, Pharm.D. ☒ ☐ ☐	
b. **For Possible Action**: Discussion and possible adoption of prior authorization criteria and/or quantity limits for Duchene Muscular Dystrophy Agents.		
i. Public comment on proposed clinical prior authorization criteria.	Telephonic and web comment was called for, and the phone lines were opened. Comment was made from Tracy Copeland of Sarepta Therapeutics that she is available to answer questions regarding Amondys 45 when it is reviewed. Senior Deputy Attorney General Woodrum encouraged comments and asked when Amondys 45 will be reviewed.	

Agenda Item	Record	Notes
	Dr. LeCheminant stated Amondys 45 will be reviewed in the January 2022 DUR meeting. Tracy Copeland noted she is available to answer questions. Comment was made from Anna Parievsky of MS Pharma, providing information on Viltepso. Dr. Parievsky reviewed package insert information. Trials demonstrating safety and efficacy were presented. Dr. Parievsky requested Viltepso be added to the PDL.	
ii. Presentation of utilization and clinical information.	Dr. LeCheminant presented information regarding Viltepso including the indication, administration, and clinical trials demonstrating efficacy. Dr. LeCheminant reviewed the proposed criteria presented in the binder. Chairwoman Wheeler announced Board member Castaneda joined the meeting and is available for voting. Dr. LeCheminant reviewed the utilization of this class and reported no utilization for Viltepso. Dr. Lim proposed a policy update to require concurrent use with a corticosteroid and reported no Viltepso utilization. Dr. Bitton proposed a policy update prohibiting concurrent use with other exon-skipping therapies and reported no Viltepso utilization. Mr. Beranek proposed a policy update to require an inadequate response to an oral corticosteroid and concurrent use with an oral corticosteroid. Mr. Beranek reported no Viltepso utilization.	
iii. Discussion by Board and review of utilization data.	Chairwoman Wheeler asked for comments from the Board Members.	

Agenda Item	Record	Notes
	Board Member Adeolokun requested clarification if the ambulatory and age requirements were removed from the criteria for Vyondys 53 at a previous DUR meeting. Dr. LeCheminant confirmed the removal of those requirements from the proposed Vyondys 53 criteria at the January 2021 DUR meeting. Chairwoman Wheeler stated the package insert was reviewed and did not include an age requirement. Board Member Castaneda discussed the benefit of this class of medications in patients under the age of four and regardless of ambulatory status.	
iv. Proposed adoption of updated prior authorization criteria.	Chairwoman Wheeler suggested removing the age requirement from the proposed criteria and removing the documentation requirement that the patient is ambulatory via the six-minute walk test from the initial authorization and reauthorization criteria. Board Member Adeolokun agreed and moved to accept the modified criteria. 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. ☐	

Agenda Item	Record	Notes
	Crystal Castaneda, MD ☒ ☐ ☐ Dave England, Pharm.D. ☒ ☐ ☐ Brian Le, DO ☒ ☐ ☐ Michael Owens, MD ☒ ☐ ☐ Jim Tran, Pharm.D. ☒ ☐ ☐	
5. DUR Board Requested Reports		
a. **For Possible Action**: Opioid utilization – top prescriber and members.		
i. Discussion by the Board and review of utilization data.	Chairwoman Wheeler asked for feedback from the Board to make the reports more efficient by possibly removing or restructuring the information. Reports could be moved to Appendices' to limit the discussion of the report to significant updates. Dr. LeCheminant presented the opioid utilization identifying total morphine equivalent dose (MED). Dr. LeCheminant highlighted the top ten members by morphine equivalent dose report and the top ten prescribers. The Board Members discussed the report highlighting useful information. Board Member Le expressed concern for opioid use seen with the top ten members and questioned what action can be taken. Board Member Le questioned if members are being monitored. Board Member England stated in the past, letters have been sent to the prescribers who were prescribing high amounts of opioids. Chief Olsen informed the Board, the internet connection for the on-site location was down for the past two minutes. Dr. Wheeler summarized what was discussed during that timeframe.	

Agenda Item	Record	Notes
	Chief Olsen stated Nevada Medicaid has a surveillance team and referrals to Pharmacy Services are passed on to the surveillance team. Chairwoman Wheeler recommends the report include the top ten members instead of the top 25 members. Board Member Castaneda agreed with the concern of the high utilization and commented on notification to the Nevada Board of Medicine as a possible action item. Board Member Canty stated advice from Council is needed for clarification on the authority of the committee. Board Member Canty is interested in reviewing opioid and diazepine claims. Senior Deputy Attorney General Woodrum stated that further information and options for a course of action can be requested from Nevada Medicaid and presented at the next meeting. The Board and Council discussed options for the motion. Chairwoman Wheeler requested guidelines on mechanisms of how to report action items identified in the opioid trend reports, specifically to act. Board Member England moved to accept the request. Clarification was made that the requested information would be assigned to HHS. Board Member England moved to update the motion to include the request for guidelines that would be assigned to the	

Agenda Item	Record	Notes
	Department of Health and Human Services. Board Member Canty seconded. A vote was held: Yes No Abst. Jennifer Wheeler, Pharm.D., Chair ☒ ☐ ☐ Netochi Adeolokun, Pharm.D., Vice Chair ☒ ☐ ☐ Mark Canty, MD ☒ ☐ ☐ Crystal Castaneda, MD ☒ ☐ ☐ Dave England, Pharm.D. ☒ ☐ ☐ Brian Le, DO ☒ ☐ ☐ Michael Owens, MD ☒ ☐ ☐ Jim Tran, Pharm.D. ☒ ☐ ☐ Chairwoman Wheeler suggested prior authorization information be provided at a future meeting and clarification on how the high amount of opioid use is approved. Chairwoman Wheeler asked when the criteria were last reviewed by the board. Dr. LeCheminant states the prior authorization information can be provided as well as member diagnosis. Dr. LeCheminant will investigate the last review of the criteria and what changes occurred. Chairwoman Wheeler motioned to review the criteria for utilization of opioids on a future agenda. Board Member Canty seconded. A vote was held: Yes No Abst.	

Agenda Item	Record	Notes
	Jennifer Wheeler, Pharm.D., Chair ☒ ☐ ☐ Netochi Adeolokun, Pharm.D., Vice Chair ☒ ☐ ☐ Mark Canty, MD ☒ ☐ ☐ Crystal Castaneda, MD ☒ ☐ ☐ Dave England, Pharm.D. ☒ ☐ ☐ Brian Le, DO ☒ ☐ ☐ Michael Owens, MD ☒ ☐ ☐ Jim Tran, Pharm.D. ☒ ☐ ☐ Dr. Lim presented the opioid utilization identifying a steady MED level over time. Dr. Lim discussed the top providers and top utilizers and highlighted the low movement of the top ten prescribers. Dr. Bitton presented the opioid utilization trends. Dr. Bitton discussed the top prescribers noting a change in two of the top ten prescribers. Antonio Gudino reminded the Board members to leave their cameras on to remain visible to members of the public. Mr. Beranek presented the opioid utilization and the top opioid prescribers highlighting a change of one of the top ten prescribers. Mr. Beranek discussed the top members noting the diagnosis of cancer for four members, sickle cell anemia for one member, chronic pain for three members, an injured wrist for one member, and a degenerated disc issue for one member.	
ii. Requests for further evaluation of proposed clinical criteria to be presented at a later date.	The board made no requests.	
6. Standard DUR Reports		

Agenda Item	Record	Notes
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 hemostatics on the top by spend amount and anticonvulsants in the top by claim count. Dr. Lim presented the top classes and identified hepatitis C agents that replaced tyrosine kinase inhibitors in 1Q2021. Dr. Bitton presented the top classes and identified the consistent amounts in the two quarters. Mr. Beranek presented the top drug classes and identified the consistency over the two quarters.	
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).		
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 yrs. without an Asthma diagnosis.	

Agenda Item	Record	Notes
	Dr. Lim highlighted the retrospective DUR programs including asthma and behavioral health programs and their respective outcomes. Controlled substance utilization management was discussed. Dr. Bitton was unable to present RetroDUR due to technical issues. Dr. LeCheminant informed the Board the RetroDUR report from the Health Plan of Nevada is available in the binder. Mr. Beranek discussed the retrospective DUR program highlighting the medication adherence program.	
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 October 14, 2021, and the location is yet to be determined.	
c. Adjournment.	The meeting adjourned at 2:56 p.m.	

Attachment A – Member of the Public in Attendance

Balen, Valerie
Booth, Robert
Cochrane, Tim M
Colabianchi, Jerry
Cooper, Emily
Copeland, Tracy
Daly, Austin
Donahue, Cheryl
Ferroli, Joseph
Germain, Joe Jr.
Hertzberg, Susan
Hill, Laura L
Large, David
Mackenzie, Kristin
Maynard, Kelly
Morgan, Suzanne
Nelson, Ann
Parievsky, Anna
Robinson, Lovell R
Stoots, Mary
Zarob, Michael

Attendees with no last name available:
Georgette
Dr. G (Guest)

Clinical Presentations

Prior Authorization Guideline

Guideline Name Entresto (sacubitiril/valsartan)

1 . Criteria

Product Name: Entresto*	
Approval Length	12 Months
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of chronic heart failure

AND

2 - Patient is 18 years of age or older

AND

3 - One of the following:

- Requested medication is prescribed by a cardiologist
- There is documentation in the patient's medical record of a cardiologist consult

AND

4 - Patient will not be treated concurrently with an ACE inhibitor

AND

5 - One of the following:

- Patient is currently receiving an individualized dose of a beta blocker
- Patient has a contraindication to beta blocker use

AND

8 - The requested dose is one tablet twice daily

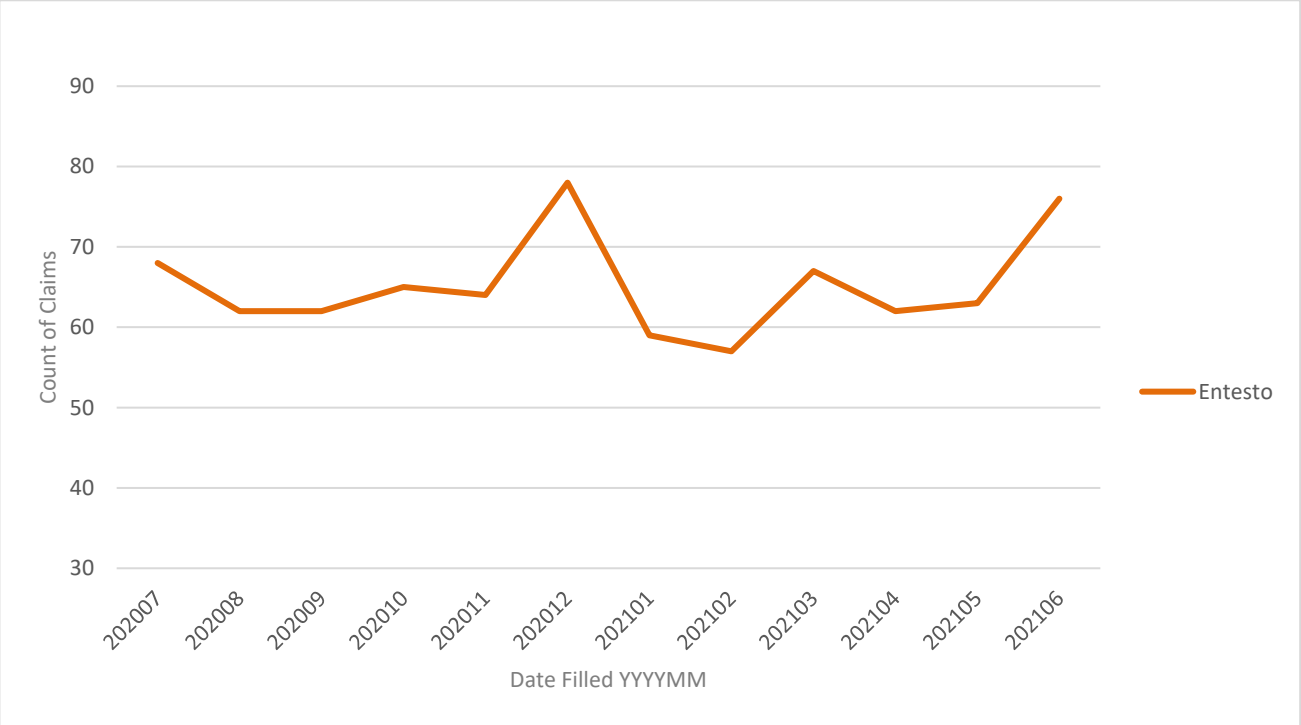
AND

10 - The requested dose does not exceed 97 mg/103 mg twice daily of Entresto

Nevada Medicaid

Top Ten Therapeutic Classes
Fee for Service
July 1, 2020 - June 30, 2021

Drug Name	Members	Claims	Total Days Supply	Total Quantity
ENTRESTO	147	783	23,296	46,071



JJJ. Entresto® (sacubitril/valsartan)

Therapeutic Class: Angiotension II Receptor Blocker
Last Reviewed by the DUR Board: January 24, 2019

Entresto® (sacubitril/valsartan) is subject to prior authorization based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

   Approval will be given if the following criteria are met and documented:

   a. The recipient has a diagnosis of chronic heart failure NYHA Class II to IV; and

   b. The recipient has reduced left ventricular ejection fraction (LVEF); and

   c. The recipient is 18 years of age or older; and

   d. The prescriber is a cardiologist or there is documentation in the recipient's medical record that a cardiologist has been consulted; and

   e. The recipient has had a trial of an angiotensin converting enzyme (ACE) or an angiotensin receptor blocker (ARB) for at least four weeks prior to the initiation of therapy; and

   f. The recipient will not concurrently receive an ACE inhibitor; and

   g. The recipient is on an individualized dose of a beta blocker or the recipient has a contraindication to beta blocker use; and

   h. Entresto® will be given twice daily with a maximum dose of 97/103 mg.

2. Prior Authorization Guidelines

   a. Prior authorization approval will be for one year.

   b. Prior Authorization forms are available at:
   http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

INTRODUCTION

- Approximately 126.9 million American adults are living with some form of cardiovascular (CV) disease (congestive heart disease, heart failure, stroke, and hypertension) according to the American Heart Association (AHA) Heart Disease and Stroke Statistics 2021 update *(Virani et al 2021)*. Cardiovascular disease accounts for an estimated 868,662 deaths in the US annually and is the leading cause of death globally.
- The estimated prevalence of heart failure (HF) is 6 million for Americans aged ≥ 20 years. Projections show that the prevalence of HF will increase 46% from 2012 to 2030, resulting in > 8 million people ≥ 18 years of age with HF (*Virani et al 2021*).
- Hypertension (HTN) is an independent risk factor for CV disease and increases the mortality risks of CV disease and other diseases *(Virani et al 2021)*. The 2017 American College of Cardiology (ACC)/AHA clinical practice guideline defines HTN as a blood pressure (BP) ≥ 130/80 mm Hg (*Whelton et al 2018)*. Nearly half of American adults (46%) have HTN based on this definition.
- Lowering of BP has been shown to reduce the risk of fatal and nonfatal CV events including stroke and myocardial infarctions (MIs). Lipid control, diabetes mellitus (DM) management, smoking cessation, exercise, weight management, and limiting sodium intake may also reduce CV risk *(Virani et al 2021)*.
- Numerous classes of antihypertensives are available to reduce BP. Some examples of antihypertensives include diuretics, angiotensin converting enzyme inhibitors (ACE-Is), angiotensin II receptor blockers (ARBs), beta-blockers, and calcium channel blockers (CCBs). Selection of antihypertensive therapy for a specific patient is determined by patient characteristics such as ethnic group, and the presence of compelling indications such as HF, DM, chronic kidney disease (CKD), history of stroke or MI, and risk factors for coronary heart disease (CHD). Some patients require 2 or more antihypertensives from different pharmacological classes to achieve BP control *(Go et al 2014, Unger et al 2020, Whelton et al 2018)*.
- In general, guideline-recommended BP goals in hypertensive adults range from < 130/80 mm Hg to < 140/90 mm Hg *(Arnett et al 2019, de Boer et al 2017, Whelton et al 2018)*.
  - Blood pressure goals for older patients have long been a point of debate. The SPRINT trial followed patients ≥ 50 years with high BP and increased CV risks under intense HTN treatment (with a systolic blood pressure [SBP] goal of < 120 mm Hg) compared to standard HTN treatment (with an SBP goal of < 140 mm Hg) over a period of 3.2 years. The trial ended early; however, results demonstrated a reduced primary composite outcome of MI, acute coronary syndrome (ACS), stroke, HF, or CV death driven mainly by reduced HF events and CV death with intense treatment compared to standard treatment. The SPRINT trial pointed to potential clinical benefits associated with more intensive treatment in certain patients, although early termination of the trial and variations in the BP-measurement technique employed have called into question the generalizability of the results *(SPRINT Research Group 2015)*.
  - A guideline from the American College of Physicians (ACP) and the American Academy of Family Physicians (AAFP) on treatment of HTN in adults aged ≥ 60 years recommends standard and intense SBP treatment goals of < 150 mm Hg and < 140 mm Hg, respectively, with more intense BP reduction reserved for patients with a history of stroke or transient ischemic attack *(Qaseem et al 2017)*.
- The cardinal symptoms of HF are dyspnea and fatigue. HF leads to exercise intolerance, fluid retention, pulmonary congestion, and peripheral edema, often resulting in hospitalization (*Yancy et al 2013*).
- There are 2 forms of HF:
  - Heart failure with reduced ejection fraction (HFrEF) or systolic HF: ejection fraction (EF) ≤ 40%
  - Heart failure with preserved ejection fraction (HFpEF) or diastolic HF: EF ≥ 50%
- HF guidelines recommend evidence-based maximally tolerated doses of ACE-Is/ARBs/ARNIs, and/or beta-blockers with diuretics, as needed, for first-line treatment in patients with HFrEF (NYHA Class I to IV; Stage C) (*Yancy et al 2013, Yancy et al 2016, Yancy et al 2017; Maddux et al 2021)*.
- Sacubitril/valsartan is administered in place of an ACE-I or other ARB; although, its role for the management of HF is not as well established as ACE-Is or other ARBs. Based on study data, there is minimal evidence of benefits and harms in

the following populations: very elderly patients, African Americans, NYHA Class I or IV, patients with low BP or co-morbid HTN refractory to treatment, and patients with HFpEF. Further studies are warranted in these groups.

- This review includes the ARBs, the ARB combination products, and the only approved ARNI (sacubitril/valsartan). ARBs work primarily through reduction of systemic vascular resistance as a result of selective antagonism of angiotensin II at the angiotensin II AT1 receptor. Angiotensin II is the primary vasoactive hormone.
  - The ARBs are Food and Drug Administration (FDA)-approved to treat HTN. Some ARBs have additional indications for HF, diabetic nephropathy, or CV risk reduction in certain high-risk populations.
  - The ARB combinations are products that combine an ARB with a diuretic (ie, chlorthalidone, hydrochlorothiazide [HCTZ]) and/or a CCB (ie, amlodipine) in a fixed-dose formulation. By combining agents from different classes, these combination products are meant to increase the effectiveness of antihypertensive therapy through complementary mechanisms of action while minimizing the potential for dose-related adverse effects. All ARB combination products are FDA-approved for the treatment of HTN. Losartan/HCTZ is also indicated to reduce the risk of stroke in patients with HTN and left ventricular (LV) hypertrophy.
  - Sacubitril/valsartan is indicated to reduce the risk of CV death and hospitalization for HF in adults with chronic HF and for the treatment of symptomatic HF with systemic left ventricular systolic dysfunction in pediatric patients 1 year of age and older.
- Medispan classes: Angiotensin II Receptor Antagonists; Antihypertensive Combinations - ARB/CCB combinations, ARB/thiazide and thiazide-like combinations, and ARB/CCB/thiazide combinations; Cardiovascular Agents, ARNI – Angiotensin II receptor antagonist/neprilysin inhibitor combination

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Single-Entity ARBs	
Atacand (candesartan)	✔
Avapro (irbesartan)	✔
Benicar (olmesartan)	✔
Cozaar (losartan)	✔
Diovan (valsartan)	✔
Edarbi (azilsartan)	-
Micardis (telmisartan)	✔
ARB/Diuretic Combinations	
Atacand HCT (candesartan/hydrochlorothiazide)	✔
Avalide (irbesartan/hydrochlorothiazide)	✔
Benicar HCT (olmesartan/hydrochlorothiazide)	✔
Diovan HCT (valsartan/hydrochlorothiazide)	✔
Edarbyclor (azilsartan/chlorthalidone)	-
Hyzaar (losartan/hydrochlorothiazide)	✔
Micardis HCT (telmisartan/hydrochlorothiazide)	✔
ARB/CCB Combinations	
Azor (olmesartan/amlodipine)	✔
Exforge (valsartan/amlodipine)	✔
Twynsta (telmisartan/amlodipine)	✔
ARB/CCB/Diuretic Combinations	
Exforge HCT (valsartan/amlodipine/hydrochlorothiazide)	✔
Tribenzor (olmesartan/amlodipine/hydrochlorothiazide)	✔
ARB/Neprilysin inhibitor Combination	
Entresto (sacubitril/valsartan)	-

Abbreviations: ARB = angiotensin II receptor blocker; CCB = calcium channel blocker

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

INDICATIONS

Table 2. FDA-approved indications for single-entity ARBs

Indication	Atacand (candesartan)	Avapro (irbesartan)	Benicar (olmesartan)	Cozaar (losartan)	Diovan (valsartan)	Edarbi (azilsartan)	Micardis (telmisartan)
Hypertension in adults	✔	✔	✔	✔	✔	✔	✔
Hypertension in children ages 1 to < 17 years	✔				✔		
Hypertension in children ages 6 to 16 years			✔	✔			
Treatment of diabetic nephropathy in hypertensive patients with type 2 DM, an elevated serum creatinine, and proteinuria		✔		✔			
Heart failure (NYHA Class II to IV) in adults	✔				✔		
Reduction in the risk of stroke in patients with hypertension and LV hypertrophy				✔			
Post-MI: Reduction of cardiovascular mortality in clinically stable patients with LV failure or LV dysfunction					✔		
Cardiovascular risk reduction in patients 55 years of age or older at high risk of developing major cardiovascular events who are unable to take ACE-Is							✔

Abbreviations: ACE-I = angiotensin converting enzyme inhibitor; LV = left ventricular; MI = myocardial infarction; NYHA = New York Heart Association

(Prescribing information: Atacand 2020, Avapro 2020, Benicar 2019, Cozaar 2020, Diovan 2021, Edarbi 2020, Micardis 2020)

Table 3. FDA-approved indications for combination products containing ARBs

Drug	Hypertension	Reduction in the Risk of CV Death and HF Hospitalization in Adults with Chronic HF	Reduction in the Risk of Stroke in Patients with Hypertension and Left Ventricular Hypertrophy	Symptomatic HF in pediatric patients ≥ 1 year
ARB/Diuretic Combinations				
Atacand HCT (candesartan/ hydrochlorothiazide)	✔ *	-	-	-
Avalide (irbesartan/ hydrochlorothiazide)	✔ †	-	-	-
Benicar HCT (olmesartan/ hydrochlorothiazide)	✔ *	-	-	-
Diovan HCT (valsartan/ hydrochlorothiazide)	✔ †	-	-	-
Edarbyclor (azilsartan/chlorthalidone)	✔ †	-	-	-

Drug	Hypertension	Reduction in the Risk of CV Death and HF Hospitalization in Adults with Chronic HF	Reduction in the Risk of Stroke in Patients with Hypertension and Left Ventricular Hypertrophy	Symptomatic HF in pediatric patients ≥ 1 year
Hyzaar (losartan/ hydrochlorothiazide)	✔ ‡	-	✔ §	-
Micardis HCT (telmisartan/ hydrochlorothiazide)	✔ *	-	-	-
ARB/CCB Combinations				
Azor (olmesartan/amlodipine)	✔ †	-	-	-
Exforge (valsartan/amlodipine)	✔ †	-	-	-
Twynsta (telmisartan/amlodipine)	✔ †	-	-	-
ARB/CCB/Diuretic Combinations				
Exforge HCT (valsartan/amlodipine/ hydrochlorothiazide)	✔ *	-	-	-
Tribenzor (olmesartan/amlodipine/ hydrochlorothiazide)	✔ *	-	-	-
ARB/Neprilysin inhibitor Combination				
Entresto (sacubitril/valsartan)	-	✔ ‖	-	✔

Abbreviations: ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; CV = cardiovascular; EF = ejection fraction; HF = heart failure

*This fixed-dose combination is not indicated for initial therapy.

†Indicated to treat HTN in patients not adequately controlled on monotherapy or as initial therapy in patients who are likely to need multiple drugs to achieve their BP goals.

‡The fixed-dose combination is not indicated for initial therapy, except when the HTN is severe enough that the value of achieving prompt BP control exceeds the risks of initiating combination therapy in these patients.

§There is evidence that this benefit does not extend to African American patients.

‖Benefits are most clearly evident in patients with LVEF below normal. LVEF is a variable measure, so use clinical judgment in deciding whom to treat.

(Prescribing information: Atacand HCT 2020, Avalide 2020, Azor 2020, Benicar HCT 2020, Diovan HCT 2020, Edarbyclor 2020, Entresto 2021, Exforge 2021, Exforge HCT 2021, Hyzaar 2020, Micardis HCT 2020, Tribenzor 2020, Twynsta 2018)

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

CLINICAL EFFICACY SUMMARY

Single-Entity ARBs

- ARBs have demonstrated efficacy for the treatment of HTN in adults. A Cochrane systematic review of 46 randomized, placebo-controlled trials evaluated the BP lowering ability of 9 different ARBs (N = 13,451) in patients with a baseline BP of 156/101 mm Hg. On average, SBP was lowered by 8 mm Hg and diastolic blood pressure (DBP) by 5 mm Hg with maximum recommended doses of ARBs. No clinically meaningful differences within the ARB class were observed in the reduction of BP *(Heran et al 2008).* A systematic review and network meta-analysis of 36 RCTs evaluated the comparative effectiveness of ARBs (vs another ARB, HCTZ, or placebo) in lowering BP and CV event rates (including MI, stroke, cardiovascular mortality, and all-cause mortality) in patients with hypertension. BP reduction and CV event

rates were found to be similar among all ARBs assessed, and the authors concluded that evidence is not sufficient to show differences in reduction of blood pressure or CV disease among members of the ARB drug class (*Tsoi et al 2018*).
  - Meta-analyses have shown that ACE-Is and ARBs have similar long-term effects on BP *(Sanders et al 2011, Savarese et al 2013).* Additionally, a Cochrane review involving 11,007 subjects with primary HTN found no evidence of a difference in total mortality or CV outcomes for ACE-Is in comparison to ARBs (*Li 2014*).
- Telmisartan is indicated to reduce CV risk in patients unable to take ACE-Is. The ONTARGET trial compared telmisartan and ramipril monotherapy and in combination with each other and demonstrated no significant difference between any groups in death from CV causes, MI, stroke, or hospitalization for HF *(ONTARGET Investigators 2008).* In the TRANSCEND trial, no significant difference was observed between telmisartan and placebo in death from CV causes, MI, stroke, or HF hospitalizations. The composite endpoint of death from CV causes, MI, and stroke occurred in significantly fewer patients in the telmisartan group, but this significance was lost after adjustment for multiplicity of comparisons and overlap with the primary outcome *(Foulquier et al 2014, TRANSCEND Investigators 2008)*.
- Losartan is indicated to reduce the risk of stroke in patients with HTN and LV hypertrophy. The efficacy of losartan was demonstrated in the LIFE trial and its corresponding sub-analyses. Losartan was compared to therapy with atenolol. Results demonstrated a 24.9% relative risk reduction for stroke in patients treated with losartan-based regimens compared to atenolol-based regimens *(Dahlöf et al 2002)*. However, a post-hoc analysis in African American patients showed an increase in the composite of CV death, MI, and stroke with losartan compared to atenolol *(Julius et al 2004)*.
- Candesartan and valsartan are indicated to treat HF. Trials demonstrated the efficacy of candesartan alone and in combination with ACE-I therapy compared to placebo in reducing the risk of all-cause mortality, CV death, and/or HF hospitalization *(McMurray et al 2003, Pfeffer et al 2003b, Yusuf et al 2003)*. When compared to enalapril in the RESOLVD trial, candesartan was not significantly better in improving 6-minute walking distance, NYHA functional class, or quality of life *(McKelvie et al 1999)*. Losartan was compared to captopril in patients with HF, and no significant difference was observed in renal function or all-cause mortality *(Pitt et al 1997, Pitt et al 2000)*. However, there was a significantly lower risk of sudden death and resuscitated cardiac arrest with losartan *(Pitt et al 2000)*. The Val-HeFT trial showed no significant difference in all-cause mortality between valsartan and placebo. However, the valsartan group demonstrated a significant improvement in NYHA functional class, HF hospitalizations, morbidity, and mortality *(Cohn et al 2001)*.
- Valsartan is indicated to reduce CV mortality in patients with post-MI LV failure or dysfunction. The VALIANT trial compared valsartan with captopril and combination therapy with valsartan plus captopril. No significant differences in all-cause mortality, CV death, reinfarction, or HF hospitalization were observed between monotherapy groups or combination therapy compared to captopril monotherapy *(Pfeffer et al 2003a)*. Losartan has also been evaluated in patients post-MI compared to and in combination with captopril. Results were similar to those of the VALIANT trial *(Dickstein et al 2002)*.
- Irbesartan and losartan are indicated for the treatment of diabetic nephropathy in patients with type 2 DM and HTN. However, clinical benefit in diabetic nephropathy has been shown with other ARBs, including candesartan, losartan, telmisartan, and valsartan *(Barnett et al 2004, Galle et al 2008, Hou et al 2007, Mogensen et al 2000, Viberti et al 2002)*.
- The ORIENT and ROADMAP studies followed patients with DM and compared the effects of olmesartan versus placebo. Outcomes demonstrated a higher rate of death from CV causes in both trials compared to placebo. This finding contradicts outcomes of other studies that include ARBs and/or olmesartan. A number of factors may have contributed to these outcomes including concomitant medications, patients with higher CV risks, and other potential confounders. Further studies in diabetic patients are needed to validate findings *(Haller et al 2011, Imai et al 2011)*.
- Studies have demonstrated that the combination of 2 inhibitors of the renin angiotensin-aldosterone system (RAAS), including an ACE-I with an ARB, provides no renal or CV benefits, with an increase in significant adverse events, particularly in patients with DM and/or renal insufficiency. Most notably, patients receiving combination therapy had increased rates of hyperkalemia, hypotension, and renal dysfunction. All agents in the class have safety warnings against combined use *(Fried et al 2013, ONTARGET Investigators 2008, Parving et al 2012, Pfeffer et al 2003a, Sakata et al 2015)*.

Combination Products Containing ARBs

- Clinical trials assessing the combination ARBs in the treatment of HTN have demonstrated that, in general, dual therapy combinations of ARBs plus a diuretic (either HCTZ or chlorthalidone) or amlodipine achieve greater reductions in BP and higher BP control rates compared to monotherapy regimens of ARBs, amlodipine, or diuretics *(Chrysant et al 2004, Chrysant et al 2008, Derosa et al 2014, Destro et al 2008, Flack et al 2009, Littlejohn et al 2009, Neutel et al 2006,*

Neutel et al 2008, Neutel et al 2012, Philipp et al 2007, Salerno et al 2004, Sharma et al 2007a, Sharma et al 2012, Zhu et al 2012). A meta-analysis by Conlin et al found that combination therapy with ARBs and HCTZ resulted in substantially greater reductions in SBP and DBP compared to ARB monotherapy *(Conlin et al 2000)*.

- Trials assessing triple therapy regimens with an ARB, amlodipine, and HCTZ demonstrate significantly greater BP reductions with triple therapy compared to combination and monotherapy *(Calhoun et al 2009a, Calhoun et al 2009b, Destro et al 2010, Ohma et al 2000, Wright et al 2011)*.
- Head-to-head trials have not consistently demonstrated superiority of one ARB combination product over another *(Bobrie et al 2005, Cushman et al 2012, Derosa et al 2014, Fogari et al 2006, Lacourcière et al 2003, Ohma et al 2000, Sharma et al 2007b, Toh et al 2016, White et al 2008, Wright et al 2011)*.
- The efficacy and safety of sacubitril/valsartan were evaluated in the PARADIGM-HF trial. (*McMurray et al 2014*). A total of 8,442 patients were randomized head-to-head to enalapril 10 mg twice daily or sacubitril/valsartan 97/103 mg twice daily.
- In the PARADIGM-HF trial, the following results were demonstrated after 2.25 years of treatment:
  - CV mortality: The absolute risk was 3.1% less for sacubitril/valsartan-treated patients than those treated with enalapril (risk reduction [RR], 20%; hazard ratio [HR], 0.8; 95% confidence interval [CI], 0.71 to 0.89; p < 0.001; number needed to treat [NNT], 32; 95% CI, 22 to 62).
  - HF hospitalization: The absolute risk was 2.8% less for sacubitril/valsartan-treated patients than those treated with enalapril (RR, 21%; HR, 0.79; 95% CI, 0.71 to 0.89; p < 0.001; NNT, 36; 95% CI, 21 to 77).
  - Combined measure of CV mortality or HF hospitalization (primary endpoint): The absolute risk was 4.7% less for sacubitril/valsartan-treated patients than those treated with enalapril (RR, 20%; HR, 0.8; 95% CI, 0.73 to 0.87; p < 0.001; NNT, 22; 95% CI, 15 to 35).
  - Symptomatic relief: Kansas City Cardiomyopathy Questionnaire (KCCQ) scores were utilized to measure a patient's physical functioning, symptoms, and quality of life (range, 0 to 100 points) with higher scores indicating better health status. At 8 months, scores significantly improved by 1.64 points favoring sacubitril/valsartan over enalapril (p = 0.001). There are different approaches to determining clinically significant KCCQ scores. Based on the varied approaches, clinically significant changes in KCCQ scores have ranged from a difference of 5-point to 10-point declines. In trials, changes of 4 points have been noted in stable HF patients; therefore, the 1.6-point difference in KCCQ for sacubitril/valsartan may not have resulted in an enhanced quality of life when compared to those treated with enalapril regardless of statistical significance (*Green et al 2000, Cardiovascular Outcomes 2008*).
- Packer et al published a follow-up analysis of the PARADIGM-HF trial, which outlined the incremental effects of sacubitril/valsartan over enalapril for those with non-fatal progression of HF in surviving patients.
  - Data demonstrated that sacubitril/valsartan-treated patients had slower progression of clinical deterioration compared to enalapril-treated patients in many endpoints that are markers for HF progression (ie, intensified outpatient therapy, emergency department visits, number of hospitalizations, etc.). However, sacubitril/valsartan was not significantly different from enalapril in the number of hospitalized days per admission per patient or in patients requiring cardiac resynchronization therapy, ventricular assist device implants, or a heart transplant (*Packer et al 2015*).
- A separate analysis of the PARADIGM-HF trial reported results for additional composite endpoint rates:
  - CV mortality, HF hospitalization, MI, stroke, and resuscitated sudden death: 24.3% with sacubitril/valsartan vs 28.4% with enalapril (HR, 0.83; 95% CI, 0.76 to 0.90; p < 0.001).
  - CV mortality, non-fatal MI, unstable or other hospitalized angina, or percutaneous or surgical coronary revascularization: 17.1% with sacubitril/valsartan vs 20.3% with enalapril (HR, 0.83; 95% CI, 0.75 to 0.92; p < 0.001) (*Mogensen et al 2017*).
- The 5-year estimated NNT was analyzed for the overall PARADIGM-HF cohort. The 5-year NNT for sacubitril/valsartan compared to enalapril for the primary outcome (CV death or HF hospitalization) and all-cause mortality was 14 and 21, respectively, in the overall cohort (*Srivastava et al 2018*).
- Lewis et al published an analysis focused specifically on the health-related quality of life outcomes in PARADIGM-HF. Consistent with the main publication, small but statistically significant improvements in KCCQ scores were reported. At 8 months, the sacubitril/valsartan group noted improvements versus the enalapril group in both KCCQ clinical summary score (CSS) (+0.64 vs -0.29; p = 0.008) and KCCQ overall summary score (OSS) (+1.13 vs -0.14; p < 0.001). Additionally, at 8 months, the proportion of patients with a clinically significant improvement (≥ 5-point increase) in KCCQ score was slightly greater with sacubitril/valsartan vs enalapril (34.5% vs 33.4% for OSS and 32.8% vs 32.6% for CSS) and the proportion with deterioration (≥ 5-point decrease) was less with sacubitril/valsartan versus enalapril (27.2% vs 30.5% for OSS and 27.2% vs 31.2% for CSS). Trends were similar through the 36-month time period but

were not statistically significant at some later time points; the ability to draw conclusions is limited by the low completion rate of 29% at 36 months (*Lewis et al 2017*).

- Chandra et al examined the effects of sacubitril/valsartan on physical and social activity limitations in patients with HF in a secondary analysis of the PARADIGM-HF trial. Patients receiving this therapy had significantly better adjusted change scores in most physical and social activities at 8 months and during 36 months as compared to patients given enalapril. The largest improvements were in household chores (adjusted change score difference, 2.35; 95% CI, 1.19 to 3.50; p < 0.001) and sexual relationships (adjusted change score difference, 2.71; 95% CI, 0.97 to 4.46; p = 0.002) (*Chandra et al 2018*).
- Based on a cohort analysis of data from the run-in period of PARADIGM-HF, a total of 2,079 patients (19.8%) discontinued treatment with sacubitril/valsartan and were identified as not tolerating treatment. A total of 55% of patients who withdrew from therapy discontinued due to adverse effects (53.7% during phase 1 of the run-in period with enalapril and 56.1% during phase 2 of the run-in period with sacubitril/valsartan).
  - According to the analysis, an increased risk of discontinuation of either drug during run-in was associated with patients with a low estimated glomerular filtration rate (adjusted odds ratio [OR], 1.49; 95% CI, 1.35 to 1.65), HF due to ischemic cause (adjusted OR, 1.25; 95% CI, 1.13 to 1.39), higher N-terminal pro-B-type natriuretic peptide (adjusted OR, 1.2 per log increment; 95% CI, 1.14 to 1.26), and lower systolic BP (adjusted OR, 1.11 per 10 mmHg decrease; 95% CI, 1.07 to 1.14).
  - In patients tolerant to enalapril, an increased risk of sacubitril/valsartan discontinuation was associated with lower DBP (adjusted OR, 1.19 per 10 mm Hg decrease; 95% CI, 1.11 to 1.27).
  - The most common adverse effects for enalapril and sacubitril/valsartan were hypotension (24.7% vs 29.8%, respectively), hyperkalemia (29.4% vs 22.5%, respectively), and worsening renal function (30.6% vs 31.6%, respectively). Of note, angioedema occurred in 0.2% of patients entering the run-in period; however, taking into account the baseline group, this may be lower than observed in a real world setting (*Desai et al 2016*).
- Sacubitril/valsartan was compared to enalapril in patients with HFrEF hospitalized for acute decompensated HF in the multicenter, randomized PIONEER-HF study. Change from baseline to weeks 4 and 8 in the primary endpoint, time-averaged proportional change in N-terminal pro-B-type natriuretic peptide (NT-proBNP), was greater with sacubitril/valsartan compared to enalapril (percent change, -46.7% vs -25.3%; ratio of change with sacubitril/valsartan vs enalapril, 0.71; 95% CI, 0.63 to 0.81). Rates of safety outcomes, including worsening renal function, hyperkalemia, and symptomatic hypotension, were not significantly different between groups. Sacubitril/valsartan also reduced the risk of composite of death, rehospitalization for HF, left ventricular device implantation, and inclusion on heart transplantation list (HR, 0.54; 95% CI, 0.37 to 0.79); however, this was an exploratory endpoint *(Velazquez et al 2019)*.
- Sacubitril/valsartan was FDA-approved in October 2019 for pediatric patients at least 1 year of age with HF due to systemic left ventricular systolic dysfunction based on 12-week data from the PANORAMA-HF trial. PANORAMA-HF is a randomized, double-blind trial comparing sacubitril/valsartan to enalapril in pediatric patients with NYHA Class II to IV HF. In an interim analysis, plasma NT-proBNP level change from baseline to 12 weeks was assessed in 110 patients, and there was no significant difference between groups (44% reduction with sacubitril/valsartan and 33% with enalapril). However, because these reductions in NT-proBNP were similar or larger than what was seen with adult patients in PARADIGM-HF and those patients had improved outcomes, it was considered reasonable to infer improved cardiovascular outcomes in pediatric patients (*Entresto prescribing information 2021, Shaddy et al 2017*).
- The PARAGON-HF trial evaluated sacubitril-valsartan efficacy in 4,822 patients with HFpEF (≥ 45%), NYHA class II to IV HF, elevated levels of natriuretic peptides, and structural heart disease. This double-blind trial randomly assigned patients to sacubitril-valsartan (target dose, 97 mg sacubitril and 103 mg of valsartan twice daily) or valsartan (target dose, 160 mg twice daily). The primary outcome was a composite of total hospitalization for HF and death from CV causes. Results did not find a significantly lower rate of the composite primary endpoint with sacubitril-valsartan compared with valsartan alone (rate ratio, 0.87; 95% CI, 0.75 to 1.01; p = 0.06) (*Solomon et al 2019*). Additionally, the incidence of death from CV causes (8.5% sacubitril-valsartan vs 8.9% valsartan; HR 0.95; 95% CI, 0.79 to 1.16) and total hospitalizations for HF (690 vs 797; rate ratio, 0.85; 95% CI, 0.72 to 1.00) were not significantly different between the groups.
- As part of the post-marketing requirements for sacubitril/valsartan, a clinical trial evaluating cognitive effects was required. This trial is not anticipated to be completed until October 2021 (*FDA approval letter 2015*). However, an analysis of cognitive-related events in HFrEF trials was conducted. Based on a search of adverse event reports, dementia-related adverse effects were similar for enalapril and sacubitril/valsartan for both the narrow (0.36% vs 0.29%, respectively; HR, 0.73; 95% CI, 0.33 to 1.59) and broad search terms (2.3% vs 2.48%, respectively; HR, 1.01; 95% CI,

0.75 to 1.37). PARADIGM-HF patients were followed for a median of 2.25 years (upper range to 4.3 years); however, longer term follow-up may be warranted in order to detect any potential impacts on cognition (*Cannon et al 2016*).

CLINICAL GUIDELINES

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

Table 4. Classification of BP measurements

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

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

  - In patients with stage 1 HTN, it is reasonable to initiate therapy with a single antihypertensive agent. In patients with stage 2 HTN and BP more than 20/10 mm Hg higher than their target, 2 first-line agents of different classes should be initiated.
    - First-line antihypertensive agents include thiazide diuretics, CCBs, and ACE-Is or ARBs.
    - Diuretics, ACE-Is, ARBs, CCBs, and beta-blockers have been shown to prevent CVD compared with placebo.
      - ACE-Is were notably less effective in preventing HF and stroke compared with CCBs in black patients. ARBs may be better tolerated than ACE-Is in black patients, with less cough and angioedema, but they offer no proven advantage over ACE-Is in preventing stroke or CVD in this population; thiazide diuretics (especially chlorthalidone) or CCBs are the best initial choice for single-drug therapy in this population.
    - ARBs are reasonable if an ACE-I is not tolerated for treatment of HTN for those with CKD stage 3, or for stage 1 or 2 with albuminuria.
- The 2019 ACC/AHA guideline on the primary prevention of CVD recommends using BP-lowering medications in hypertensive adults: with an estimated 10-year ASCVD risk ≥ 10% and a SBP ≥ 130 mm Hg or DBP ≥ 80 mmHg; with diabetes and a BP > 130/80 mm Hg; or with an estimated 10-year ASCVD risk < 10% and a SBP ≥ 140 mm Hg or DBP ≥ 90 mmHg (*Arnett et al 2019*). A target BP of < 130/80 mmHg is recommended for most patients.
- The American Diabetes Association *(American Diabetes Association 2021, de Boer et al 2017)* recommends that patients with DM and HTN be treated to a goal BP of at least < 140/90 mm Hg. Target BPs should be individualized, and lower BP targets such as < 130/80 mm Hg may be appropriate for individuals at high risk of CVD.
  - Treatment for HTN should include drug classes demonstrated to reduce CV events in patients with DM: ACE-Is, ARBs, thiazide diuretics, or dihydropyridine CCBs.

- Patients with BP ≥ 160/100 mm Hg should have prompt initiation of 2 drugs or a single-pill combination of drugs demonstrated to reduce CV events in patients with DM.
- An ACE-I or ARB, at the maximum tolerated dose indicated for BP treatment, is the recommended first-line treatment for HTN in patients with DM and urine albumin-to-creatinine ratio ≥ 30 mg/g creatinine.

- The American Academy of Pediatrics clinical practice guideline for high BP in children and adolescents *(Flynn et al 2017)* recommends that the treatment goal with nonpharmacologic and pharmacologic therapy should be a reduction in SBP and DBP to < 90th percentile and < 130/80 mm Hg in adolescents ≥ 13 years old.
  - In hypertensive children and adolescents who have failed lifestyle modifications, clinicians should initiate pharmacologic treatment with an ACE-I, ARB, long-acting CCB, or thiazide diuretic.
  - Children and adolescents with CKD, HTN, and proteinuria should be treated with an ACE-I or ARB.
- Various other guidelines and position statements place ARBs as first-line therapy in patients with DM and microalbuminuria; with stable CAD and HTN; and after an MI. ARBs have demonstrated clinical benefit and reductions in morbidity and mortality in these populations *(Amsterdam et al 2014, Go et al 2014, Rosendorff et al 2015, Unger et al 2020).*
  - Due to differences in the activity of the RAAS, ARBs are often less effective as HTN monotherapy in black patients (African or Caribbean descent). Alternative first-line options for these patients include combination therapy with a CCB plus thiazide diuretic or CCB plus ARB *(Unger et al 2020).*
- HF guidelines recommend evidence-based maximally tolerated doses of ACE-Is/ARBs/ARNIs, and/or beta-blockers with diuretics, as needed, for first-line treatment in patients with HFrEF (NYHA Class I to IV; Stage C) (*Yancy et al 2013, Yancy et al 2016, Yancy et al 2017, Maddux et al 2021).*
- Key recommendations from the 2021 update to the 2017 ACC expert consensus decision pathway for optimization of HF treatment include (*Maddux et al 2021*)*:*
  - In a patient with new-onset Stage C HFrEF, an ACE-I/ARB/ARNI or beta-blocker should be started. In some cases, an ACE-I/ARB/ARNI and a beta-blocker can be started at the same time. Regardless, both classes of agents should be up-titrated to the maximum tolerated or target doses in a timely fashion.
  - In patients without prior exposure to an ACE-I or ARB, recent data, along with aggregate clinical experience, suggest that directly initiating ARNI therapy, rather than a pretreatment period ACE-I or ARB, is a safe and effective strategy.
  - ARNI therapy should not be administered concomitantly with ACE-Is or within 36 hours of the last dose of an ACE-I. This delay is not required when switching from an ARB to ARNI therapy.
  - ARNI therapy should not be administered to patients with a history of angioedema.
  - ARNI therapy may exert a more noteworthy effect on BP when compared with ACE-Is/ARBs; therefore, in patients with borderline BP, careful administration and follow-up are advised.

SAFETY SUMMARY

- In July 2018, the FDA first issued a recall of several valsartan products that exceeded acceptable levels of a probable carcinogen, N-nitrosodimethylamine (NDMA). In October 2018, the presence of another impurity, N-nitrosodiethylamine (NDEA), was also discovered in certain valsartan products. Since then, voluntary recalls of other valsartan-, losartan-, and irbesartan-containing products have been announced due to nitrosamine impurities. NDMA is also found in water and certain foods and has been shown to increase risk of cancer in animal studies. To provide context on the risk, the FDA has stated that if 8,000 people took 320 mg daily of the recalled valsartan for 4 years, one additional cancer case may occur over the course of the 8,000 people's lifetimes. To mitigate potential drug shortages, the FDA has announced interim limits for the nitrosamine impurities in ARBs, temporarily allowing distribution of medications that have between 0.96 and 9.82 parts per million of NDMA, to help ensure that an adequate supply is available on the market. In March 2019, the FDA announced that it expects that adequate supplies of losartan without nitrosamine impurities will be available in approximately 6 months. The FDA website is maintaining an updated list of recalled products and should be consulted to determine if a specific manufacturer and lot is recalled *(FDA drug safety alert 2019, FDA drug shortages 2021).*

Boxed Warnings

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

Contraindications

- ARBs are contraindicated in patients with DM who are also receiving Tekturna (aliskiren) therapy.
- ARB combinations containing diuretics (ie, HCTZ, chlorthalidone) are contraindicated in patients with anuria.
- Sacubitril/valsartan is contraindicated in patients with a history of angioedema related to previous ACE-I or ARB therapy, concomitant use with aliskiren in patients with diabetes, or ACE-Is in all patients. Sacubitril/valsartan should not be administered within 36 hours of switching from or to an ACE-I.

Warnings and Precautions

- In general, ARBs have warnings for fetal toxicity, hypotension (especially in volume- or salt-depleted patients), impaired renal function, and hyperkalemia/electrolyte imbalances. Treatment should be discontinued when pregnancy is detected.
  - Candesartan and olmesartan have warnings for morbidity in infants < 1 year of age.
  - Olmesartan has a unique warning for sprue-like enteropathy, which is manifested by severe, chronic diarrhea with substantial weight loss.
  - Telmisartan has a unique warning for use in patients with impaired hepatic function, as it is eliminated mostly by biliary excretion.
- Diuretics (ie, HCTZ, chlorthalidone) may alter glucose tolerance and raise levels of cholesterol, triglycerides, and serum uric acid levels (which may precipitate gout). Diuretics may cause elevations of serum calcium and monitoring is recommended in patients with hypercalcemia.
  - HCTZ may also cause an idiosyncratic reaction resulting in acute transient myopia and acute angle-closure glaucoma.
  - Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus.
  - HCTZ is associated with an increased risk of non-melanoma skin cancer.
- Amlodipine has warnings for increased angina and acute myocardial infarction, and hepatic impairment.
- Sacubitril/valsartan has additional warnings for angioedema, hypotension, a risk of decreased or impaired renal function in susceptible patients, and hyperkalemia.

Adverse Effects

- Common adverse effects with ARBs include hypotension, dizziness, back pain, and headache.
  - The most common adverse reaction with azilsartan is diarrhea.
- The CCB, amlodipine, may cause peripheral edema.
- The most common adverse effects reported (incidence ≥ 5%) with sacubitril/valsartan include hypotension, hyperkalemia, cough, dizziness, and renal failure.
- The FDA has required post-marketing studies for sacubitril/valsartan in order to assess the incidence of angioedema in patients of African or Caribbean descent (Black patients) and the risk of cognitive dysfunction in HF patients with HFpEF (*FDA approval letter 2015*). Postmarketing reports include hypersensitivity, including rash, pruritus, and anaphylactic reactions.
- Experts have raised questions regarding the potential for impact on cognitive dysfunction due to the mechanism of action of sacubitril/valsartan, particularly in patients with Alzheimer's disease. The concern is specifically around the sacubitril component and issues with neprilysin inhibition in the brain. Theoretically, neprilysin inhibition could lead to amyloid deposits, which has been linked to dementia.
- According to pharmacodynamic studies, sacubitril/valsartan 400 mg (2 x 97/103 mg tablets) once daily increased cerebrospinal fluid amyloid-β ($A\beta_{1-38}$) concentrations after 2 weeks in healthy patients. Also, the active metabolite (LBQ657) does minimally cross the blood brain barrier. The clinical relevance of increased concentrations is unknown (*Vodovar et al 2015*).

Important Drug Interactions

- Dual blockade of the RAAS with ACE-Is, ARBs, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure).
  - Most patients receiving the combination of 2 RAAS inhibitors do not obtain any additional benefit compared to monotherapy.
  - Avoid use of aliskiren with ARBs in patients with renal impairment (glomerular filtration rate < 60 mL/min).

- In patients who are elderly, volume-depleted (including those on diuretic therapy), or with compromised renal function, concomitant use of non-steroidal anti-inflammatory agents (NSAIDs) with ARBs may result in deterioration of renal function, including acute renal failure. The antihypertensive effect of ARBs may be attenuated by NSAIDs.
- Concomitant use of ARBs and potassium-sparing diuretics (eg, spironolactone, amiloride, triamterene) can increase the risk of hyperkalemia.
- ARBs may increase serum lithium concentration; lithium levels should be monitored.
- Concurrent administration of the bile acid sequestering agent, colesevelam hydrochloride, reduces the systemic exposure and peak plasma concentration of olmesartan.
- Concomitant use of telmisartan and ramipril is not recommended due to increased exposure to ramipril and ramiprilat.
- HCTZ absorption is impaired in the presence of anionic exchange resins (ie, cholestyramine and colestipol resins).
- Concomitant use of HCTZ with carbamazepine has been associated with an increased risk for symptomatic hyponatremia.
- Amlodipine should not be coadministered with doses higher than 20 mg of simvastatin per day.
- Exposure to amlodipine is increased with CYP3A4 inhibitors.

DOSING AND ADMINISTRATION

- In general, the safety and efficacy of ARBs have not been established in severe hepatic impairment.
- ARB combination products containing diuretics are not recommended in patients with severe renal impairment.
- Some ARB combination products are not recommended as initial therapy in patients with hepatic impairment because the recommended ARB starting dose is not available in the fixed-dose combination product.
- ARB combination products containing amlodipine are not recommended as initial therapy in elderly patients or patients with severe hepatic impairment because the recommended amlodipine starting dose of 2.5 mg is not available in the fixed-dose combination product.

Table 5. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Single-Entity ARBs				
Atacand (candesartan)	Tablets	Oral	HTN: Once or twice daily HF: Once daily	Initiate with 8 mg once daily in moderate hepatic impairment.
Avapro (irbesartan)	Tablets	Oral	Once daily	
Benicar (olmesartan)	Tablets	Oral	Once daily	
Cozaar (losartan)	Tablets	Oral	Once daily	Initiate with 25 mg once daily in mild to moderate hepatic impairment.
Diovan (valsartan)	Tablets	Oral	HTN: Once daily HF/post-MI: Twice daily	Safety and efficacy not established in severe renal impairment
Edarbi (azilsartan)	Tablets	Oral	Once daily	
Micardis (telmisartan)	Tablets	Oral	Once daily	
ARB/Diuretic Combinations				
Atacand HCT (candesartan/hydrochlorothiazide)	Tablets	Oral	Once daily	
Avalide (irbesartan/hydrochlorothiazide)	Tablets	Oral	Once daily	
Benicar HCT (olmesartan/hydrochlorothiazide)	Tablets	Oral	Once daily	
Diovan HCT (valsartan/hydrochlorothiazide)	Tablets	Oral	Once daily	
Edarbyclor (azilsartan/chlorthalidone)	Tablets	Oral	Once daily	

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Hyzaar (losartan/hydrochlorothiazide)	Tablets	Oral	Once daily	
Micardis HCT (telmisartan/hydrochlorothiazide)	Tablets	Oral	Once daily	
ARB/CCB Combinations				
Azor (olmesartan/amlodipine)	Tablets	Oral	Once daily	
Exforge (valsartan/amlodipine)	Tablets	Oral	Once daily	
Twynsta (telmisartan/amlodipine)	Tablets	Oral	Once daily	
ARB/CCB/Diuretic Combinations				
Exforge HCT (valsartan/ amlodipine/hydrochlorothiazide)	Tablets	Oral	Once daily	
Tribenzor (olmesartan/ amlodipine/hydrochlorothiazide)	Tablets	Oral	Once daily	
ARB/Neprilysin inhibitor Combination				
Entresto (sacubitril/valsartan)	Tablets	Oral	Twice daily	Reduce initial dose for: • ACE-I/ARB naïve • Prior low dose of ACE-I/ ARB before initiating sacubitril/valsartan • Severe renal or moderate hepatic impairment

Abbreviations: ACE-I = angiotensin converting enzyme-inhibitor; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; HF = heart failure; HTN = hypertension; MI = myocardial infarction
See the current prescribing information for full details

CONCLUSION

- The single-entity and combination ARB products are FDA-approved for the treatment of HTN, and most are generically available. Some ARBs have additional indications for HF, diabetic nephropathy, or CV risk reduction in certain high-risk populations.
- Sacubitril/valsartan is FDA-approved for HF and is the sole agent in this class approved for HF in pediatric patients.
- Evidence-based guidelines recognize the important role ARBs play in the treatment of HTN and other CV and renal diseases. The current ACC/AHA guidelines recommend a BP goal of < 130/80 mm Hg for most patients *(Arnett et al 2019, Whelton et al 2018)*.
- ARBs have demonstrated efficacy in lowering SBP and DBP in patients with HTN.
  - Head-to-head trials have not consistently demonstrated superiority of one ARB compared to another.
  - Clinical trials assessing the ARB combination products in the treatment of HTN have demonstrated that, in general, dual therapy combinations of ARBs plus either HCTZ or amlodipine achieve greater reductions in BP and higher BP control rates compared to monotherapy regimens. Head-to-head trials have not consistently demonstrated superiority of one combination product over another.
  - ARBs have generally demonstrated comparable efficacy to ACE-Is across indications.
- Studies have demonstrated that the combination of 2 inhibitors of the RAAS, including an ACE-I with an ARB, provides no renal or CV benefits and increases the risk of adverse events, including hyperkalemia, hypotension, and renal dysfunction. All agents in this class have safety warnings against combined use.
- All ARBs have a boxed warning for use in pregnancy and are contraindicated in patients with DM who are also receiving aliskiren therapy. Other warnings include hypotension, renal failure, and hyperkalemia.
- Common adverse effects of ARBs include hypotension, dizziness, back pain, and headache.
- Current guidelines recommend ARBs as a first-line therapy for patients with HTN, DM with microalbuminuria, stable CAD with HTN, and post-MI *(Amsterdam et al 2014, de Boer et al 2017, Go et al 2014, Rosendorff et al 2015, Unger et al 2020, Whelton et al 2018)*.

- Due to differences in the activity of the RAAS, ARBs are often less effective as HTN monotherapy in black patients; alternative first-line options for these patients include combination therapy with a CCB plus thiazide diuretic or CCB plus ARB.

- HF guidelines recommend evidence-based maximally tolerated doses of ACE-Is/ARBs/ARNIs, and/or beta-blockers with diuretics, as needed, for first-line treatment in patients with HFrEF (NYHA Class I to IV; Stage C) (*Yancy et al 2013, Yancy et al 2016, Yancy et al 2017; Maddux et al 2021*).
- Key recommendations from the 2021 update to the 2017 ACC expert consensus decision pathway for optimization of HF treatment include (*Maddux et al 2021*):
  - In a patient with new-onset Stage C HFrEF, an ACE-I/ARB/ARNI or beta-blocker should be started. In some cases, an ACE-I/ARB/ARNI and a beta-blocker can be started at the same time. Regardless, both classes of agents should be up-titrated to the maximum tolerated or target doses in a timely fashion.
  - In patients without prior exposure to an ACE-I or ARB, recent data, along with aggregate clinical experience, suggest that directly initiating ARNI therapy, rather than a pretreatment period ACE-I or ARB, is a safe and effective strategy.

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Publication Date: July 1, 2021

Prior Authorization Guideline

Guideline Name Targeted Immunomodulators

1 . Criteria

Product Name: Humira, Humira Pen, Humira Pediatric	
Approval Length	1 year(s)
Guideline Type	Prior Authorization

Approval Criteria

1 - All of the following:

- Patient has had a negative tuberculin test
- Patient does not have an active infection or a history of recurring infections
- Patient will not be treated with more than one biologic at a time

AND

2 - One of the following:

2.1 Patient has a diagnosis of moderately to severely active rheumatoid arthritis (RA) and all of the following:

2.1.1 Patient is 18 years of age or older

AND

2.1.2 Documentation that the patient has had a rheumatology consult, including date of visit

AND

2.1.3 One of the following:

2.1.3.1 All of the following:

- Patient has early disease duration (less than 6 months)
- Patient has high disease activity
- Patient has had an inadequate response or adverse reaction to at least one disease modifying antirheumatic drug (DMARD) (e.g., methotrexate, hydroxychloroquine, leflunomide, minocycline, or sulfasalazine) (Document tried medication)

OR

2.1.3.2 All of the following:

- Patient has intermediate or long-term disease duration (greater than or equal to 6 months)
- Patient has moderate disease activity
- Patient has had an inadequate response to at least one disease modifying antirheumatic drug (DMARD) (e.g., methotrexate, hydroxychloroquine, leflunomide, minocycline, or sulfasalazine) (Document tried medication)

OR

2.1.3.3 All of the following:

- Patient has intermediate or long-term disease duration (greater than or equal to 6 months)
- Patient has high disease activity

OR

2.2 Patient has a diagnosis of moderate or severe psoriatic arthritis and all of the following:

2.2.1 Patient is 18 years of age or older

AND

2.2.2 Documentation that the patient has had a rheumatology or dermatology consult, including date of visit

AND

2.2.3 Patient had an inadequate response or a contraindication to treatment with one of the following:

- Any one NSAID (Document medication)
- At least one of the following disease modifying antirheumatic drugs (DMARDs): methotrexate, cyclosporine, leflunomide, or sulfasalazine) (Document medication)

OR

2.3 Patient has a diagnosis of ankylosing spondylitis and all of the following:

2.3.1 Patient is 18 years of age or older

AND

2.3.2 Patient has had an inadequate response to NSAIDs

AND

2.3.3 Patient has had an inadequate response to any one DMARD (e.g., methotrexate, hydroxychloroquine, leflunomide, minocycline, or sulfasalazine) (Document tried medication)

OR

2.4 Patient has a diagnosis of moderately or severely active juvenile rheumatoid arthritis/juvenile idiopathic arthritis and all of the following:

2.4.1 Patient is 2 years of age or older

AND

2.4.2 Patient has at least 5 swollen joints

AND

2.4.3 Patient has 3 or more joints with limitation of motion and pain, tenderness or both

AND

2.4.4 Patient has had an inadequate response to at least one disease modifying antirheumatic drug (DMARD) (e.g., methotrexate, hydroxychloroquine, leflunomide, minocycline, or sulfasalazine) (Please document medication)

OR

2.5 Patient has a diagnosis of chronic, moderate to severe plaque psoriasis and all of the following:

2.5.1 Patient is 18 years of age or older

AND

2.5.2 Medication is being prescribed by a dermatologist

AND

2.5.3 Patient has had an inadequate response with a topical agent (Document tried medication)

AND

2.5.4 Patient has had an inadequate response with at least one oral agent (Document tried medication)

OR

2.6 Patient has a diagnosis of moderate to severe Crohn's Disease and all of the following:

2.6.1 Patient is 6 years of age or older

AND

2.6.2 One of the following:

2.6.2.1 Patient has fistulizing Crohn's Disease

OR

2.6.2.2 Patient has had an inadequate response to treatment with conventional therapy (e.g., sulfasalazine, mesalamine, antibiotics, corticosteroids, azathioprine, 6-mercaptopurine, leflunomide) (Document tried medication)

OR

2.7 Patient has a diagnosis of moderate to severe ulcerative colitis and all of the following:

2.7.1 Patient is 5 years of age or older

AND

2.7.2 Patient has failed to adequately respond to one or more of the following standard therapies: (Document tried medication)

- Corticosteroids
- 5-aminosalicylic acid agents
- Immunosuppressants
- Thiopurines

OR

2.8 Patient has a diagnosis of moderate to severe hidradenitis suppurativa and is 18 years of age or older

OR

2.9 Patient has a diagnosis of uveitis and is 2 years of age or older

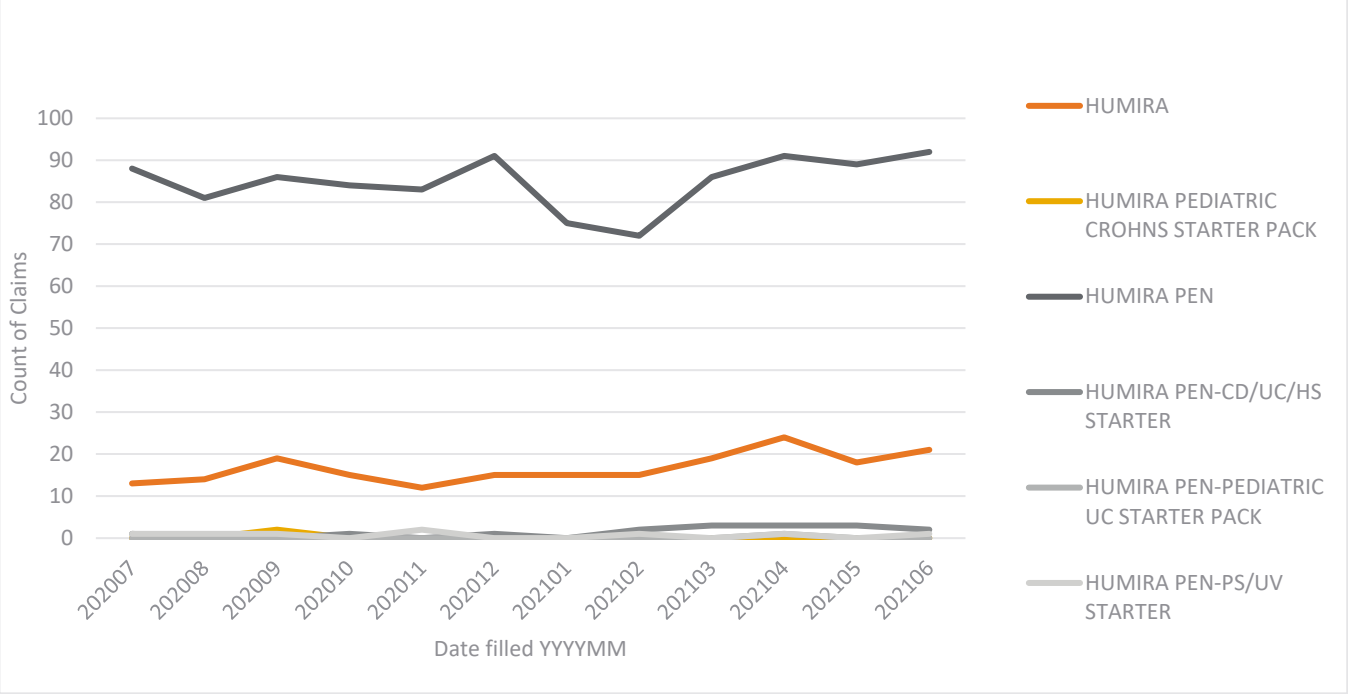
Nevada Medicaid

Top Ten Therapeutic Classes

Fee for Service

July 1, 2020 - June 30, 2021

Drug Name	Members	Claims	Total Days Supply	Total Quantity
HUMIRA PEN-PS/UV STARTER	8	8	266	24
HUMIRA PEN	149	1,018	29,055	2,462
HUMIRA PEN-CD/UC/HS STARTER	15	16	435	48
HUMIRA PEN-PEDIATRIC UC STARTER PACK	1	1	28	4
HUMIRA PEDIATRIC CROHNS STARTER PACK	2	2	42	4



L. Immunomodulator Drugs

Therapeutic Class: Immunomodulators
Last Reviewed by the DUR Board: October 18, 2018

Actemra® (tocilizumab)	Ilaris® (canakinumab)	Remicade® (infliximab)
Amevive® (alefacept)	Ilumya® (tildrakizumab)	Renflexis® (infliximab)
Arcalyst® (rilonacept)	Infle ctra® (infliximab)	Siliq® (brodalumab)
Cimzia® (certolizumab pegol)	Kevzara® (sarilumab)	Simponi® (golimumab)
Consentyx® (secukinumab)	Kineret® (ankinra)	Simponi® ARIA™ (golimumab)
Enbrel® (etanercept)	Olumiant® (baricitinib)	Stelara® (ustekinumab)
Entyvio® (vedolizumab)	Orencia® (abatacept)	Taltz® (ixekizumab)
Humira® (adalimumab)	Otezla® (apremilast)	Xeljanz® (tofacitinib)

Immunomodulator Drugs are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

Approval will be given if the following criteria are met and documented:

a. For all recipients:

1. The recipient has had a negative tuberculin test; and

2. The recipient does not have an active infection or a history of recurring infections; and

3. The approval will not be given for the use of more than one biologic at a time (combination therapy); and

4. Each request meets the appropriate diagnosis-specific criteria (b-j).

b. Rheumatoid Arthritis (RA):

1. The recipient has a diagnosis of moderately to severely active RA; and

2. The recipient is 18 years of age or older; and

3. The recipient has had a rheumatology consultation, including the date of the visit; and one of the following:

a. The recipient has had RA for less than six months (early RA) and has high disease activity; and an inadequate or adverse reaction to a disease modifying antirheumatic drug (DMARD) (methotrexate, hydroxychloroquine, leflunomide, minocycline and sulfasalazine); or

b. The recipient has had RA for greater than or equal to six months (intermediate or long-term disease duration) and has moderate disease activity and has an inadequate response to a DMARD (methotrexate, hydroxychloroquine, leflunomide, minocycline or sulfasalazine); or

c. The recipient has had RA for greater than or equal to six months (intermediate or long-term disease duration) and has high disease activity.

a. Psoriatic Arthritis:

1. The recipient has a diagnosis of moderate or severe psoriatic arthritis; and

2. The recipient is 18 years of age or older; and

3. The recipient has had a rheumatology consultation including the date of the visit or a dermatology consultation including the date of the visit; and

4. The recipient had an inadequate response or a contraindication to treatment with any one nonsteroidal anti-inflammatory (NSAID) or to any one of the following DMARDs: methotrexate, leflunomide, cyclosporine or sulfasalazine.

b. Ankylosing Spondylitis:

1. The recipient has a diagnosis of ankylosing spondylitis; and

2. The recipient is 18 years or older; and

3. The recipient has had an inadequate response to NSAIDs; and

4. The recipient has had an inadequate response to any one of the DMARDs (methotrexate, hydroxychloroquine, sulfasalazine, leflunomide, minocycline).

c. Juvenile Rheumatoid Arthritis/Juvenile Idiopathic Arthritis:

1. The recipient has a diagnosis of moderately or severely active juvenile RA or juvenile idiopathic arthritis; and

2. The recipient is at an appropriate age, based on the requested agent, and:

a. Abatacept: Six years of age or older

b. Adalimumab, canakinumab, etanercept, tocilizumab: Two years of age or older.

3. And the recipient has at least five swollen joints; and

4. The recipient has three or more joints with limitation of motion and pain, tenderness or both; and

5. The recipient has had an inadequate response to one DMARD.

d. Plaque Psoriasis:

1. The recipient has a diagnosis of chronic, moderate to severe plaque psoriasis; and

2. The recipient is 18 years of age of older; and

3. The agent is prescribed by a dermatologist; and

4. The recipient has failed to adequately respond to a topical agent; and

5. The recipient has failed to adequately respond to at least one oral treatment.

g. Crohn's Disease:

1. The recipient has a diagnosis of moderate to severe Crohn's Disease; and

2. The recipient is at an appropriate age, based on the requested agent:

a. Adalimumab, infliximab: Six years of age or older.

b. All others: 18 years of age or older.

3. And the recipient has failed to adequately respond to conventional therapy (e.g. sulfasalazine, mesalamine, antibiotics, corticosteroids, azathioprine, 6-mercaptopurine, leflunomide); or

4. The recipient has fistulizing Crohn's Disease.

h. Ulcerative Colitis:

1. The recipient has a diagnosis of moderate to severe ulcerative colitis; and

2. The recipient is at an appropriate age, based on the requested agent:

a. Infliximab: Six years of age or older.

b. All others: 18 years of age or older.

3. And the recipient has failed to adequately respond to one or more of the following standard therapies:

a. Corticosteroids;

b. 5-aminosalicylic acid agents;

c. Immunosuppressants; and/or

d. Thiopurines.

i. Cryopyrin-Associated Periodic Syndromes (CAPS): Familial Cold Autoinflammatory Syndromes (FCAS) or Muckle-Wells Syndrome (MWS):

1. The recipient has a diagnosis of FCAS or MWS; and

2. The recipient is at an appropriate age, based on the requested agent:

a. Canakinumab: Four years of age or older.

b. Rilonacept: 12 years of age or older.

j. Cryopyrin-Associated Periodic Syndromes (CAPS): Neonatal-Onset Multisystem Inflammatory Disease (NOMID):

1. The recipient has a diagnosis of NOMID.

2. Prior Authorization Guidelines

a. Prior authorization approval will be for 12 months.

b. Prior Authorization forms are available at: https://www.medicaid.nv.gov/providers/rx/rxforms.aspx

INTRODUCTION

- Immunomodulators treat a wide variety of conditions, including rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), plaque psoriasis (PsO), psoriatic arthritis (PsA), ankylosing spondylitis (AS), Crohn's disease (CD), ulcerative colitis (UC), hidradenitis suppurativa (HS), and uveitis (UV), as well as several less common conditions.
- 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 Food and Drug Administration (FDA) has currently approved 5 originator TNF inhibitors: Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Remicade (infliximab), and Simponi/Simponi Aria (golimumab), as well as numerous biosimilar TNF inhibitors: Abrilada (adalimumab-afzb), Cyltezo (adalimumab-adbm), Hadlima (adalimumab-bwwd), Hulio (adalimumab-fkjp), Hyrimoz (adalimumab-adaz), Erelzi (etanercept-szzs), Eticovo (etanercept-ykro), 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. These include Orencia (abatacept), which inhibits CD28-B7 mediated costimulation of the T-cell; Rituxan (rituximab), which targets CD20, a molecule that is found on the surface of B-cells; Actemra (tocilizumab) and Kevzara (sarilumab), which have activity directed against the IL-6 receptor; and Kineret (anakinra), which targets the IL-1 receptor. Of these agents, 3 biosimilar products have been approved: Truxima (rituximab-abbs), Ruxience (rituximab-pvvr), and Riabni (rituximab-arrx). Oral agents on the market, Xeljanz/Xeljanz XR/Xeljanz oral solution (tofacitinib), Rinvoq (upadacitinib), and Olumiant (baricitinib) target Janus-associated kinase (JAK) pathways. By inhibiting the JAK pathway, the ability of cytokines to produce inflammation is reduced.
- Other immunomodulators include Ilaris (canakinumab), which binds to the IL-1ß receptor and is approved to treat JIA, and Entyvio (vedolizumab), which binds to the α4β7 integrin and is approved to treat CD and UC. Otezla (apremilast), an oral, small-molecule phosphodiesterase 4 (PDE-4) inhibitor, and Stelara (ustekinumab), which targets the IL-12 and IL-23 cytokines, are each approved for the treatment of PsA and PsO; Stelara is additionally indicated for the treatment of CD and UC. Cosentyx (secukinumab) and Taltz (ixekizumab) bind and neutralize IL-17A and are indicated for the treatment of PsO, PsA, and AS. Siliq (brodalumab), an IL-17 receptor antagonist, as well as Tremfya (guselkumab), Skyrizi (risankizumab), and Ilumya (tildrakizumab-asmn), IL-23 antagonists, are indicated for selected patients with PsO. Tremfya is additionally indicated for PsA.
- Certain rare conditions for which immunomodulators are indicated are mentioned in this review but not discussed in detail. These include:
  - Ilaris for the treatment of 1) cryopyrin-associated periodic syndromes (CAPS), specifically the subtypes familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS); 2) TNF receptor associated periodic syndrome (TRAPS); 3) hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD); 4) familial Mediterranean fever (FMF); and 5) adult-onset Still's disease.
  - Kineret for the treatment of deficiency of interleukin-1 receptor antagonist (DIRA) and CAPS, specifically neonatal-onset multisystem inflammatory disease (NOMID).
  - Actemra for giant cell arteritis (GCA) and cytokine release syndrome (CRS).
  - Cimzia, Cosentyx, and Taltz for non-radiographic axial spondyloarthritis (NRAS) with objective signs of inflammation.
  - Otezla for treatment of adults with oral ulcers associated with Behçet disease.
- Rituxan is also approved for non–Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), granulomatosis with polyangiitis (GPA) (Wegener's granulomatosis) and microscopic polyangiitis (MPA), and pemphigus vulgaris. These indications will not be discussed in this review.
- Tysabri (natalizumab), an integrin receptor antagonist, is indicated for multiple sclerosis and CD for patients who have had an inadequate response to, or are unable to tolerate conventional therapies and TNF inhibitors; it is not included as a drug product in this review (*Tysabri prescribing information 2020*). Arcalyst (rilonacept), an interleukin-1 blocker indicated for CAPS, is also not included in this review (*Arcalyst prescribing information 2020*).
- Although FDA-approved, the launch plans for the biosimilar drugs Abrilada (adalimumab-afzb), Erelzi (etanercept-szzs), Eticovo (etanercept-ykro), Cyltezo (adalimumab-adbm), Hadlima (adalimumab-bwwd), Hulio (adalimumab-fkjp), and Hyrimoz (adalimumab-adaz) are pending and may be delayed; therefore, these agents are not currently included in this review. Ixifi (infliximab-qbtx) was FDA-approved as a biosimilar to infliximab, but the manufacturer to date does not have

plans to launch Ixifi in the United States; Ixifi is listed as discontinued in the FDA Purple Book. Amjevita (adalimumab-atto) was approved as an adalimumab biosimilar but never launched; it is listed as discontinued in the FDA Purple Book (*Purple Book: Database of Licensed Biological Products 2021*).

- Medispan Classes: Antineoplastic-Monoclonal Antibodies, Antipsoriatics, Antirheumatic-Enzyme Inhibitors, Anti-TNF-Alpha-Monoclonal Antibodies, Integrin Receptor Antagonists, Interleukin-1 Receptor Antagonists, Interleukin-1beta Receptor Inhibitors, Interleukin-6 Receptor Inhibitors, PDE-4 Inhibitors, Selective Costimulation Modulators, Soluble Tumor Necrosis Factor Receptor Agents, Tumor Necrosis Factor Alpha Blockers

Table 1. Medications Included Within Class Review

Drug	Biosimilar or Generic Availability	Type of Agent
Actemra (tocilizumab)	-	Human monoclonal antibody targeting the IL-6 receptor
Avsola (infliximab-axxq)	N/A†	TNFα inhibitor
Cimzia (certolizumab)	-	TNFα inhibitor
Cosentyx (secukinumab)	-	Human monoclonal antibody to IL-17A
Enbrel (etanercept)	-*	sTNFR fusion protein, TNFα inhibitor
Entyvio (vedolizumab)	-	Human monoclonal antibody binds to the α4β7 integrin
Humira (adalimumab)	-*	TNFα inhibitor
Ilaris (canakinumab)	-	Human monoclonal antibody that binds to IL-1ß
Ilumya (tildrakizumab-asmn)	-	Human monoclonal antibody to IL-23
Inflectra (infliximab-dyyb)	N/A†	TNFα inhibitor
Kevzara (sarilumab)	-	Human monoclonal antibody targeting IL-6 receptor
Kineret (anakinra)	-	IL-1 receptor antagonist
Olumiant (baricitinib)	-	Small molecule Janus kinase (JAK) inhibitor
Orencia (abatacept)	-	sCTLA-4-Ig recombinant fusion protein
Otezla (apremilast)	-	Small-molecule phosphodiesterase 4 inhibitor
Remicade (infliximab)	-†	TNFα inhibitor
Renflexis (infliximab-abda)	N/A†	TNFα inhibitor
Rinvoq (upadacitinib)	-	Small molecule Janus kinase (JAK) inhibitor
Rituxan (rituximab)	-†	Anti-CD20 monoclonal antibody
Siliq (brodalumab)	-	Human monoclonal antibody directed against the IL-17 receptor A (IL-17RA)
Simponi/ Simponi Aria (golimumab)	-	TNFα inhibitor
Skyrizi (risankizumab-rzaa)	-	Human monoclonal antibody to IL-23
Stelara (ustekinumab)	-	Human monoclonal antibody targeting the IL-12 and IL-23 cytokines
Taltz (ixekizumab)	-	Human monoclonal antibody to IL-17A
Tremfya (guselkumab)	-	Human monoclonal antibody to IL-23 cytokine
Truxima (rituximab-abbs)	N/A†	Anti-CD20 monoclonal antibody
Xeljanz/Xeljanz XR/Xeljanz oral solution (tofacitinib)	-	Small molecule Janus kinase (JAK) inhibitor

*Erelzi (etanercept-szzs) and Eticovo (etanercept-ykro) have been FDA-approved as biosimilars to Enbrel (etanercept). Abrilada (adalimumab-afzb), Cyltezo (adalimumab-adbm), Hadlima (adalimumab-bwwd), Hulio (adalimumab-fkjp), and

Hyrimoz (adalimumab-adaz) have been FDA-approved as biosimilars to Humira (adalimumab). Further information on Erelzi, Eticovo, Abrilada, Cyltezo, Hadlima, Hulio, and Hyrimoz will be included in this review after these products have launched. None of these agents is FDA-approved as an interchangeable biologic.
†Inflectra (infliximab-dyyb), Renflexis (infliximab-abda), and Avsola (infliximab-axxq) have been FDA-approved as biosimilar agents to Remicade (infliximab). Truxima (rituximab-abbs), Ruxience (rituximab-pvvr), and Riabni (rituximab-arrx) have been FDA-approved as biosimilar agents to Rituxan (rituximab), but Ruxience (rituximab-pvvr) and Riabni (rituximab-arrx) are only approved for adult patients with NHL, CLL, and GPA/MPA. None of these agents is FDA-approved as an interchangeable biologic.

(Drugs@FDA, 2021; Purple Book: Database of Licensed Biological Products 2021; Prescribing information: Actemra 2020; Avsola 2019; Cimzia 2019; Cosentyx 2020; Enbrel 2020; Entyvio 2020; Humira,2020; Ilaris 2020; Ilumya 2021; Inflectra 2019; Kevzara 2018; Kineret 2020; Olumiant 2020; Orencia 2020; Otezla 2020; Remicade 2020; Renflexis 2020; Rinvoq 2020; Rituxan 2020; Siliq 2020; Simponi 2019; Simponi Aria 2021; Skyrizi 2020; Stelara 2020; Taltz 2020; Tremfya 2020; Truxima 2020; Xeljanz/Xeljanz XR/Xeljanz oral solution 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.

INDICATIONS

Table 2. Food and Drug Administration Approved Indications (see footnotes for less common indications: oral ulcers associated with Behçet disease, CAPS, CRS, FMF, GCA, HIDS/MKD, NRAS, and TRAPS)***

Drug	Rheumatoid Arthritis (RA)	Crohn's Disease (CD)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Ulcerative Colitis (UC)	Hidradenitis Suppurativa (HS)	Uveitis (UV)
Actemra♀ (tocilizumab)	✔ *		✔ **	✔ **						
Avsola (infliximab-axxq)	✔ ⊥	✔ ⌐⌐			✔ ‡‡‡	✔	✔	✔ ⊥⊥		
Cimzia~~ (certolizumab)	✔	✔			✔ ‡	✔	✔			
Cosentyx~~ (secukinumab)					✔ ‡	✔	✔			
Enbrel (etanercept)	✔ †			✔ **	✔ ‡	✔ †	✔			
Entyvio (vedolizumab)		✔						✔		

Drug	Rheumatoid Arthritis (RA)	Crohn's Disease (CD)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Ulcerative Colitis (UC)	Hidradenitis Suppurativa (HS)	Uveitis (UV)
Humira (adalimumab)	✔ ‡‡	✔ ⌐		✔ ∫	✔ ‡	✔ ∫∫	✔	✔	✔ ↑	✔ ▼
Ilaris" (canakinumab)			✔ **							
Ilumya (tildrakizumab-asmn)					✔ ‡					
Inflectra (infliximab-dyyb)	✔ ⊥	✔ ⌐⌐			✔ ‡‡‡	✔	✔	✔ ⊥⊥		
Kevzara (sarilumab)	✔ *									
Kineret▼▼ (anakinra)	✔ ∞									
Olumiant (baricitinib)	✔ *									

Drug	Rheumatoid Arthritis (RA)	Crohn's Disease (CD)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Ulcerative Colitis (UC)	Hidradenitis Suppurativa (HS)	Uveitis (UV)
Orencia (abatacept)	✔ ∞∞			✔ ⌂		✔				
Otezla~~~ (apremilast)					✔ ‡	✔				
Remicade (infliximab)	✔ ⊥	✔ ⌐⌐			✔ ‡‡‡	✔	✔	✔ ⊥⊥		
Renflexis (infliximab-abda)	✔ ⊥	✔ ⌐⌐			✔ ‡‡‡	✔	✔	✔ ⊥⊥		
Rinvoq (upadacitinib)	✔ †									
Rituxan‴ (rituximab)	✔ ⫩									
Siliq (brodalumab)					✔ ⫩⫩					

Drug	Rheumatoid Arthritis (RA)	Crohn's Disease (CD)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Ulcerative Colitis (UC)	Hidradenitis Suppurativa (HS)	Uveitis (UV)
Simponi (golimumab)	✔┤					✔┤┤	✔	✔˜		
Simponi Aria (golimumab)	✔┤			✔**		✔**	✔			
Skyrizi (risankizumab-rzaa)					✔‡					
Stelara (ustekinumab)		✔⌐⌐⌐			✔‡	✔		✔		
Taltz˜˜ (ixekizumab)					✔‡	✔	✔			
Tremfya (guselkumab)					✔‡	✔				
Truxima (rituximab-abbs)''''	✔╪									

Drug	Rheumatoid Arthritis (RA)	Crohn's Disease (CD)	Systemic Juvenile Idiopathic Arthritis (SJIA)	Polyarticular Juvenile Idiopathic Arthritis (PJIA)	Plaque Psoriasis (PsO)	Psoriatic Arthritis (PsA)	Ankylosing Spondylitis (AS)	Ulcerative Colitis (UC)	Hidradenitis Suppurativa (HS)	Uveitis (UV)
Xeljanz/ Xeljanz XR/Xeljanz oral solution (tofacitinib)	✔‡‡‡			✔ **		✔		✔		

ϒActemra is also indicated for treatment of giant cell arteritis in adults and chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome in adults and pediatric patients ≥ 2 years.
*Patients with moderately to severely active RA who have had an inadequate response (or intolerance [Kevzara]) to ≥ 1 Disease-Modifying Anti-Rheumatic Drugs (DMARDs) or [≥ 1 TNF antagonists (Olumiant)].
**Patients 2 years and older.
†In combination with methotrexate (MTX) or used alone.
‡Indicated for the treatment of adult patients (18 years or older) with chronic moderate to severe PsO who are candidates for systemic therapy or phototherapy, with the exception of Enbrel, which is indicated for the treatment of patients 4 years and older with chronic moderate to severe PsO who are candidates for systemic therapy or phototherapy, Taltz, which is indicated for the treatment of patients 6 years and older with moderate-to-severe PsO who are candidates for systemic therapy or phototherapy, and Stelara, which is indicated for the treatment of patients 6 years and older with moderate to severe PsO.
‡‡Indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. Can be used alone or in combination with MTX or other DMARDs.
‡‡‡ Indicated for the treatment of adult patients with chronic severe (ie, extensive and/or disabling) PsO who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.
∫Indicated for reducing signs and symptoms of JIA for patients 2 years of age and older. Can be used alone or in combination with MTX.
∫∫Indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with active PsA. Can be used alone or in combination with non-biologic DMARDs.
▼ Treatment of non-infectious intermediate, posterior and panuveitis in adult and pediatric patients 2 years of age or older.
↑ Treatment of moderate to severe hidrandenitis suppurative in patients 12 years of age or older.
▼▼Kineret is also indicated for the treatment of cryopyrin-associated periodic syndromes (CAPS), including neonatal-onset multisystem inflammatory disease (NOMID), and for the treatment of deficiency of interleukin-1 receptor antagonist (DIRA).
"Ilaris also indicated for the treatment of CAPS in adults and children 4 years of age and older including: familial cold autoinflammatory syndrome (FCAS) and Muckle-Wells syndrome (MWS); tumor necrosis factor receptor associated periodic syndrome (TRAPS) in adult and pediatric patients; hyperimmunoglobulin D syndrome (HIDS)/mevalonate kinase deficiency (MKD) in adult and pediatric patients; familial Mediterranean fever (FMF) in adult and pediatric patients; and adult-onset Still's disease.
∞Indicated for the reduction in signs and symptoms and slowing the progression of structural damage in moderately to severely active RA, in patients 18 years of age or older who have failed one or more DMARDs. Can be used alone or in combination with DMARDs other than TNF blocking agents.
∞∞Indicated for reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active RA. May be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.
⌂ Indicated for reducing signs and symptoms in pediatric patients 2 years and older with moderate to severely active PJIA. May be used as monotherapy or with MTX.
⌐For all patients 6 years of age and older, indicated for reducing signs and symptoms and inducing and maintaining clinical remission in patients who have had an inadequate response to conventional therapy. For adults, also indicated for reducing signs and symptoms and inducing clinical remission if patients have also lost a response to or are intolerant of infliximab.
⌐⌐Indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy and for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing CD. And for patients 6 years of age and older for reducing signs and symptoms and inducing and maintaining clinical remission with moderately to severely active disease who have had an inadequate response to conventional therapy.
⌐⌐⌐Indicated for treatment of adult patients with moderately to severely active CD who have: 1) failed or were intolerant to treatment with immunomodulators or corticosteroids but never failed a TNF blocker, or 2) failed or were intolerant to treatment with ≥ 1 TNF blockers
⊥In combination with MTX, is indicated for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active RA.

┴┴For reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy. Also for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active disease who have had an inadequate response to conventional therapy (Remicade, Inflectra, Renflexis, Avsola).
'''Rituxan also indicated for Non–Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), granulomatosis with polyangiitis (GPA) (Wegener's Granulomatosis) and microscopic polyangiitis (MPA), and pemphigus vulgaris.
╪In combination with MTX is indicated for the treatment of adult patients with moderately- to severely- active RA who have had an inadequate response to ≥ 1 TNF antagonist therapies.
╪╪Treatment of moderate to severe PsO in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.
┼ In combination with MTX, is indicated for the treatment of adult patients with moderately to severely active RA.
┼┼ Alone or in combination with MTX, is indicated for the treatment of adult patients with active PsA.
╪╪╪Indicated for the treatment of adult patients with moderately to severely active RA who have had an inadequate response or intolerance to MTX. It may be used as monotherapy or in combination with MTX or other nonbiologic DMARDs. Use in combination with biologic DMARDs or with potent immunosuppressants such as azathioprine and cyclosporine is not recommended.
˜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-mercaptopurine 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.
˜˜Cimzia, Cosentyx, and Taltz also indicated for treatment of adults with active non-radiographic axial spondyloarthritis (NRAS) with objective signs of inflammation.
~~~Otezla also indicated for treatment of adults with oral ulcers associated with Behçet disease.
†Indicated for treatment of adults with moderately to severely active disease who have had an inadequate response or intolerance to MTX.
''''Truxima is also indicated for adults with NHL, CLL, GPA (Wegener's Granulomatosis) and MPA.
***Ruxience is indicated for NHL, CLL, GPA (Wegener's Granulomatosis) and MPA.
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CLINICAL EFFICACY SUMMARY

Rheumatoid arthritis (RA)

- The approval of the subcutaneous (SQ) formulation of Orencia (abatacept) was based on a double-blind, double-dummy, randomized trial demonstrating noninferiority to the intravenous (IV) formulation. The trial enrolled patients with RA who had an inadequate response to methotrexate (MTX). The proportion of patients achieving American College of Rheumatology 20% improvement (ACR 20) was not significantly different between the groups (*Genovese et al 2011*).
- Orencia (abatacept), Remicade (infliximab), and placebo were compared in a Phase 3, randomized, double-blind trial (n = 431). Enrolled patients had an inadequate response to MTX, and background MTX was continued during the trial. Although efficacy was comparable between abatacept and infliximab after 6 months of treatment, some differences in favor of abatacept were evident after 1 year of treatment. After 1 year, the mean changes from baseline in disease activity score based on erythrocyte sedimentation rate (DAS28-ESR) were -2.88 and -2.25 in the abatacept and infliximab groups, respectively (estimate of difference, -0.62; 95% confidence interval [CI], -0.96 to -0.29). Abatacept demonstrated greater efficacy vs infliximab on some (but not all) secondary endpoints, including the proportion of patients with a good European League Against Rheumatism (EULAR) response (32.0% vs 18.5%), low disease activity score (LDAS) (35.3% vs 22.4%), ACR 20 responses (72.4% vs 55.8%), and improvements in the Medical Outcomes Study short-form-36 (SF-36) physical component summary (PCS) (difference of 1.93). Overall, abatacept had a relatively more acceptable safety and tolerability profile, with fewer serious adverse events (AEs) and discontinuations due to AEs than the infliximab group (*Schiff et al 2008*).
- Treatment with Orencia (abatacept) was directly compared to treatment with Humira (adalimumab), when added to MTX, in a multicenter, investigator-blind, randomized controlled trial (n = 646) of RA patients with inadequate response to MTX. After 2 years, the proportions of patients achieving ACR 20 responses were comparable between abatacept and adalimumab treatment groups (59.7 and 60.1%, respectively; difference 1.8%; 95% CI, -5.6 to 9.2%). ACR 50 and ACR 70 responses were also similar between the 2 groups after 2 years of treatment. Rates of AEs were similar between treatment groups (*Schiff et al 2014*).
- The RAPID-1 and RAPID-2 studies compared Cimzia (certolizumab) in combination with MTX to placebo plus MTX in adults with active RA despite MTX therapy (*Keystone et al 2008, Smolen et al 2009a*). A significantly greater proportion of patients on certolizumab 400 mg plus MTX at weeks 0, 2, and 4 then 200 or 400 mg every 2 weeks attained greater ACR 20, ACR 50 and ACR 70 responses compared to patients on placebo and MTX, respectively, after 24 weeks ($p \leq 0.01$). The response rates were sustained with active treatment over 52 weeks (*Keystone et al 2008*). The Modified Total Sharp Score (mTSS) was significantly lower with certolizumab in combination with MTX compared to MTX in combination with placebo (*Keystone et al 2008, Smolen et al 2009a*). A trial evaluated Cimzia (certolizumab) monotherapy vs placebo in patients with active disease who had failed at least 1 prior DMARD. After 24 weeks, ACR 20 response rates were significantly greater with active treatment (45.5%) compared to placebo (9.3%; $p < 0.001$). Significant improvements in secondary endpoints (ACR 50, ACR 70, individual ACR component scores, and patient reported outcomes) were also associated with certolizumab therapy (*Fleischmann et al 2009*).
- More Cimzia (certolizumab)-treated patients achieved clinical disease activity index (CDAI) remission than placebo-treated patients (18.8% vs 6.1%, $p \leq 0.05$) in a randomized, double-blind, placebo-controlled trial of certolizumab over 24 weeks in 194 patients with RA who were on DMARD therapy with MTX, leflunomide, sulfasalazine and/or hydroxychloroquine for at least 6 months (*Smolen et al 2015a*).
- A randomized, double-blind, placebo-controlled trial (n = 316) conducted in Japan compared Cimzia (certolizumab) plus MTX to placebo plus MTX in MTX-naïve patients with early RA (≤ 12 months persistent disease) and poor prognostic factors: high anti-cyclic citrullinated peptide (anti-CCP) antibody and either positive rheumatoid factor and/or presence of bone erosions (*Atsumi et al 2016*). The primary endpoint was inhibition of radiographic progression (change from baseline in mTSS at week 52). The certolizumab plus MTX group showed significantly greater inhibition of radiographic progression vs MTX alone (mTSS change, 0.36 vs 1.58; $p < 0.001$). Clinical remission rates were higher in patients treated with certolizumab plus MTX vs MTX alone. The authors suggest that certolizumab plus MTX could be used as possible first-line treatment in this patient population. In a long-term extension, a higher percentage of patients treated with certolizumab plus MTX experienced inhibition of radiographic progression (change from baseline in mTSS) at week 104 vs MTX alone (84.2% vs 67.5%; $p < 0.001$) (*Atsumi et al 2017*).
- The FDA approval of Simponi (golimumab) for RA was based on 3 multicenter, double-blind, randomized, controlled trials in 1,542 patients ≥ 18 years of age with moderate to severe active disease. A greater percentage of patients from all 3 trials treated with the combination of golimumab and MTX achieved ACR responses at week 14 and week 24 vs patients treated with MTX alone (*Emery et al 2009, Keystone et al 2009, Smolen et al 2009b*). Additionally, the golimumab 50 mg groups demonstrated a greater improvement compared to the control groups in the change in mean

Health Assessment Questionnaire (HAQ) Disability Index (HAQ-DI) (*Keystone et al 2009, Smolen et al 2009b*). Response with golimumab + MTX was sustained for up to 5 years (*Keystone et al 2013a, Smolen et al 2015b*).

- Simponi Aria (golimumab) was studied in patients with RA. In 1 trial, 643 patients could receive golimumab 2 mg/kg or 4 mg/kg intravenously (IV) every 12 weeks with or without MTX, or placebo with MTX. The proportion of patients meeting the primary endpoint of ACR 50 response was not significantly different between the golimumab with or without MTX groups and the placebo group. However, significantly more patients receiving golimumab plus MTX achieved an ACR 20 response at week 14 compared with patients receiving placebo plus MTX (53 vs 28%; p < 0.001) (*Kremer et al 2010*). In the GO-FURTHER trial (n = 592), golimumab 2 mg/kg IV or placebo was given at weeks 0, 4 and then every 8 weeks. An increased percentage of patients treated with golimumab + MTX achieved ACR 20 response at week 14 (58.5% [231/395] of golimumab + MTX patients vs 24.9% [49/197] of placebo + MTX patients [p < 0.001]) (*Weinblatt et al 2013*). In an open-label extension period, treatment was continued through week 100, with placebo-treated patients crossing over to golimumab at week 16 (early escape) or week 24. Clinical response was maintained through week 100, with an ACR 20 response of 68.1%. There was a very low rate of radiographic progression throughout the study, and patients treated with IV golimumab plus MTX from baseline had significantly less radiographic progression to week 100 compared to patients who had initially received placebo plus MTX. No unexpected AEs occurred (*Bingham et al 2015*). In the GO-MORE trial, investigators treated patients with golimumab SQ for 6 months. If patients were not in remission, they could be randomized to receive golimumab SQ or IV. The percentages of patients who achieved DAS28-ESR remission did not differ between the combination SQ + IV group and the SQ golimumab group (*Combe et al 2014*).
- The efficacy and safety of Actemra (tocilizumab) were assessed in several randomized, double-blind, multicenter studies in patients age ≥ 18 years with active RA. Patients were diagnosed according to ACR criteria, with at least 8 tender and 6 swollen joints at baseline. Tocilizumab was given every 4 weeks as monotherapy (AMBITION), in combination with MTX (LITHE and OPTION) or other DMARDs (TOWARD) or in combination with MTX in patients with an inadequate response to TNF antagonists (RADIATE). In all studies, mild to moderate AEs were reported, occurring in similar frequencies in all study groups. The most common AEs in all studies were infections and gastrointestinal symptoms (*Emery et al 2008, Genovese et al 2008, Jones et al 2010, Kremer et al 2011, Smolen et al 2008*).
  - AMBITION evaluated the safety and efficacy of tocilizumab monotherapy vs MTX in patients with active RA for whom previous treatment with MTX or biological agents had not failed. A total of 673 patients were randomized to 1 of 3 treatment arms, tocilizumab 8 mg/kg every 4 weeks, MTX 7.5 mg/week and titrated to 20 mg/week within 8 weeks, or placebo for 8 weeks followed by tocilizumab 8 mg/kg. The primary endpoint was the proportion of patients achieving ACR 20 response at week 24. The results showed that tocilizumab monotherapy when compared to MTX monotherapy produced greater improvements in RA signs and symptoms, and a favorable benefit-risk ratio in patients who had not previously failed treatment with MTX or biological agents. Additionally, more patients treated with tocilizumab achieved remission at week 24 when compared to patients treated with MTX (*Jones et al 2010*).
  - LITHE evaluated 1,196 patients with moderate to severe RA who had an inadequate response to MTX. Patients treated with tocilizumab had 3 times less progression of joint damage, measured by Total Sharp Score, when compared to patients treated with MTX alone. Significantly more patients treated with tocilizumab 8 mg/kg were also found to achieve remission at 6 months as compared to MTX (33% vs 4%), and these rates continued to increase over time to 1 year (47% vs 8%) (*Kremer et al 2011*). These benefits were maintained or improved at 2 years with no increased side effects (*Fleishmann et al 2013*).
  - OPTION evaluated tocilizumab in 623 patients with moderate to severely active RA. Patients received tocilizumab 8 mg/kg, 4 mg/kg, or placebo IV every 4 weeks, with MTX at stable pre-study doses (10 to 25 mg/week). Rescue therapy with tocilizumab 8 mg/kg was offered at week 16 to patients with < 20% improvement in swollen and tender joint counts. The primary endpoint was ACR 20 at week 24. The findings showed that ACR 20 was seen in significantly more patients receiving tocilizumab than in those receiving placebo at week 24 (p < 0.001). Significantly more patients treated with tocilizumab achieved ACR 50 and ACR 70 responses at week 24 as well (p < 0.001). Greater improvements in physical function, as measured by the HAQ-DI, were seen with tocilizumab when compared to MTX (-0.52 vs -0.55 vs -0.34; p < 0.0296 for 4 mg/kg and p < 0.0082 for 8 mg/kg) (*Smolen et al 2008*).
  - TOWARD examined the efficacy and safety of tocilizumab combined with conventional DMARDs in 1220 patients with active RA. Patients remained on stable doses of DMARDs and received tocilizumab 8 mg/kg or placebo every 4 weeks for 24 weeks. At week 24, significantly more patients taking tocilizumab with DMARDs achieved an ACR 20 response than patients in the control group. The authors concluded that tocilizumab, combined with any of the DMARDs evaluated (MTX, chloroquine, hydroxychloroquine, parenteral gold, sulfasalazine, azathioprine, and leflunomide), was safe and effective in reducing articular and systemic symptoms in patients with an inadequate response to these agents. A greater percentage of patients treated with tocilizumab also had clinically meaningful

improvements in physical function when compared to placebo (60% vs 30%; p value not reported) (*Genovese et al 2008).*

- RADIATE evaluated the safety and efficacy of tocilizumab in patients with RA refractory to TNF antagonist therapy. A total of 499 patients with inadequate response to ≥ 1TNF antagonists were randomly assigned to 8 or 4 mg/kg tocilizumab or placebo every 4 weeks with stable MTX doses (10 to 25 mg/week) for 24 weeks. ACR 20 responses and safety endpoints were assessed. This study found that tocilizumab plus MTX is effective in achieving rapid and sustained improvements in signs and symptoms of RA in patients with inadequate response to TNF antagonists and has a manageable safety profile. The ACR 20 response in both tocilizumab groups was also found to be comparable to those seen in patients treated with Humira (adalimumab) and Remicade (infliximab), irrespective of the type or number of failed TNF antagonists (*Emery et al 2008*). In the ADACTA trial, patients with severe arthritis who could not take MTX were randomized to monotherapy with tocilizumab or adalimumab. The patients in the tocilizumab group had a significantly greater improvement in DAS28 at week 24 than patients in the adalimumab group (*Gabay et al 2013*).

- More recently, results of a randomized, double-blind trial evaluating Actemra (tocilizumab) in early RA were published (*Bijlsma et al 2016*). Patients (n = 317) had been diagnosed with RA within 1 year, were DMARD-naïve, and had a DAS28 score of ≥ 2.6. Patients were randomized to 1 of 3 groups: tocilizumab plus MTX, tocilizumab plus placebo, or MTX plus placebo. Tocilizumab was given at a dose of 8 mg/kg every 4 weeks (maximum 800 mg per dose), and MTX was given at a dose of 10 mg orally per week, increased to a maximum of 30 mg per week as tolerated. Patients not achieving remission switched from placebo to active treatments, and patients not achieving remission in the tocilizumab plus MTX group switched to a standard of care group (usually a TNF inhibitor plus MTX). The primary endpoint was the proportion of patients achieving sustained remission (defined as DAS28 < 2.6 with a swollen joint count ≤4, persisting for at least 24 weeks). The percentages of patients achieving a sustained remission on the initial regimen were 86%, 84%, and 44% in the tocilizumab plus MTX, tocilizumab monotherapy, and MTX monotherapy groups, respectively (p < 0.0001 for both comparisons vs MTX). The percentages of patients achieving sustained remission during the entire study were 86%, 88%, and 77% in the tocilizumab plus MTX, tocilizumab monotherapy, and MTX monotherapy groups, respectively (p = 0.06 for tocilizumab plus MTX vs MTX; p = 0.0356 for tocilizumab vs MTX). The authors concluded that immediate initiation of tocilizumab is more effective compared to initiation of MTX in early RA.
- The FDA approval of the SQ formulation of Actemra (tocilizumab) was based on 1 multicenter, double-blind, randomized, controlled trial in patients (n = 1262) with RA. Weekly tocilizumab SQ 162 mg was found to be non-inferior to tocilizumab IV 8 mg/kg every 4 weeks through 24 weeks. A higher incidence of injection-site reactions were reported with the SQ formulation (*Burmester et al 2014a*). In an open-label extension period, patients in both treatment arms were re-randomized to receive either IV or SQ tocilizumab through week 97. The proportions of patients who achieved ACR 20/50/70 responses, DAS28 remission, and improvement from baseline in HAQ-DI ≥ 0.3 were sustained through week 97 and comparable across arms. IV and SQ treatments had a comparable safety profile with the exception of higher injection-site reactions with the SQ formulation (*Burmester et al 2016*). A placebo-controlled trial in 656 patients further confirmed the efficacy of SQ Actemra administered every other week (*Kivitz et al 2014*).
- A phase 3 trial (MONARCH) evaluating the efficacy of Kevzara (sarilumab) monotherapy vs Humira (adalimumab) monotherapy for the treatment of patients with active RA with an inadequate response or intolerance to MTX reported superiority of sarilumab over adalimumab based on change from baseline in DAS28-ESR at week 24 (-3.28 vs -2.20; difference, -1.08; 95% CI, -1.36 to -0.79; p < 0.0001) (*Burmester et al 2017*). DAS28-ESR remission, ACR 20/50/70 response rates, and improvements in HAQ-DI scores were also more likely with sarilumab. Aside from the MONARCH trial, sarilumab has not been directly compared to any other biologic or tofacitinib. Nonetheless, 2 pivotal trials have shown the agent to be superior in achievement of ACR 50 when compared to MTX plus placebo, in both MTX inadequate responders and TNF inhibitor inadequate responder patients (*Genovese et al 2015, Fleischmann et al 2017*). Additionally, a meta-analysis of 4 randomized controlled trials (RCTs) has shown that ACR 50 response rates were significantly higher with sarilumab 200 mg and sarilumab 200 mg plus MTX when compared to MTX plus placebo (OR, 4.05; 95% CI, 2.04 to 8.33 and OR, 3.75; 95% CI, 2.37 to 5.72, respectively). Ranking probability based on the surface under the cumulative ranking curve (SUCRA) suggested that sarilumab 200 mg was most likely to achieve ACR 50 response rate, followed by sarilumab 200 mg plus MTX, sarilumab 150 mg plus MTX, adalimumab 40 mg, and MTX plus placebo (*Bae et al 2018).*
- In a Phase 3 trial, the percentage of patients who met criteria for RA disease remission was not significantly different in the Xeljanz (tofacitinib) groups (5 mg and 10 mg twice daily) vs placebo. However, significantly more patients in the tofacitinib groups did meet criteria for decrease of disease activity. The tofacitinib groups also had significant decreases in fatigue and pain (*Fleishmann et al 2012*). In another Phase 3 study, Xeljanz (tofacitinib), when administered with

background MTX, was superior to placebo with respect to all clinical outcomes. Although not directly compared to Humira (adalimumab), the clinical efficacy of tofacitinib was numerically similar to that observed with adalimumab. Safety of tofacitinib continues to be monitored for long term effects (*van Vollenhoven et al 2012*). The ORAL Scan trial showed the ACR 20 response rates at month 6 for patients receiving tofacitinib 5 mg and 10 mg twice daily were 51.5% and 61.8%, respectively, vs 25.3% for patients receiving placebo ($p < 0.0001$ for both comparisons) (*van der Heijde et al 2013*). Treatment effects were maintained through month 24 in the ORAL Scan trial, with an ACR 20 response rate of 50.5% and 58.3% for tofacitinib 5 mg and 10 mg twice daily, respectively (*van der Heijde et al 2019*). The ORAL START trial evaluated tofacitinib and MTX in 956 patients with active RA over 24 months. The primary endpoint of mean change from baseline in modified total Sharp score was significantly less with tofacitinib (0.6 for 5 mg; 0.3 for 10 mg) compared to MTX (2.1; $p < 0.001$) (*Lee et al 2014*). No radiographic progression was defined as a change from baseline in the modified total Sharp score of < 0.5 points. However, a minimal clinically important difference in modified total Sharp score is 4.6 points; this study did not meet this minimal clinical meaningful difference threshold.

- In the ORAL Step study, patients with RA who had an inadequate response to ≥ 1 TNF inhibitors were randomized to Xeljanz (tofacitinib) 5 mg or 10 mg twice daily or placebo; all patients were on MTX (*Burmester et al 2013a, Strand et al 2015a*). The primary outcome, ACR 20 response rate, was significantly higher with tofacitinib 5 mg (41.7%; 95% CI, 6.06 to 28.41; $p = 0.0024$) and 10 mg (48.1%; 95% CI, 12.45 to 34.92; $p < 0.0001$) compared to placebo (24.4%). Improvements in HAQ-DI was reported as -0.43 (95% CI, -0.36 to -0.157; $p < 0.0001$) for tofacitinib 5 mg and -0.46 (95% CI, -0.38 to -0.17; $p < 0.0001$) for tofacitinib 10 mg groups compared to -0.18 for placebo. Common AEs included diarrhea, nasopharyngitis, headache, and urinary tract infections in the tofacitinib groups.
- The approval of Olumiant (baricitinib) was based on 2 confirmatory, 24-week, phase 3 trials in patients with active RA. In RA-BEACON, enrolled patients (N = 527) had moderate to severe RA and an inadequate response or intolerance to ≥ 1 TNF antagonist(s) (*Genovese et al 2016*). Patients received baricitinib once daily or placebo along with continuing a stable dose of a conventional DMARD. The primary endpoint, ACR 20 response at week 12, was achieved by 49% and 27% of patients in the baricitinib 2 mg and placebo groups, respectively ($p \leq 0.001$). In RA-BUILD, enrolled patients (N = 684) had moderate to severe RA and an inadequate response or intolerance to ≥ 1 conventional DMARD(s) (*Dougados et al 2017*). Patients received baricitinib once daily or placebo; concomitant conventional DMARDs were permitted but not required. The primary endpoint, ACR20 response at week 12, was achieved by 66% and 39% of patients in the baricitinib 2 mg and placebo groups, respectively ($p \leq 0.001$).
- Approval of Rinvoq (upadacitinib) was based on clinical trials from the SELECT program in patients with RA. In SELECT-EARLY (n = 947), 52% of MTX-naïve patients treated with upadacitinib 15 mg daily achieved ACR 50 vs 28% treated with MTX at week 12, and at week 24, significantly more patients treated with upadacitinib 15 mg daily had no radiographic progression (87.5% vs 77.7%; $p < 0.01$) *(van Vollenhoven et al 2018)*. In SELECT-MONOTHERAPY (n = 648), 68% of patients with an inadequate response or intolerance to MTX (MTX-IR) treated with upadacitinib 15 mg daily achieved ACR 20 vs 41% treated with continued MTX at week 14 *(Smolen et al 2019)*. In SELECT-COMPARE, which evaluated MTX-IR patients (n = 1629), ACR 20 was significantly more frequent with upadacitinib 15 mg daily vs placebo and vs adalimumab at week 12 (70.5% vs 36.4% and 63%, respectively; $p < 0.001$ and $p < 0.05$) and at week 26 (67.4% vs 35.6% and 57.2%, respectively; $p <0.001$ and $p <0.01$). At week 26, significantly more patients treated with upadacitinib had no radiographic progression vs placebo (83.5% vs 76.0%; $p < 0.001$) *(Fleischman et al 2018)*. In SELECT-BEYOND (n = 499), 65% of biologic-IR patients treated with upadacitinib 15 mg daily plus conventional DMARDs achieved ACR 20 vs 28% treated with placebo plus conventional DMARDs at week 12 ($p <0.0001$) *(Genovese et al 2018)*. A network meta-analysis of the SELECT trials found that upadacitinib plus MTX was more effective than MTX alone, and upadacitinib 15 mg plus MTX was most likely to achieve the best ACR 20 response rate (followed by upadacitinib 30 mg plus MTX, adalimumab 40 mg plus MTX, upadacitinib 30 mg, upadacitinib 15 mg, and MTX, in order) (*Song and Lee 2020*).
- A 24-week, phase 3, double-blind trial explored the efficacy of upadacitinib compared with abatacept in 612 patients with RA. The mean change in the Disease Activity Score for 28 joints based on C-reactive protein (DAS28-CRP) was -2.52 in the upadacitinib group and -2.00 in the abatacept group from baseline to week 12 (difference, -0.52 points; 95% CI, -0.69 to -0.35; $p < 0.001$ for noninferiority; $p < 0.001$ for superiority). Additionally, 30% of patients in the upadacitinib group and 13.3% of patients in the abatacept group achieved remission (difference, 16.8%; 95% CI, 10.4 to 23.2; $p <$ 0.001 for superiority) (*Rubbert-Roth et al 2020*).
- Inflectra (infliximab-dyyb) was evaluated and compared to Remicade (infliximab; European Union formulation) in PLANETRA (N=606), a double-blind, multicenter, randomized trial (*Yoo et al 2013, Yoo et al 2016, Yoo et al 2017*). The primary endpoint, ACR 20 at week 30, was achieved by 58.6% and 60.9% of patients in the Remicade and Inflectra groups, respectively (treatment difference [TD], 2%; 95% CI, -6% to 10%) (intention-to-treat population). Corresponding

results in the per-protocol population were 69.7% and 73.4%, respectively (TD, 4%; 95% CI, -4% to 12%). Equivalence was demonstrated between the 2 products.
  - Secondary endpoints included several other disease activity scales and a quality-of-life scale; no significant differences were noted in any of these endpoints at either the 30-week or 54-week assessments.
  - In the extension study (n = 302) through 102 weeks, all patients received Inflectra. Response rates were maintained, with no differences between the Inflectra maintenance group and the group who switched from Remicade to Inflectra.
- Renflexis (infliximab-abda) was evaluated and compared to Remicade (infliximab; European Union formulation) in 584 patients in a double-blind, multicenter, randomized phase 3 trial (*Choe et al 2017*). The primary endpoint, ACR 20 at week 30, was achieved by 64.1% and 66.0% of patients in the Renflexis and Remicade groups, respectively (TD, -1.88%; 95% CI, -10.26% to 6.51%) (per-protocol population). Equivalence was demonstrated between the 2 products.
  - Secondary endpoints were also very similar between the 2 groups.
  - At week 54 of this trial, patients transitioned into the switching/extension phase, in which patients initially taking Remicade were re-randomized to continue Remicade or switch to Renflexis; patients initially taking Renflexis continued on the same treatment. Although slight numerical differences were observed, there was consistent efficacy over time across treatments and the proportions of patients achieving ACR responses were comparable between groups (*Renflexis FDA clinical review 2017*).
- Avsola (infliximab-axxq) was evaluated and compared to Remicade (infliximab) in 558 patients in a double-blind, multicenter, randomized equivalence trial (*Genovese et al 2020*). The primary endpoint, ACR 20 at week 22, was achieved by 68.1% and 59.1% of patients in the Avsola and Remicade groups, respectively (TD, 9.37%; 90% CI, 2.67% to 15.96%). The upper bound exceeded the pre-specified equivalence criteria by 0.96% such that superiority could not be ruled out statistically. In a post hoc analysis with adjustment for imbalances in baseline factors, the CI was narrowed (90% CI, 0.75% to 13.62%). Secondary endpoints were also very similar between the 2 groups.
- Two studies, 1 double-blind and 1 open-label, evaluated Rituxan (rituximab) in patients who had failed treatment with a TNF blocker (*Cohen et al 2006, Haraoui et al 2011*). All patients continued to receive MTX. Both studies showed > 50% of patients achieving ACR 20 response. AEs were generally mild to moderate in severity.
- A Cochrane review (*Lopez-Olivo et al 2015*) examined Rituxan (rituximab) for the treatment of RA. Eight studies and a total of 2720 patients were included. Rituximab plus MTX, compared to MTX alone, resulted in more patients achieving ACR 50 at 24 weeks (29% vs 9%, respectively) and clinical remission at 52 weeks (22% vs 11%). In addition, rituximab plus MTX compared to MTX alone resulted in more patients having no radiographic progression (70% vs 59% at 24 weeks, with similar results at 52 through 56 and 104 weeks). Benefits were also shown for physical function and quality of life (QoL).
- In the open-label ORBIT study (n = 295), adults with active, seropositive RA and an inadequate response to DMARDs who were biologic-naïve were randomized to either Rituxan (rituximab) (n = 144) or a TNF inhibitor (physician/patient choice of Enbrel [etanercept] or Humira [adalimumab]; n = 151) (*Porter et al 2016*). Medication doses were generally consistent with FDA-approved recommendations. Patients were able to switch over to the alternative treatment due to side effects or lack of efficacy. The primary endpoint was the change in DAS28-ESR in the per-protocol population at 12 months.
  - The changes in DAS28-ESR were -2.6 and -2.4 in patients in the rituximab and TNF inhibitor groups, respectively. The difference of -0.19 (95% CI, -0.51 to 0.13) was within the prespecified non-inferiority margin of 0.6 units. The authors concluded that initial treatment with rituximab was non-inferior to initial TNF inhibitor treatment in this patient population. However, interpretation of these results is limited due to the open-label study design and the high percentage of patients switching to the alternative treatment (32% in the TNF inhibitor group and 19% in the rituximab group). The indication for rituximab is limited to patients with an inadequate response to TNF inhibitor(s).
- Truxima (rituximab-abbs) was evaluated and compared to Rituxan (rituximab) in 372 patients in a double-blind, multicenter, randomized phase 3 trial (*Park et al 2018*). The primary efficacy endpoint, change from baseline in DAS28 based on C-reactive protein (CRP) at week 24, was -2.13 and -2.09 for Truxima and Rituxan, respectively (TD, -0.04; 95% CI, -0.29 to 0.21). Equivalence was demonstrated between the 2 products. Secondary endpoints were also very similar between the 2 groups.
  - In an extension of this study, 330 patients received a second 24-week course of their assigned study drug (Truxima or Rituxan) (*Suh et al 2019*). Mean change in DAS28-CRP from baseline to week 48 was similar between groups (-2.7 and -2.6 for Truxima and Rituxan, respectively). ACR 20/50/70 responses were also similar between groups at week 48.
  - After week 48, 295 patients entered a second extension phase that continued until week 72; during this extension phase, patients who were previously receiving Truxima or Rituxan (European Union formulation) received Truxima,

while patients who were previously receiving Rituxan (United States formulation) were randomized 1:1 to continue receiving Rituxan (United States formulation) or switch to Truxima (*Shim et al 2019*). All patients experienced similar improvements in disease activity parameters, including DAS28 and ACR response rates. Switching from Rituxan to Truxima did not result in any clinically meaningful efficacy differences.

- A randomized, open-label trial evaluated biologic treatments in patients with RA who had had an inadequate response to a TNF inhibitor (*Gottenberg et al 2016*). Patients (n = 300) were randomized to receive a second TNF inhibitor (n = 150) or a non-TNF-targeted biologic (n = 150) of the prescriber's choice. The second TNF inhibitors, in order of decreasing frequency, included Humira (adalimumab), Enbrel (etanercept), Cimzia (certolizumab), and Remicade (infliximab), and the non-TNF biologics included Actemra (tocilizumab), Rituxan (rituximab), and Orencia (abatacept). The primary endpoint was the proportion of patients with a good or moderate EULAR response at week 24, defined as a decrease in DAS28-ESR of > 1.2 points resulting in a score of ≤ 3.2.
  - At week 24, 52% of patients in the second anti-TNF group and 69% of patients in the non-TNF group achieved a good or moderate EULAR response (p = 0.003 or p = 0.004, depending on how missing data were handled). Secondary disease activity scores also generally supported better efficacy for the non-TNF biologics; however, HAQ scores did not differ significantly between groups. Among the non-TNF biologics, the proportion of EULAR good and moderate responders at week 24 did not significantly differ between abatacept, rituximab, and tocilizumab (67%, 61%, and 80%, respectively). There were 8 patients (5%) in the second TNF inhibitor group and 16 patients (11%) in the non-TNF biologic group that experienced serious AEs (p = 0.10), predominantly infections and cardiovascular events. There were some limitations to this trial; notably, it had an open-label design, and adherence may have differed between groups because all non-TNF biologics were given as infusions under observation and most of the TNF inhibitor drugs were self-injected by patients. The authors concluded that among patients with RA inadequately treated with TNF inhibitors, a non-TNF biologic was more effective in achieving a good or moderate disease activity response at 24 weeks; however, a second TNF inhibitor was also often effective in producing clinical improvement.
- Another recent randomized trial (*Manders et al 2015*) evaluated the use of Orencia (abatacept) (n = 43), Rituxan (rituximab) (n = 46), or a different TNF inhibitor (n = 50) in patients (n =139) with active RA despite previous TNF inhibitor treatment. Actemra (tocilizumab) was not included. In this trial, there were no significant differences with respect to DAS28, HAQ-DI, or SF-36 over the 1-year treatment period, and AEs also appeared similar. A cost-effectiveness analysis was also included in this publication, but results are not reported in this review.
- A Cochrane review examined Orencia (abatacept) for the treatment of RA. ACR 50 response was not significantly different at 3 months but was significantly higher in the abatacept group at 6 and 12 months compared to placebo (relative risk [RR], 2.47; 95% CI, 2 to 3.07 and RR, 2.21; 95% CI, 1.73 to 2.82). Similar results were seen in ACR 20 and ACR 70 (*Maxwell et al 2009*).
- The safety and efficacy of Humira (adalimumab) for the treatment of RA were assessed in a Cochrane systematic review. Treatment with adalimumab in combination with MTX was associated with a RR of 1.52 to 4.63, 4.63 (95% CI, 3.04 to 7.05) and 5.14 (95% CI, 3.14 to 8.41) for ACR 20, ACR 50, and ACR 70 responses, respectively, at 6 months when compared to placebo in combination with MTX. Adalimumab monotherapy was also proven efficacious (*Navarro-Sarabia et al 2005*). In another study, patients received adalimumab 20 mg or 40 mg every other week for 1 year, and then could receive 40 mg every other week for an additional 9 years. At Year 10, 64.2%, 49%, and 17.6% of patients achieved ACR 50, ACR 70, and ACR 90 responses, respectively (*Keystone et al 2013b*).
- A Phase 3, open-label study evaluated the long-term efficacy of Humira (adalimumab) for RA. Patients receiving adalimumab in 1 of 4 early assessment studies could receive adalimumab for up to 10 years in the extension study. Of 846 enrolled patients, 286 (33.8%) completed 10 years of treatment. In patients completing 10 years, adalimumab led to sustained clinical and functional responses, with ACR 20, ACR 50, and ACR 70 responses being achieved by 78.6%, 55.5%, and 32.8% of patients, respectively. The authors stated that patients with shorter disease duration achieved better outcomes, highlighting the need for early treatment. No unexpected safety findings were observed. This study demonstrated that some patients with RA can be effectively treated with adalimumab on a long-term basis; however, the study is limited by its open-label design, lack of radiographic data, and the fact that only patients who continued in the study were followed (*Furst et al 2015*).
- A Cochrane review was performed to compare Kineret (anakinra) to placebo in adult patients with RA. Significant improvements in both primary (ACR 20, 38% vs 23%; RR, 1.61; 95% CI, 1.32 to 1.98) and secondary (ACR 50 and ACR 70) outcomes were detected. The only significant difference in AEs noted with anakinra use was the rate of injection site reactions (71% vs 28% for placebo) (*Mertens et al 2009*).
- In another Cochrane review, Enbrel (etanercept) was compared to MTX or placebo in adult patients with RA and found that at 6 months, 64% of individuals on etanercept 25 mg twice weekly attained an ACR 20 vs 15% of patients on either

MTX alone or placebo (RR, 3.8; number needed to treat [NNT], 2). An ACR 50 and ACR 70 were achieved by 39% and 15%, respectively, in the etanercept group compared to 4% (RR, 8.89; NNT, 3) and 1% (RR, 11.31; NNT, 7) in the control groups, respectively. Etanercept 10 mg twice weekly was only associated with significant ACR 20 (51% vs 11% of controls; RR, 4.6; 95% CI, 2.4 to 8.8; NNT, 3) and ACR 50 responses (24% vs 5% of controls; RR, 4.74; 95% CI, 1.68 to 13.36; NNT, 5). Seventy-two percent of patients receiving etanercept had no increase in Sharp erosion score compared to 60% of MTX patients. Etanercept 25 mg was associated with a significantly reduced total Sharp score (weighted mean difference, -10.5; 95% CI, -13.33 to -7.67). The Sharp erosion scores and joint space narrowing were not significantly reduced by either etanercept dose (*Blumenauer et al 2003*). In a trial of 353 patients with RA, patients received a triple therapy combination of sulfasalazine, hydroxychloroquine and MTX or etanercept and MTX. Triple therapy was shown to be noninferior to etanercept + MTX (*O'Dell et al 2013*).

- A more recent Cochrane review (*Singh et al 2016a*) evaluated the benefits and harms of 10 agents for the treatment of RA in patients failing treatment with MTX or other DMARDs. Agents included Xeljanz (tofacitinib) and 9 biologics (Orencia [abatacept], Humira [adalimumab], Kineret [anakinra], Cimzia [certolizumab], Enbrel [etanercept], Simponi [golimumab], Remicade [infliximab], Rituxan [rituximab], and Actemra [tocilizumab]), each in combination with MTX or other DMARDS, compared to comparator agents such as DMARDs or placebo. Data from 79 randomized trials (total 32,874 participants) were included. Key results from this review are as follows:
  - ACR 50: Biologic plus MTX/DMARD was associated with a statistically significant and clinically meaningful improvement in ACR 50 vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics. Differences between treatments in individual comparisons were small.
  - HAQ: Biologic plus MTX/DMARD was associated with a clinically and statistically significant improvement in function measured by HAQ vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics.
  - Remission: Biologic plus MTX/DMARD was associated with clinically and statistically significantly greater proportion of patients achieving RA remission, defined by DAS < 1.6 or DAS28 < 2.6, vs comparators. TNF inhibitors did not differ significantly from non-TNF biologics.
  - Radiographic progression: Radiographic progression was statistically significantly reduced in those on biologic plus MTX/DMARD vs comparator. The absolute reduction was small and clinical relevance is uncertain.
  - Safety: Biologic plus MTX/DMARD was associated with a clinically significantly increased risk of serious AEs; statistical significance was borderline. TNF inhibitors did not differ significantly from non-TNF biologics.
- A similar Cochrane review focused on the use of biologic or Xeljanz (tofacitinib) monotherapy for RA in patients with traditional DMARD failure (*Singh et al 2016[b]*). A total of 41 randomized trials (n = 14,049) provided data for this review. Key results are as follows:
  - Biologic monotherapy was associated with a statistically significant and clinically meaningful improvement in ACR 50 and HAQ vs placebo and vs MTX or other DMARDs.
  - Biologic monotherapy was associated with a statistically significant and clinically meaningful greater proportion of patients with disease remission vs placebo.
  - Based on a single study, the reduction in radiographic progression was statistically significant for biologic monotherapy compared to active comparators, but the absolute reduction was small and of unclear clinical relevance.
- Another Cochrane review evaluated the use of biologics or Xeljanz (tofacitinib) in patients with RA who had been unsuccessfully treated with a previous biologic (*Singh et al 2017[a]*). The review included 12 randomized trials (n = 3,364). Key results are as follows:
  - Biologics, compared to placebo, were associated with statistically significant and clinically meaningful improvement in RA as assessed by ACR 50 and remission rates. Information was not available for HAQ or radiographic progression.
  - Biologics plus MTX, compared to MTX or other traditional DMARDs, were associated with statistically significant and clinically meaningful improvement in ACR 50, HAQ, and RA remission rates. Information was not available for radiographic progression.
  - There were no published data for tofacitinib monotherapy vs placebo.
  - Based on a single study, tofacitinib plus MTX, compared to MTX, was associated with a statistically significant and clinically meaningful improvement in ACR 50 and HAQ. RA remission rates were not statistically significantly different, and information was not available for radiographic progression.
- In another meta-analysis, ACR 20 and ACR 70 response rates for Xeljanz (tofacitinib) 5 mg and 10 mg were comparable to the other monotherapies (Orencia [abatacept], Humira [adalimumab], Kineret [anakinra], Cimzia [certolizumab], Enbrel [etanercept], Simponi [golimumab], Remicade [infliximab], Actemra [tocilizumab]) at 24 weeks (*Bergrath et al 2017*). ACR 50 response rates were also comparable for tofacitinib 10 mg and other monotherapies. At 24 weeks, ACR 20/50/70 response rates for the combination of tofacitinib 5 mg or 10 mg plus conventional DMARD were comparable to

other biologic plus conventional DMARD therapies except tofacitinib 5 mg plus conventional DMARD and tofacitinib 10 mg plus conventional DMARD were both superior to certolizumab 400 mg every 4 weeks plus conventional DMARD for achieving ACR 70 response (OR, 59.16; [95% CI, 2.70 to infinity]; and OR, 77.40; [95% CI, 3.53 to infinity], respectively).

- A Bayesian network meta-analysis of 5 randomized trials (n = 1,547) examined the efficacy and safety of tofacitinib, baricitinib, upadacitinib, filgotinib (not approved in the U.S.) and peficitinib (not approved in the U.S.) in patients with RA. The ranking probability based on SUCRA revealed the following agents with the highest probability to achieve the ACR 20 response rate: perficitinib 150 mg (highest probability) followed by peficitinib 100 mg, filgotinib 200 mg, filgotinib 100 mg, tofacitinib 5 mg, upadacitinib 15 mg, baricitinib 4 mg, and placebo *(Ho Lee at al 2020)*.
- A meta-analysis of 20 randomized trials (n = 8,982) assessed the efficacy of tofacitinib, baricitinib, and upadacitinib in patients with RA. Tofacitinib 10 mg (RR, 2.48; 95% CI, 1.97 to 3.14; p < 0.001) had to the highest ACR20 response rates followed by tofacitinib 5 mg (RR, 2.16; 95% CI, 1.81 to 2.58; p < 0.001). Tofacitinib displayed higher ACR 20 response rates compared with baricitinib and upadacitinib (*Wang et al 2020*).
- Another recent Cochrane review (*Hazlewood et al 2016*) compared MTX and MTX-based DMARD combinations for RA in patients naïve to or with an inadequate response to MTX; DMARD combinations included both biologic and non-biologic agents. A total of 158 studies and over 37,000 patients were included. Evidence suggested that efficacy was similar for triple DMARD therapy (MTX plus sulfasalazine plus hydroxychloroquine) and MTX plus most biologic DMARDs or Xeljanz (tofacitinib). MTX plus some biologics were superior to MTX in preventing joint damage in MTX-naïve patients, but the magnitude of effect was small.
- A network meta-analysis of individual patient data from 38 randomized controlled trials compared various MTX-biologic combinations for RA in patients with an inadequate response to MTX alone (*Janke et al 2020*). Anakinra plus MTX showed relatively less benefit than other combinations in terms of clinical remission or low disease activity, and certolizumab plus MTX showed relatively higher rates of serious adverse events or infections; however, differences between combinations were generally minor.
- An additional Cochrane review evaluated biologics for RA in patients naïve to MTX in 19 studies (*Singh et al 2017[b]*). Agents included in the review were Humira (adalimumab), Enbrel (etanercept), Simponi (golimumab), Remicade (infliximab), Orencia (abatacept), and Rituxan (rituximab). When combined with MTX, use of biologics showed a benefit in ACR 50 vs comparator (MTX/MTX plus methylprednisolone) (RR, 1.40; 95% CI, 1.30 to 1.49) and in RA remission rates (RR, 1.62; 95% CI, 1.33 to 1.98), but no difference was found for radiographic progression. When used without MTX, there was no significant difference in efficacy between biologics and MTX.
- A meta-analysis evaluated the efficacy of Remicade (infliximab) in combination with MTX compared to placebo plus MTX. There was a higher proportion of patients in the infliximab group that achieved an ACR 20 at 30 weeks compared to patients in the placebo group (RR, 1.87; 95% CI, 1.43 to 2.45). These effects were similar in the proportion of patients achieving ACR 50 and ACR 70 (RR, 2.68; 95% CI, 1.79 to 3.99 and RR, 2.68; 95% CI, 1.78 to 4.03) (*Wiens et al 2009*).
- Another meta-analysis of randomized controlled trials included Humira (adalimumab), Kineret (anakinra), Enbrel (etanercept), and Remicade (infliximab) with or without MTX. The odds ratio (OR) for an ACR 20 was 3.19 (95% CI, 1.97 to 5.48) with adalimumab, 1.7 (95% CI, 0.9 to 3.29) with anakinra, 3.58 (95% CI, 2.09 to 6.91) with etanercept and 3.47 (95% CI, 1.66 to 7.14) with infliximab compared to placebo. The OR to achieve an ACR 50 with adalimumab was 3.97 (95% CI, 2.73 to 6.07), 2.13 (95% CI, 1.27 to 4.22) with anakinra, 4.21 (95% CI, 2.74 to 7.43) and with etanercept 4.14 (95% CI, 2.42 to 7.46) compared to placebo. Further analysis of each agent against another was performed, and no significant difference was determined between individual agents in obtaining an ACR 20 and ACR 50. However, the TNF-blockers as a class showed a greater ACR 20 and ACR 50 response compared to anakinra (OR, 1.96; 95% CI, 1.03 to 4.01 and OR, 1.93; 95% CI,1.05 to 3.5; p < 0.05) (*Nixon et al 2007*).
- The Agency for Healthcare Research and Quality published a review of drug therapy to treat adults with RA (*Donahue et al 2012*). They concluded that there is limited head-to-head data comparing the biologics. Studies that are available are generally observational in nature or mixed treatment comparison meta-analysis. At this time, there appears to be no significant differences amongst the agents. Clinical trials have shown better efficacy with combination biologics and MTX and no additional increased risk of AEs. However, combinations of 2 biologic agents showed increased rate of serious AEs with limited or no increase in efficacy.
- A meta-analysis of 6 trials (n = 1,927) evaluated the efficacy of withdrawing biologics from patients with RA who were in sustained remission or had low disease activity (*Galvao et al 2016*). The biologics in the identified trials were TNF inhibitors, most commonly Enbrel (etanercept) or Humira (adalimumab). Compared to withdrawing the medication, continuing the biologic increased the probability of having low disease activity (RR, 0.66; 95% CI, 0.51 to 0.84) and remission (RR, 0.57; 95% CI, 0.44 to 0.74). Although outcomes were worse in patients withdrawing the biologic, the

investigators noted that almost half of the patients maintained a low disease activity after withdrawal. The authors suggested that further research is necessary to identify subgroups for which withdrawal may be more appropriate.

Ankylosing spondylitis (AS)

- The FDA approval of Humira (adalimumab) for the treatment of AS was based on 1 randomized, double-blind, placebo-controlled study (n = 315) in which a significantly greater proportion of patients achieved a 20% improvement in the Assessment of SpondyloArthritis International Society criteria (ASAS 20) (primary endpoint) with adalimumab (58% vs 21% with placebo; p < 0.001). A greater than 50% improvement in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score, a measure of fatigue severity, spinal and peripheral joint pain, localized tenderness, and morning stiffness that is considered clinically meaningful, was detected in 45% of adalimumab-treated patients compared to 16% of placebo-treated patients (p < 0.001) at week 12. This response was sustained through week 24, with 42% in the adalimumab group achieving a greater than or equal to 50% improvement in BASDAI score compared to 15% in the placebo group (p < 0.001) (*van der Heijde et al 2006*).
- In 2 double-blind, randomized, placebo-controlled trials, the efficacy of Enbrel (etanercept) was evaluated in patients with AS (*Calin et al 2004, Gorman et al 2002*). Etanercept had a significantly greater response to treatment compared to placebo (p < 0.001) (*Gorman et al 2002*). More patients achieved an ASAS 20 response compared to placebo (p < 0.001) (*Calin et al 2004*). An open-label extension study, evaluating the long-term safety and efficacy of etanercept in patients with AS, was conducted. Safety endpoints included AEs, serious AEs, serious infection, and death while efficacy endpoints included ASAS 20 response, ASAS 5/6 response and partial remission rates. After up to 192 weeks of treatment, the most common AEs were injection site reactions, headache, and diarrhea. A total of 71% of patients were ASAS 20 responders at week 96 and 81% of patients were responders at week 192. The ASAS 5/6 response rates were 61% at week 96 and 60% at week 144, and partial remission response rates were 41% at week 96 and 44% at week 192. Placebo patients who switched to etanercept in the open-label extension trial showed similar patterns of efficacy maintenance (*Davis et al 2008*). A multicenter, randomized, double-blind trial compared etanercept and sulfasalazine in adult patients with active AS that failed treatment with nonsteroidal anti-inflammatory drugs (NSAIDs). A significantly greater proportion of patients treated with etanercept compared to patients treated with sulfasalazine achieved the primary outcome of ASAS 20 at week 16 (p < 0.0001). There were also significantly more patients that achieved ASAS 40 and ASAS 5/6 in the etanercept group compared to the sulfasalazine group (p < 0.0001 for both) (*Braun et al 2011*).
- The FDA approval of Simponi (golimumab) for AS was based on a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with active disease for at least 3 months (n = 356). Golimumab with or without a DMARD was compared to placebo with or without a DMARD and was found to significantly improve the signs and symptoms of AS as demonstrated by the percentage of patients achieving an ASAS 20 response at week 14 (*Inman et al 2008*). Sustained improvements in ASAS 20 and ASAS 40 response rates were observed for up to 5 years in an open-label extension trial (*Deodhar et al 2015*). Safety profile through 5 years was consistent with other TNF inhibitors.
- The efficacy of Remicade (infliximab) in the treatment of AS was demonstrated in 12- and 24-week double-blind, placebo-controlled trials. There were significantly more patients that achieved a 50% BASDAI score in the infliximab group compared to the placebo group at 12 weeks (p < 0.0001) (*Braun et al 2002*), At 24 weeks, significantly more patients in the infliximab group achieved ASAS 20 compared to the placebo group (p < 0.001) (*van der Heijde et al 2005*).
- Inflectra (infliximab-dyyb) was evaluated alongside Remicade (infliximab; European Union formulation) for the treatment of AS in PLANETAS (n = 250), a double-blind, multicenter, randomized trial (*Park et al 2013, Park et al 2016, Park et al 2017*). The primary endpoints related to pharmacokinetic equivalence. Secondary efficacy endpoints supported similar clinical activity between Inflectra and Remicade. An ASAS 20 response was achieved by 72.4% and 70.5% of patients in the Remicade and Inflectra groups, respectively, at 30 weeks, and by 69.4% and 67.0% of patients at 54 weeks. Other disease activity endpoints and a quality-of-life scale were also similar between groups.
  - In the extension study (n = 174) through 102 weeks, all patients received Inflectra. From weeks 54 to 102, the proportion of patients achieving a clinical response was maintained at a similar level to that of the main study in both the maintenance and switch groups and was comparable between groups.
- The efficacy of Cimzia (certolizumab) for the treatment of AS was established in 1 randomized, double-blind, placebo-controlled study (n = 325) in which a significantly greater proportion of patients achieved ASAS 20 response with certolizumab 200 mg every 2 weeks and certolizumab 400 mg every 4 weeks compared to placebo at 12 weeks (*Landewe et at 2014*). Patient-reported outcomes measured by the SF-36, health-related quality of life (HRQoL), and reports of pain, fatigue and sleep were significantly improved with certolizumab in both dose groups (*Sieper et al 2015a*).

A Phase 3, randomized, placebo-controlled trial found that 62.5% of patients on certolizumab maintained ASAS 20 response to week 96 in a population of patients with axial spondyloarthritis, which includes AS (*Sieper et al 2015b*).

- The efficacy and safety of Cosentyx (secukinumab) were evaluated in the double-blind, placebo-controlled, randomized MEASURE 1 and 2 studies (*Baeten et al 2015*). MEASURE 1 enrolled 371 patients and MEASURE 2 enrolled 219 patients with active AS with radiologic evidence treated with NSAIDs. Patients were treated with secukinumab 75 or 150 mg SQ every 4 weeks (following IV loading doses) or placebo. The primary outcome, ASAS 20 response at week 16, was significantly higher in the secukinumab 75 mg (60%) and 150 mg (61%) groups compared to placebo (29%, $p < 0.001$ for each dose) for MEASURE 1. For MEASURE 2 at week 16, ASAS 20 responses were seen in 61% of the secukinumab 150 mg group, 41% of the 75 mg group, and 28% of the placebo group ($p < 0.001$ for secukinumab 150 mg vs placebo; $p = 0.10$ for secukinumab 75 mg vs placebo). Common AEs reported included nasopharyngitis, headache, diarrhea, and upper respiratory tract infections. Improvements were observed from week 1 and sustained through week 52. In a long-term extension of MEASURE 1, ASAS 20 response rates were 73.7% with secukinumab 150 mg and 68.0% with 75 mg at week 104 and in MEASURE 2, ASAS 20 response rates were 71.5% with both doses at week 104 (*Braun et al 2017, Marzo-Ortega et al 2017*). In a 3-year extension of MEASURE-1, ASAS 20/40 response rates were 80.2%/61.6% for secukinumab 150 mg and 75.5%/50.0% for secukinumab 75 mg at week 156 (*Baraliakos et al 2017*). Four-year results from MEASURE-1 demonstrated sustained efficacy with ASAS 20/40 response rates of 79.7%/60.8% and 71%/43.5% with secukinumab 150 mg and 75 mg, respectively, at week 208 (*Braun et al 2018*).
- The efficacy and safety of Taltz (ixekizumab) were evaluated in the phase 3 randomized, double-blind, placebo-controlled COAST-V and COAST-W trials. In total, 657 patients were studied in these trials, including biologic DMARD-naïve patients in COAST-V and patients with previous inadequate response or intolerance to TNF inhibitors in COAST-W. The primary endpoint in both trials, ASAS 40 response at week 16, was significantly improved with ixekizumab every 4 weeks vs placebo (48% vs 18% in COAST-V, $p < 0.0001$; 25% vs 13% in COAST-W, $p < 0.017$). Common adverse events included nasopharyngitis, upper respiratory tract infection, neutropenia, and infection *(van der Heijde et al 2018[a]; Deodhar et al 2019[a])*. The ASAS 40 response seen at week 16 was sustained through week 52 in both trials (*Dougados et al 2020*).
- In 2 systematic reviews of TNF blockers for the treatment of AS, patients taking Simponi (golimumab), Enbrel (etanercept), Remicade (infliximab), and Humira (adalimumab) were more likely to achieve ASAS 20 or ASAS 40 responses compared with patients from control groups. The RR of reaching ASAS 20 after 12 or 14 weeks was 2.21 (95% CI, 1.91 to 2.56) (*Machado et al 2013*). After 24 weeks, golimumab, etanercept, infliximab, and adalimumab were more likely to achieve ASAS 40 compared to placebo (*Maxwell et al 2015*). A systematic review and network meta-analysis evaluated biologic agents for the treatment of AS, including adalimumab, etanercept, golimumab, infliximab, Cosentyx (secukinumab), and Actemra (tocilizumab; not FDA-approved for AS) (*Chen et al 2016*). A total of 14 studies were included. Infliximab was ranked best and secukinumab second best for achievement of ASAS 20 response; however, differences among agents were not statistically significant with the exception of infliximab 5 mg compared to tocilizumab (OR, 4.81; 95% credible interval [CrI], 1.43 to 17.04). Safety endpoints were not included in this analysis.

Crohn's disease (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 greater than or equal to 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 for CD in patients who responded inadequately to immunomodulator therapy, TNF blockers, and/or corticosteroids. In 1 trial, a higher percentage of Entyvio-treated patients achieved clinical response and remission at week 52 compared to placebo. However, in the second trial, Entyvio did not achieve a statistically significant clinical response or clinical remission over placebo at week 6 (*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 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*).
- A systematic review of 8 randomized clinical trials with Tysabri (natalizumab) or Entyvio (vedolizumab) for the management of CD evaluated the rates of failure of remission induction (*Chandar et al 2015*). Fewer failures of remission induction were reported with natalizumab and vedolizumab compared to placebo (RR 0.87; 95% CI, 0.84 to 0.91; I^2=0%). The summary effect sizes were similar for both natalizumab (RR 0.86; 95% CI, 0.80 to 0.93) and vedolizumab (RR 0.87; 95% CI, 0.79 to 0.95). No significant difference was detected between the 2 active treatments (p = 0.95). No significant differences between natalizumab and vedolizumab were observed for rates of serious AEs, infections (including serious infections), and treatment discontinuation. Rates of infusion reactions in induction trials were more common with natalizumab over vedolizumab (p = 0.007). Progressive multifocal leukoencephalopathy (PML) has been reported with natalizumab but has not been reported with vedolizumab.
- 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 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 1,281 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.

Hidradenitis suppurativa (HS)

- Two 36-week, Phase 3, double-blind, multicenter, placebo-controlled, randomized trials, PIONEER I and II, evaluated Humira (adalimumab) for the treatment of HS (*Kimball et al 2016*). A total of 633 adults (307 in PIONEER I and 326 in PIONEER II) with moderate to severe HS were enrolled. The study consisted of 2 treatment periods; in the first period, patients were randomized to placebo or weekly adalimumab for 12 weeks; in the second period, patients initially assigned to placebo received weekly adalimumab (PIONEER I) or placebo (PIONEER II) for 24 weeks and patients initially assigned to adalimumab were re-randomized to placebo, weekly adalimumab, or every-other-week adalimumab. The adalimumab dosage regimen was 160 mg at week 0, followed by 80 mg at week 2, followed by 40 mg doses starting at week 4.
  - The primary endpoint was HS clinical response (HiSCR) at week 12, defined as at least 50% reduction in total abscess and inflammatory nodule count with no increase in abscess count and no increase in draining fistula count compared to baseline. HiSCR rates at week 12 were significantly higher for the groups receiving adalimumab than for the placebo groups: 41.8% vs 26.0% in PIONEER I (p = 0.003) and 58.9% vs 27.6% in PIONEER II (p < 0.001).
  - Among patients with a clinical response at week 12, response rates in all treatment groups subsequently declined over time. During period 2, there were no significant differences in clinical response rates in either trial between

patients randomly assigned to adalimumab at either a weekly dose or an every-other-week dose and those assigned to placebo, regardless of whether the patients had a response at week 12. For patients who received placebo in period 1, 41.4% of those assigned to adalimumab weekly in period 2 (PIONEER I) and 15.9% of those reassigned to placebo in period 2 (PIONEER II) had a clinical response at week 36.
  - The authors noted that the magnitude of improvement with adalimumab treatment was modest compared with adalimumab treatment in other disease states, and patients were unlikely to achieve complete symptom resolution.

Juvenile idiopathic arthritis (JIA)

- In a trial of pediatric patients (6 to 17 years of age) with JIA (extended oligoarticular, polyarticular, or systemic without systemic manifestations), the patients treated with placebo had significantly more flares than the patients treated with Orencia (abatacept) (p = 0.0003). The time to flare was significantly different favoring abatacept (p = 0.0002) (*Ruperto et al 2008*).
- Humira (adalimumab) was studied in a group of patients (4 to 17 years of age) with active polyarticular JIA who had previously received treatment with NSAIDs. Patients were stratified according to MTX use and received 24 mg/m^2 (maximum of 40 mg) of adalimumab every other week for 16 weeks. The patients with an American College of Rheumatology Pediatric 30 (ACR Pedi 30) response at week 16 were randomly assigned to receive adalimumab or placebo in a double-blind method every other week for up to 32 weeks. The authors found that 74% of patients not receiving MTX and 94% of those receiving MTX had an ACR Pedi 30 at week 16. Among those not receiving MTX, flares occurred in 43% receiving adalimumab and 71% receiving placebo (p = 0.03). In the patients receiving MTX, flares occurred in 37 and 65% in the adalimumab and placebo groups, respectively (p = 0.02). ACR Pedi scores were significantly greater with adalimumab than placebo and were sustained after 104 weeks of treatment (*Lovell et al 2008*).
- A double-blind, multicenter, randomized controlled trial compared Humira (adalimumab) and placebo in 46 children ages 6 to 18 years with enthesitis-related arthritis (*Burgos-Vargas et al 2015*). Patients were TNF inhibitor naïve. At week 12, the percentage change from baseline in the number of active joints with arthritis was significantly reduced with adalimumab compared to placebo (-62.6% vs -11.6%, p = 0.039). A total of 7 patients (3 placebo; 4 adalimumab) escaped the study early during the double-blind phase and moved to open-label adalimumab therapy. Analysis excluding these patients produced similar results (adalimumab, -83.3 vs placebo -32.1; p = 0.018). At week 52, adalimumab-treated patients had a mean reduction in active joint count from baseline of 88.7%. A total of 93.5% of patients achieved complete resolution of their swollen joints with a mean of 41 days of adalimumab therapy.
- In a trial involving 69 pediatric patients with active polyarticular JIA despite treatment with NSAIDs and MTX, Enbrel (etanercept) was associated with a significant reduction in flares compared to placebo (28% vs 81%; p = 0.003) (*Lovell et al 2000*). Ninety-four percent of patients who remained in an open-label 4 year extension trial met ACR Pedi 30; CRP levels, articular severity scores, and patient pain assessment scores all decreased. There were 5 cases of serious AEs related to etanercept therapy after 4 years (*Lovell et al 2006*).
- The approval of Actemra (tocilizumab) for the indication of SJIA was based on a randomized, placebo-controlled trial (n = 112). Children age 2 to 17 years of age with active SJIA and inadequate response to NSAIDs and corticosteroids were included in the study. The primary endpoint was ACR 30 and absence of fever at week 12. At week 12, the proportion of patients achieving ACR 30 and absence of fever was significantly greater in the tocilizumab-treated patients compared to the placebo treated patients (85% vs 24%; p < 0.0001) (*De Benedetti et al 2012*). The double-blind, randomized CHERISH study evaluated tocilizumab for JIA flares in patients ages 2 to 17 years with JIA with an inadequate response or intolerance to MTX (*Brunner et al 2015*). Tocilizumab-treated patients experienced significantly fewer JIA flares at week 40 compared to patients treated with placebo (25.6% vs 48.1%; p < 0.0024).
- The approval of Simponi Aria (IV golimumab) for polyarticular JIA was based on an open-label phase 3 study (n = 127). Children 2 to < 18 years of age with active polyarticular course JIA and inadequate response to MTX were enrolled. The primary endpoints were pharmacokinetic exposure and model-predicted steady-state area under the curve (AUC_{ss}) over an 8-week dosing interval at weeks 28 and 52. Other endpoints included ACR response rates. The ACR 30, 50, 70, and 90 response rates were 84%, 80%, 70%, and 47%, respectively, at week 28. Golimumab serum concentrations and AUC_{ss} were 0.40 mcg/mL and 399 mcg•day/mL at week 28. ACR response rates, serum concentrations, and AUC_{ss} were maintained at week 52 (*Ruperto et al 2021*).
- The approval of Xeljanz/Xeljanz oral solution (tofacitinib) for polyarticular JIA was based on a 44-week study (n = 225) that enrolled patients 2 to 17 years old with polyarticular course JIA and inadequate responses to at least 2 DMARDs. The primary endpoint was the occurrence of disease flare at week 44. Compared with patients receiving placebo, patients receiving tofacitinib experienced significantly fewer disease flares (31% with tofacitinib vs 55% with placebo; difference in proportions -25% [95% CI, -39% to -10%]; p = 0.0007) (*Xeljanz prescribing information 2020*).

- In 2 trials in patients with SJIA, Ilaris (canakinumab) was more effective at reducing flares than placebo. It also allowed for glucocorticoid dose tapering or discontinuation. More patients treated with canakinumab experienced infections than patients treated with placebo (*Ruperto et al 2012*). Patients enrolled in these trials were eligible for an open-label extension and were followed for 5 years. At 3 years, aJIA-ACR 50/70/90 response rates were 54.8%, 53.7%, and 49.7%, respectively (*Ruperto et al 2018*).
- A meta-analysis of trials evaluating biologics for the treatment of SJIA included 5 trials; 1 each for Kineret (anakinra), Ilaris (canakinumab), and Actemra (tocilizumab), and 2 for rilonacept (not FDA-approved for JIA and not included in this review) (*Tarp et al 2016*). The primary endpoint, the proportion of patients achieving a modified ACR Pedi 30 response, was superior to placebo for all agents, but did not differ significantly among anakinra, canakinumab, and tocilizumab. However, comparisons were based on low-quality, indirect evidence and no firm conclusions can be drawn on their relative efficacy. No differences among drugs for serious AEs were demonstrated.

Plaque psoriasis (PsO)

- In a randomized, double-blind, double-dummy trial, Humira (adalimumab) was compared to MTX and placebo in patients with moderate to severe PsO despite treatment with topical agents. The primary outcome was the proportion of patients that achieved Psoriasis Area and Severity Index (PASI) 75 at 16 weeks. Significantly more patients in the adalimumab group achieved the primary endpoint compared to patients in the MTX ($p < 0.001$) and placebo ($p < 0.001$) groups, respectively (*Saurat et al 2008*).
- More than 2,200 patients were enrolled in 2 published, pivotal, phase III trials that served as the primary basis for the FDA approval of Stelara (ustekinumab) in PsO. PHOENIX 1 and PHOENIX 2 enrolled patients with moderate to severe PsO to randomly receive ustekinumab 45 mg, 90 mg or placebo at weeks 0, 4, and every 12 weeks thereafter (*Leonardi et al 2008, Papp et al 2008, Langley et al 2015*). In PHOENIX 1, patients who were initially randomized to ustekinumab at week 0 and achieved long-term response (at least PASI 75 at weeks 28 and 40) were re-randomized at week 40 to maintenance ustekinumab or withdrawal from treatment. Patients in the 45 mg ustekinumab and 90 mg ustekinumab groups had higher proportion of patients achieving PASI 75 compared to patients in the placebo group at week 12 ($p < 0.0001$ for both). PASI 75 response was better maintained to at least 1 year in those receiving maintenance ustekinumab than in those withdrawn from treatment at week 40 ($p < 0.0001$) (*Leonardi et al 2008*). In PHOENIX 2, the primary endpoint (the proportion of patients achieving a PASI 75 response at week 12) was achieved in significantly more patients receiving ustekinumab 45 and 90 mg compared to patients receiving placebo ($p < 0.0001$). Partial responders were re-randomized at week 28 to continue dosing every 12 weeks or escalate to dosing every 8 weeks. More partial responders at week 28 who received 90 mg every 8 weeks achieved PASI 75 at week 52 than did those who continued to receive the same dose every 12 weeks. There was no such response to changes in dosing intensity in partial responders treated with 45 mg. AEs were similar between groups (*Papp et al 2008*). A total of 70% (849 of 1212) of ustekinumab-treated patients completed therapy through week 244. At week 244, the proportions of patients initially randomized to ustekinumab 45 mg and 90 mg who achieved PASI 75 were 76.5% and 78.6%, respectively. A total of 50.0% and 55.5% of patients, respectively, achieved PASI 90 (*Langley et al 2015*).
- In a study comparing Enbrel (etanercept) and Stelara (ustekinumab), a greater proportion of PsO patients achieved the primary outcome (PASI 75 at week 12) with ustekinumab 45 (67.5%) and 90 mg (73.8%) compared to etanercept 50 mg (56.8%; $p = 0.01$ vs ustekinumab 45 mg; $p < 0.001$ vs ustekinumab 90 mg). In this trial, etanercept therapy was associated with a greater risk of injection site erythema (14.7% vs 0.7% of all ustekinumab patients) (*Griffiths et al 2010).*
- Approval of Otezla (apremilast) for moderate to severe PsO was based on results from the ESTEEM trials. In the trials, 1,257 patients with moderate to severe PsO were randomized 2:1 to apremilast 30 mg twice daily (with a titration period) or placebo. The primary endpoint was the number of patients with a 75% improvement on the PASI 75. In ESTEEM 1, significantly more patients receiving apremilast achieved PASI 75 compared to placebo (33.1% vs 5.3%; $p < 0.0001$) at 16 weeks. In ESTEEM 2, significantly more patients receiving apremilast also achieved PASI 75 compared to placebo (28.8% vs 5.8%; $p < 0.0001$) at 16 weeks (*Papp et al 2015, Paul et al 2015a*).
  - Additional analyses of the ESTEEM trials have been published. In 1 analysis (*Thaçi et al 2016*), the impact of apremilast on HRQoL, general function, and mental health was evaluated using patient-reported outcome assessments. The study demonstrated improvement with apremilast vs placebo, including improvements on the dermatology life quality index (DLQI) and SF-36 mental component summary (MCS) that exceeded minimal clinically important differences. In another analysis (*Rich et al 2016*), effects of apremilast on difficult-to-treat nail and scalp psoriasis were evaluated. At baseline in ESTEEM 1 and ESTEEM 2, respectively, 66.1% and 64.7% of patients had nail psoriasis and 66.7% and 65.5% had moderate to very severe scalp psoriasis. At week 16, apremilast produced greater improvements in Nail Psoriasis Severity Index (NAPSI) score vs placebo; greater NAPSI-50 response (50%

reduction from baseline in target nail NAPSI score) vs placebo; and greater response on the Scalp Physician Global Assessment (ScPGA) vs placebo. Improvements were generally maintained over 52 weeks in patients with a PASI response at week 32.

- Otezla (apremilast) has additionally been studied in patients with moderate to severe PsO of the scalp in the phase IIIb, double-blind, randomized, placebo-controlled STYLE trial. In this trial, 303 patients with moderate to severe scalp PsO who had an inadequate response to 1 or more topical scalp therapies were randomized 2:1 to receive apremilast 30 mg twice daily (with a titration period) or placebo for 16 weeks. The primary endpoint was the proportion of patients achieving ScPGA response (score of 0 or 1 with a ≥ 2-point reduction from baseline) at week 16. Patients receiving apremilast were more likely to achieve ScPGA response at week 16 (43.3% vs 13.7%; $p < 0.0001$) (*Van Voorhees et al 2020*).
- Cosentyx (secukinumab) was evaluated in 2 large, phase 3, double-blind trials in patients with moderate to severe PsO. The co-primary endpoints were the proportions of patients achieving PASI 75 and the proportions of patients with clear or almost clear skin (score 0 or 1) on the modified investigator's global assessment (IGA) at 12 weeks.
  - In ERASURE (n = 738), 81.6%, 71.6%, and 4.5% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 65.3%, 51.2%, and 2.4% achieved a score of 0 or 1 on the IGA (*Langley et al 2014*).
  - In FIXTURE (n = 1306), 77.1%, 67%, 44%, and 4.9% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, Enbrel (etanercept) at FDA-recommended dosing, and placebo, respectively, and 62.5%, 51.1%, 27.2%, and 2.8% achieved a score of 0 or 1 on the IGA (*Langley et al 2014*).
- Two smaller, phase 3, double-blind, placebo-controlled trials evaluated Cosentyx (secukinumab) given by prefilled syringe (FEATURE) or auto-injector/pen (JUNCTURE). Again, co-primary endpoints were the proportions of patients achieving PASI 75 and obtaining a score of 0 or 1 on the modified IGA at 12 weeks.
  - In FEATURE (n = 177), 75.9%, 69.5%, and 0% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 69%, 52.5%, and 0% achieved a score of 0 or 1 on the IGA (*Blauvelt et al 2015*).
  - In JUNCTURE (n = 182), 86.7%, 71.7%, and 3.3% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, and placebo, respectively, and 73.3%, 53.3%, and 0% achieved a score of 0 or 1 on the IGA (*Paul et al 2015b*).
- Secondary endpoints, including the proportions of patients demonstrating a reduction of 90% or more on the PASI (PASI 90), a reduction of 100% (PASI 100), and change in the DLQI further support the efficacy of Cosentyx (secukinumab) (*Blauvelt et al 2015, Langley et al 2014, Paul et al 2015b*).
- In the CLEAR study, Cosentyx (secukinumab) 300 mg SQ every 4 weeks and Stelara (ustekinumab) 45 mg or 90 mg SQ (based on body weight) every 12 weeks were compared for safety and efficacy in a double-blind, randomized controlled trial in 676 patients with moderate to severe PsO (*Thaçi et al 2015*). The primary endpoint, proportion of patients achieving PASI 90 at week 16, was significantly higher with secukinumab compared to ustekinumab (79% vs 57.6%; $p < 0.0001$). Achievement of PASI 100 response at week 16 was also significantly higher with secukinumab over ustekinumab (44.3% vs 28.4%; $p < 0.0001$). Infections and infestations were reported in 29.3% of secukinumab- and 25.3% of ustekinumab-treated patients. Most infections were not serious and were managed without discontinuation. The most commonly reported AEs included headache and nasopharyngitis. Serious AEs were reported in 3% of each group.
- Cosentyx (secukinumab) and Stelara (ustekinumab) were also compared in the 16-week randomized, double-blind CLARITY trial, which included 1102 patients with moderate to severe PsO. The co-primary endpoints were proportion of patients achieving PASI 90 response at week 12 and modified IGA score of 0/1 at week 12. Secukinumab was found be to superior to ustekinumab for both PASI 90 response (66.5% vs 47.9%; $p < 0.0001$) and modified IGA score of 0/1 (72.3% vs 55.3%; $p < 0.0001$) (*Bagel et al 2018*).
- A meta-analysis of 7 Phase 3 clinical trials demonstrated the efficacy of Cosentyx (secukinumab) vs placebo and vs Enbrel (etanercept) in patients with PsO (*Ryoo et al 2016*). The ORs for achieving PASI 75 and for achieving IGA 0 or 1 were both 3.7 for secukinumab vs etanercept. Secukinumab 300 mg was significantly more effective than 150 mg. Secukinumab was well-tolerated throughout the 1-year trials.
- The use of Taltz (ixekizumab) for the treatment of PsO was evaluated in the UNCOVER-1, UNCOVER-2, and UNCOVER-3 trials. All were Phase 3, double-blind, randomized trials.
  - UNCOVER-1 (n = 1296) compared ixekizumab 160 mg loading dose then 80 mg every 2 weeks, ixekizumab 160 mg loading dose then 80 mg every 4 weeks, and placebo (*Gordon et al 2016, Taltz product dossier 2016*). Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving a physician's

global assessment (PGA) score of 0 or 1 (clear or almost clear) at week 12. In the ixekizumab every 2 week, ixekizumab every 4 week, and placebo groups, PASI 75 was achieved by 89.1%, 82.6%, and 3.9% of patients, respectively ($p < 0.001$ for both doses vs placebo), and PGA 0 or 1 was achieved by 81.8%, 76.4%, and 3.2% of patients, respectively ($p < 0.001$ for both doses vs placebo). Improvements for ixekizumab vs placebo were also seen in secondary endpoints including PASI 90, PASI 100, PGA 0, and change in DLQI.
  - UNCOVER-2 (n = 1224) compared ixekizumab 160 mg loading dose then 80 mg every 2 weeks, ixekizumab 160 mg then 80 mg every 4 weeks, etanercept 50 mg twice weekly, and placebo (*Griffiths et al 2015*). Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving a PGA 0 or 1 at week 12. The proportions of patients achieving PASI 75 were 89.7%, 77.5%, 41.6%, and 2.4% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). The proportions of patients achieving PGA 0 or 1 were 83.2%, 72.9%, 36%, and 2.4% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). Improvements were also greater for ixekizumab vs placebo, etanercept vs placebo, and ixekizumab vs etanercept for all secondary endpoints including PGA 0, PASI 90, PASI 100, and DLQI.
  - UNCOVER-3 (n = 1346) had the same treatment groups and primary and secondary endpoints as UNCOVER-2 (*Griffiths et al 2015*). The proportions of patients achieving PASI 75 were 87.3%, 84.2%, 53.4%, and 7.3% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). The proportions of patients achieving PGA 0 or 1 were 80.5%, 75.4%, 41.6%, and 6.7% in the ixekizumab every 2 week, ixekizumab every 4 week, etanercept, and placebo groups, respectively ($p < 0.0001$ for all active treatments vs placebo and for both ixekizumab arms vs etanercept). Improvements were also greater for ixekizumab vs placebo, etanercept vs placebo, and ixekizumab vs etanercept for all secondary endpoints including PGA 0, PASI 90, PASI 100, and DLQI.
  - Results through week 60 for UNCOVER-1, UNCOVER-2, and UNCOVER-3 have been reported (*Gordon et al 2016*). At week 12 in UNCOVER-1 and UNCOVER-2, patients responding to ixekizumab (PGA 0 or 1) were re-randomized to receive ixekizumab 80 mg every 4 weeks, ixekizumab 80 mg every 12 weeks, or placebo through week 60. Among the patients who were randomly reassigned at week 12 to receive 80 mg of ixekizumab every 4 weeks (the approved maintenance dosing), 80 mg of ixekizumab every 12 weeks, or placebo, a PGA score of 0 or 1 was maintained by 73.8%, 39.0%, and 7.0% of the patients, respectively, and high rates were maintained or attained for additional measures such as PASI 75, PASI 90, and PASI 100 (pooled data for UNCOVER-1 and UNCOVER-2). At week 12 in UNCOVER-3, patients entered a long-term extension period in which they received ixekizumab 80 mg every 4 weeks through week 60. At week 60, at least 73% had a PGA score of 0 or 1 and at least 80% had a PASI 75 response. In addition, most patients had maintained or attained PASI 90 or PASI 100 at week 60.
- The IXORA-Q study (n = 149) evaluated the efficacy of Taltz (ixekizumab) to placebo in patients with moderate-to-severe genital psoriasis. At week 12, ixekizumab was superior to placebo for the primary endpoint of the proportion of patients achieving a score of 0 or 1 on the static PGA of genitalia (73% vs 8%, $p < 0.001$) (*Ryan et al 2018*).
- The IXORA-S study (n = 676) was a head-to-head study that compared Taltz (ixekizumab) (160 mg LD, then 80 mg every 2 weeks for 12 weeks, then 80 mg every 4 weeks) to Stelara (ustekinumab) (45 mg or 90 mg weight-based dosing per label) (*Reich et al 2017[b]).* The primary endpoint, PASI 90 response at week 12, was achieved by 72.8% and 42.2% of patients in the ixekizumab and ustekinumab groups, respectively ($p < 0.001$); superior efficacy of ixekizumab was maintained through week 24. Response rates for PASI 75, PASI 100, and PGA 0 or 1 also favored ixekizumab over ustekinumab (adjusted $p < 0.05$).
- The use of Siliq (brodalumab) for the treatment of PsO was evaluated in the AMAGINE-1, AMAGINE-2, and AMAGINE-3 trials. All were Phase 3, double-blind, randomized trials.
  - AMAGINE-1 (n = 661) compared brodalumab 210 mg, brodalumab 140 mg, and placebo; each treatment was given at weeks 0, 1, and 2, followed by every 2 weeks to week 12 (*Papp et al 2016*). This 12-week induction phase was followed by a withdrawal/retreatment phase through week 52: patients receiving brodalumab who achieved PGA 0 or 1 (PGA success) were re-randomized to the placebo or induction dose, and patients randomized to brodalumab with PGA ≥ 2 and those initially receiving placebo received brodalumab 210 mg every 2 weeks. Patients in the withdrawal phase who had disease recurrence (PGA ≥ 3) between weeks 16 and 52 were retreated with their induction doses of brodalumab. Co-primary endpoints were the proportion of patients achieving PASI 75 and the proportion of patients achieving PGA success at week 12. PASI 75 was achieved by 83% (95% CI, 78 to 88), 60% (95% CI, 54 to 67), and 3% (95% CI, 1 to 6) of patients in the brodalumab 210 mg, brodalumab 140 mg, and placebo groups, respectively; PGA success was achieved by 76% (95% CI, 70 to 81), 54% (95% CI, 47 to 61), and 1% (95% CI, 0 to 4),

respectively (p < 0.001 for all comparisons of brodalumab vs placebo). Differences in key secondary endpoints at week 12 also favored brodalumab vs placebo, including PASI 90, PASI 100, and PGA 0. In the randomized withdrawal phase, high response rates were maintained in those who continued brodalumab, while most patients re-randomized to placebo experienced return of disease (but were able to recapture disease control with retreatment).

- AMAGINE-2 (n = 1831) and AMAGINE-3 (n = 1881) were identical in design and compared brodalumab 210 mg, brodalumab 140 mg, Stelara (ustekinumab), and placebo (*Lebwohl et al 2015*). Brodalumab was given at weeks 0, 1, and 2, followed by every 2 weeks to week 12. Ustekinumab was given in weight-based doses per its FDA-approved labeling. At week 12, patients receiving brodalumab were re-randomized to receive brodalumab at a dose of 210 mg every 2 weeks or 140 mg every 2, 4, or 8 weeks; patients receiving ustekinumab continued ustekinumab; and patients receiving placebo were switched to brodalumab 210 mg every 2 weeks; maintenance continued though week 52. The primary endpoints included a comparison of both brodalumab doses vs placebo with regard to the proportion of patients achieving PASI 75 and the proportion of patients achieving PGA success (PGA 0 or 1) at week 12, as well as a comparison of brodalumab 210 mg vs ustekinumab with regard to the proportion of patients achieving PASI 100 at week 12.
  - In AMAGINE-2, the proportion of patients achieving PASI 75 was 86% (95% CI, 83 to 89), 67% (95% CI, 63 to 70), 70% (95% CI, 65 to 75), and 8% (95% CI, 5 to 12) in the brodalumab 210 mg, brodalumab 140 mg, ustekinumab, and placebo groups, respectively, and the proportion of patients achieving PGA success was 79% (95% CI, 75 to 82), 58% (95% CI, 54 to 62), 61% (95% CI, 55 to 67), and 4% (95% CI, 2 to 7), respectively (p < 0.001 for all comparisons of brodalumab vs placebo). The proportion of patients achieving PASI 100 was 44% (95% CI, 41 to 49), 26% (95% CI, 22 to 29), 22% (95% CI, 17 to 27), and 1% (95% CI, 0 to 2), respectively (p < 0.001 for both brodalumab doses vs placebo and for brodalumab 210 mg vs ustekinumab; p = 0.08 for brodalumab 140 mg vs ustekinumab). After week 52, patients receiving ustekinumab or placebo were switched to brodalumab and treatment was continued to week 120 (*Puig et al 2020*). At 120 weeks, 84.4%, 75.6%, and 61.1% of patients achieved PASI 75, PASI 90, and PASI 100, respectively, with brodalumab treatment.
  - In AMAGINE-3, the proportion of patients achieving PASI 75 was 85% (95% CI, 82 to 88), 69% (95% CI, 65 to 73), 69% (95% CI, 64 to 74), and 6% (95% CI, 4 to 9) in the brodalumab 210 mg, brodalumab 140 mg, ustekinumab, and placebo groups, respectively, and the proportion of patients achieving PGA success was 80% (95% CI, 76 to 83), 60% (95% CI, 56 to 64), 57% (95% CI, 52 to 63), and 4% (95% CI, 2 to 7), respectively (p < 0.001 for all comparisons of brodalumab vs placebo). The proportion of patients achieving PASI 100 was 37% (95% CI, 33 to 41), 27% (95% CI, 24 to 31), 19% (95% CI, 14 to 23), and 0.3% (95% CI, 0 to 2), respectively (p < 0.001 for both brodalumab doses vs placebo and for brodalumab 210 mg vs ustekinumab; p = 0.007 for brodalumab 140 mg vs ustekinumab).
  - In both studies, the 2 brodalumab doses were superior to placebo with regard to all key secondary endpoints. Patients receiving brodalumab 210 mg throughout the induction and maintenance phases demonstrated an increase in PASI response rates through week 12 and a stabilization during weeks 16 to 52. Based on PGA success rates, maintenance with brodalumab 210 mg or 140 mg every 2 weeks was superior to the use of the less frequent maintenance regimens, and the 210 mg regimen was superior to the 140 mg regimen.

- The use of Tremfya (guselkumab) for the treatment of moderate to severe PsO was evaluated in the VOYAGE 1, VOYAGE 2, NAVIGATE, and ECLIPSE trials. All were phase 3, double-blind, randomized trials.
  - Patients in both VOYAGE 1 and VOYAGE 2 were initially assigned to receive guselkumab (100 mg at weeks 0 and 4, then every 8 weeks), placebo, or Humira (adalimumab) (80 mg at week 0, 40 mg at week 1, then every 2 weeks). Patients in the placebo group were switched to guselkumab at week 16. The coprimary endpoints included the proportion of patients achieving an IGA score of 0 or 1 at week 16 as well as the proportion of patients achieving a PASI 90 response at week 16 in the guselkumab group compared with placebo. Comparisons between guselkumab and adalimumab were assessed as secondary endpoints at weeks 16, 24, and 48. To evaluate maintenance and durability of response in VOYAGE 2, subjects randomized to guselkumab at week 0 and who were PASI 90 responders at week 28 were re-randomized to either continue treatment with guselkumab every 8 weeks or be withdrawn from therapy (ie, receive placebo).
    - In VOYAGE 1 (n = 837), IGA 0 or 1 was achieved in more patients treated with guselkumab (85.1%) compared to placebo (6.9%) at week 16 (p < 0.001), and a higher percentage of patients achieved PASI 90 with guselkumab (73.3%) compared to placebo (2.9%; p<0.001) (*Blauvelt et al 2017*). Additionally, IGA 0 or 1 was achieved in more patients with guselkumab vs adalimumab at week 16 (85.1% vs 65.9%), week 24 (84.2% vs 61.7%), and week 48 (80.5% vs 55.4%; p < 0.001). PASI 90 score was also achieved in a higher percentage of patients with guselkumab

vs adalimumab at week 16 (73.3% vs 49.7%), week 24 (80.2% vs 53%), and week 48 (76.3% vs 47.9%; p < 0.001).
    - In VOYAGE 2 (n = 992), IGA 0 or 1 and PASI 90 were achieved by a higher proportion of patients who received guselkumab (84.1% and 70%) vs placebo (8.5% and 2.4%) (p < 0.001 for both comparisons). At week 16, IGA score of 0 or 1 and PASI 90 were achieved in more patients with guselkumab (84.1% and 70%) vs adalimumab (67.7% and 46.8%) (p < 0.001). PASI 90 was achieved in 88.6% of patients who continued on guselkumab vs 36.8% of patients who were rerandomized to placebo at week 48. In patients who were nonresponders to adalimumab and switched to guselkumab, PASI 90 was achieved by 66.1% of patients.
  - In NAVIGATE (n = 871), patients were assigned to open-label ustekinumab 45 or 90 mg at weeks 0 and 4 (*Langley et al 2018*). Patients with IGA 0 or 1 at week 16 were continued on ustekinumab, while patients with an inadequate response to ustekinumab at week 16 (IGA ≥ 2) were randomized to blinded guselkumab 100 mg or ustekinumab. Patients treated with guselkumab had a higher mean number of visits with IGA of 0 or 1 and ≥ 2-grade improvement (relative to week 16) compared to randomized ustekinumab from week 28 to 40 (1.5 vs 0.7; p < 0.001). A higher proportion of patients achieved IGA of 0 or 1 with ≥ 2 grade improvement at week 28 with guselkumab (31.1%) vs randomized ustekinumab (14.3%; p = 0.001); at week 52, 36.2% of guselkumab-treated patients achieved this response vs 17.3% of the ustekinumab-treated patients. The proportion of patients with PASI 90 response at week 28 was 48.1% for the guselkumab group vs 22.6% for the ustekinumab group (p ≤ 0.001).
  - In ECLIPSE (n = 1048), patients with moderate-to-severe plaque PsO were randomly assigned to Tremfya (guselkumab) 100 mg SQ at weeks 0 and 4 and then every 8 weeks (n = 534) or Cosentyx (secukinumab) 300 mg SQ at weeks 0, 1, 2, 3, and 4, and then every 4 weeks (n = 514) (*Reich et al 2019[a]*). Results revealed that the proportion of patients with a PASI 90 response at week 48 was greater in the guselkumab group as compared to the secukinumab group (84% vs 70%; p < 0.0001). The proportion of patients with adverse events, infections, and serious adverse events were similar between the treatments.
- The approval of Ilumya (tildrakizumab-asmn) was based on 2 randomized, double-blind, multicenter, phase 3 trials: reSURFACE1 (772 patients) and reSURFACE2 (1,090 patients). Enrolled adult patients with moderate-to-severe chronic PsO received tildrakizumab-asmn 200 mg, tildrakizumab-asmn 100 mg, or placebo in both studies; reSURFACE 2 also included an Enbrel (etanercept) arm. Only the tildrakizumab-asmn 100 mg dose was approved by the FDA. The coprimary endpoints included the proportion of patients achieving PASI 75 and PGA response (score of 0 or 1 with ≥ 2 reduction from baseline) at week 12 (*Reich et al 2017[a]*).
  - In reSURFACE 1, PASI 75 response was achieved by 64% and 6% of the tildrakizumab-asmn 100 mg and placebo arms at week 12, respectively; a PGA response was achieved by 58% vs 7% of the tildrakizumab-asmn 100 mg and placebo groups, respectively (p < 0.0001 for both comparisons).
  - In reSURFACE 2, PASI 75 response was achieved by 61% and 6% of the tildrakizumab-asmn 100 mg and placebo arms, respectively; a PGA response was achieved by 55% vs 4% of the tildrakizumab-asmn 100 mg and placebo groups, respectively (p < 0.0001 for both comparisons). A higher proportion of patients in the tildrakizumaz 100 mg group achieved PASI 75 vs etanercept (61% vs 48%, respectively; p = 0.001), but the rates of PGA responses did not differ significantly between groups (55% vs 48%, respectively; p = 0.0663).
- The approval of Skyrizi (risankizumab-rzaa) was based on 4 randomized, double-blind, multicenter trials. In two replicate placebo- and active-controlled trials (UltIMMa-1 and -2), patients with moderate to severe chronic PsO (n = 997) assigned to risankizumab 150 mg every 12 weeks experienced significantly higher rates of PASI 90 response at week 16 (75.3% and 74.8% in UltIMMa-1 and -2, respectively) vs patients assigned to placebo (4.9% and 2.0% in UltIMMa-1 and -2, respectively) and Stelara (ustekinumab) 45 or 90 mg (42.0% and 47.5% in UltIMMa-1 and -2, respectively; p < 0.0001 for both comparisons from both trials) *(Gordon et al 2018)*. In an active controlled trial (IMMvent) in patients with moderate-to-severe chronic PsO (n = 605), PASI 90 was achieved by 72% of patients receiving risankizumab-rzaa vs 47% receiving Humira (adalimumab) (p < 0.0001) at week 16 (*Reich et al 2019[b]*). In a trial with a randomized withdrawal and retreatment design (IMMhance) (n = 507), PASI 90 was achieved by 73.2% of risankizumab-rzaa-treated patients vs 2.0% of placebo-treated patients (p < 0.001) at week 16 (*Langley et al 2019)*
- For most immunomodulators that are FDA-approved for the treatment of PsO, the indication is limited to adults. In 2016, Enbrel (etanercept) received FDA approval for treatment of PsO in pediatric patients age ≥ 4 years. Limited information from published trials is also available on the use of Stelara (ustekinumab) and Taltz (ixekizumab) in pediatric patients (age 6 to 17 years).
  - A 48-week, double-blind, placebo-controlled trial (n = 211) evaluated the use of etanercept in patients 4 to 17 years of age with moderate-to-severe PsO (*Paller et al 2008*). Patients received etanercept 0.8 mg SQ once weekly or placebo for 12 weeks, followed by 24 weeks of open-label etanercept; 138 patients underwent a second

randomization to placebo or etanercept at week 36 to investigate effects of withdrawal and retreatment. The primary endpoint, PASI 75 at week 12, was achieved by 57% and 11% of patients receiving etanercept and placebo, respectively. A significantly higher proportion of patients in the etanercept group than in the placebo group achieved PASI 90 (27% vs 7%) and a PGA of 0 or 1 (53% vs 13%) at week 12 ($p < 0.001$). During the withdrawal period from week 36 to week 48, response was lost by 29 of 69 patients (42%) assigned to placebo at the second randomization. Four serious AEs (including 3 infections) occurred in 3 patients during treatment with open-label etanercept; all resolved without sequelae. The authors concluded that etanercept significantly reduced disease severity in this population. Results of a 5-year, open-label extension study (n = 182) demonstrated that etanercept was generally well tolerated and efficacy was maintained in those who remained in the study for up to 264 weeks (69 of 181 patients) (*Paller et al 2016*).

- A 52-week, double-blind, placebo-controlled trial (n = 110) evaluated the use of ustekinumab in patients 12 to 17 years of age with moderate-to-severe PsO (*Landells et al 2015*). Patients received a weight-based standard dose (SD), a half-strength dose (HSD), or placebo. The primary endpoint, the proportion of patients achieving a PGA 0 or 1 at week 12, was significantly greater in the SD (69.4%) and HSD (67.6%) groups vs placebo (5.4%) ($p < 0.001$ for both doses vs placebo). The proportions of patients achieving PASI 75 at this time point were 80.6%, 78.4%, and 10.8% in the SD, HSD, and placebo groups, respectively ($p < 0.001$ for both doses vs placebo), and the proportions of patients achieving PASI 90 were 61.1%, 54.1%, and 5.4% in the SD, HSD, and placebo groups, respectively ($p < 0.001$ for both doses vs placebo). In both groups, the proportions of patients achieving these endpoints were maintained from week 12 through week 52. The authors concluded that ustekinumab appears to be a viable treatment option for moderate-to-severe PsO in the adolescent population. The standard dose provided a response comparable to that in adults with no unexpected AEs through 1 year of treatment.
- An open-label, single arm, multicenter, phase 3 trial evaluated the efficacy and safety of ustekinumab in patients 6 to < 12 years of age with moderate to severe PsO (*Philipp et al 2020*). A total of 44 patients received weight-based ustekinumab at weeks 0 and 4, then every 12 weeks through week 40. At week 12, 77% of patients achieved PGA 0 or 1, 84% achieved PASI 75, and 64% achieved PASI 90. No new safety concerns were identified.
- The IXORA-PEDS study (n = 171) evaluated the efficacy of Taltz (ixekizumab) in pediatric patients aged 6 to < 18 years with moderate to severe PsO (*Paller et al 2020*). At week 12, weight-based ixekizumab every 4 weeks was superior to placebo for the co-primary endpoints of proportion of patients achieving PASI 75 (89% vs 25%; $p < 0.001$) and proportion of patients achieving PGA 0 or 1 (81% vs 11%; $p < 0.001$). Responses were sustained or further improved through week 48.

- Combination therapy is commonly utilized, such as with different topical therapies, systemic plus topical therapies, and combinations of certain systemic therapies with phototherapy (*Feldman 2015*). Combinations of different systemic therapies have not been adequately studied; however, there are some data to show that combined therapy with Enbrel (etanercept) plus MTX may be beneficial for therapy-resistant patients (*Busard et al 2014; Gottlieb et al 2012*).
- In a meta-analysis evaluating the efficacy and tolerability of biologic and nonbiologic systemic treatments for moderate to severe PsO, Humira (adalimumab) use was associated with a risk difference of 64% compared to placebo in achieving a PASI 75 response ($p < 0.00001$) while Enbrel (etanercept) 25 and 50 mg twice weekly were associated with a risk difference of 30 and 44% compared to placebo ($p < 0.00001$ for both strengths vs placebo). The Remicade (infliximab) group had the greatest response with a risk difference of 77% compared to the placebo group ($p < 0.0001$). The withdrawal rate was 0.5% with adalimumab, 0.4 to 0.5% with etanercept and 1.3% with infliximab (*Schmitt et al 2008*).
- Another meta-analysis evaluated the efficacy and safety of long-term treatments (≥24 weeks) for moderate-to-severe PsO (*Nast et al 2015*). A total of 25 randomized trials (n = 11,279) were included. Compared to placebo, RRs for achievement of PASI 75 were 13.07 (95% CI, 8.60 to 19.87) for Remicade (infliximab), 11.97 (95% CI, 8.83 to 16.23) for Cosentyx (secukinumab), 11.39 (95% CI, 8.94 to 14.51) for Stelara (ustekinumab), 8.92 (95% CI, 6.33 to 12.57) for Humira (adalimumab), 8.39 (95% CI, 6.74 to 10.45) for Enbrel (etanercept), and 5.83 (95% CI, 2.58 to 13.17) for Otezla (apremilast). Head-to-head studies demonstrated better efficacy for secukinumab and infliximab vs etanercept, and for infliximab vs MTX. The biologics and apremilast also had superior efficacy vs placebo for endpoints of PASI 90 and PGA 0 or 1. The investigators stated that based on available evidence, infliximab, secukinumab, and ustekinumab are the most efficacious long-term treatments, but noted that additional head-to-head comparisons and studies on safety and patient-related outcomes are desirable.
- In a meta-analysis of 41 RCTs that used hierarchical clustering to rate efficacy and tolerability, Humira (adalimumab), Cosentyx (secukinumab), and Stelara (ustekinumab) were characterized by high efficacy and tolerability, Remicade (infliximab) and Taltz (ixekizumab) were characterized by high efficacy and poorer tolerability, and Enbrel (etanercept),

MTX, and placebo were characterized by poorer efficacy and moderate tolerability in patients with PsO (*Jabbar-Lopez et al 2017*).

- A Cochrane review evaluated biologics in patients with moderate to severe PsO in 140 studies (*Sbidian E et al 2020*). The network meta-analysis showed that compared to placebo, the biologics infliximab, ixekizumab, risankizumab, guselkumab, secukinumab, and brodalumab were the best choices for achieving PASI 90 in patients with moderate-to-severe PsO on the basis of moderate- to high-certainty evidence.
- A network meta-analysis of 41 randomized clinical trials (N = 19,248) assessed the proportion of patients with moderate-to-severe PsO who achieved PASI 100, PASI 90, and PASI 75 at weeks 10, 12, and 16 while using agents such as infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, risankizumab or guselkumab. The results revealed higher rates of PASI 100 and PASI 90 with brodalumab, ixekizumab, and risankizumab (*Tada et al 2020*).

Psoriatic arthritis (PsA)

- In 2 trials, PsA patients receiving Humira (adalimumab) 40 mg every other week achieved an ACR 20 at a higher rate than with placebo. Thirty-nine percent in the active treatment group vs 16% in the placebo group achieved this endpoint by week 12 ($p = 0.012$) in a trial (n = 100); while 58 and 14% of patients, respectively, achieved this endpoint in a second trial ($p < 0.001$) (*Genovese et al 2007, Mease et al 2005*). Adalimumab use was also associated with an improvement in structural damage, as measured by the mTSS, compared to those receiving placebo (-0.2 vs 1; $p < 0.001$) (*Mease et al 2005*).
- In a 12-week trial in adult patients with PsA despite NSAID therapy, 87% of Enbrel (etanercept) treated patients met PsA response criteria, compared to 23% of those on placebo ($p < 0.0001$). A PASI 75 improvement and ACR 20 response were detected in 26 and 73% of etanercept-treated patients vs 0 ($p = 0.0154$) and 13% ($p < 0.0001$) of placebo-treated patients (*Mease et al 2000*). In a second trial, the mean annualized rate of change in the mTSS with Enbrel (etanercept) was -0.03 unit, compared to 1 unit with placebo ($p < 0.0001$). At 24 weeks, 23% of etanercept patients eligible for PsO evaluation achieved at least a PASI 75, compared to 3% of placebo patients ($p = 0.001$). Additionally, HAQ scores were significantly improved with etanercept (54%) over placebo (6%; $p < 0.0001$). Injection site reaction occurred at a greater rate with etanercept than placebo (36% vs 9%; $p < 0.001$) (*Mease et al 2004*).
- A 24-week trial of adult patients with PsA randomized 851 patients to oral methotrexate monotherapy, etanercept monotherapy, or combination therapy. At week 24, ACR 20 response rates were significantly greater with etanercept monotherapy (60.9%) compared to methotrexate monotherapy (50.7%), but combination therapy (65%) did not provide any significant improvement over etanercept monotherapy (*Mease et al 2019*).
- The FDA approval of Simponi (golimumab) for PsA was based on the GO-REVEAL study, a multicenter, randomized, double-blind, placebo-controlled trial in adult patients with moderate to severely active PsA despite NSAID or DMARD therapy (n = 405). Golimumab with or without MTX compared to placebo with or without MTX, resulted in significant improvement in signs and symptoms as demonstrated by the percentage of patients achieving a ACR 20 response at week 14. The ACR responses observed in the golimumab-treated groups were similar in patients receiving and not receiving concomitant MTX therapy (*Kavanaugh et al 2009*).
  - Subcutaneous golimumab for patients with active PsA demonstrated safety and efficacy over 5 years in the long-term extension of the GO-REVEAL study. Approximately one-half of patients took MTX concurrently. ACR 20 response rates at year 5 were 62.8 to 69.9% for golimumab SQ 50 or 100 mg every 4 weeks (*Kavanaugh et al 2014b*).
  - Post-hoc analyses of the 5-year GO-REVEAL results evaluated the relationship between achieving minimal disease activity (MDA; defined as the presence of ≥5 of 7 PsA outcomes measures [≤1 swollen joint, ≤1 tender joint, PASI ≤1, patient pain score ≤15, patient global disease activity score ≤20, HAQ disability index [HAQ DI] ≤0.5, and ≤1 tender enthesis point]) and long-term radiographic outcomes including radiographic progression. Among golimumab-treated patients, achieving long-term MDA was associated with better long-term functional improvement, patient global assessment, and radiographic outcomes. Radiographic benefit was more pronounced in patients using MTX at baseline. The authors conclude that in patients with active PsA, aiming for MDA as part of a treat-to-target strategy may provide long-term functional and radiographic benefits (*Kavanaugh et al 2016*).
- In another trial, more Remicade (infliximab) treated patients achieved ACR 20 at weeks 12 and 24 compared to placebo treated patients ($p < 0.001$) (*Antoni et al 2005*).
- The efficacy of Cimzia (certolizumab) in the treatment of PsA was established in 1 multicenter, double-blind, placebo controlled trial (n = 409). Patients were randomized to receive placebo, Cimzia 200 mg every 2 weeks, or Cimzia 400 mg every 4 weeks. At week 12, ACR 20 response was significantly greater in both active treatment groups compared to placebo (*Mease et al 2014*).
- The FDA-approval of Stelara (ustekinumab) for PsA was based on the results of 2 randomized, double-blind, placebo-controlled trials in adult patients with active PsA despite NSAID or DMARD therapy (PSUMMIT 1 and PSUMMIT 2). In

PSUMMIT 1 (n = 615), a greater proportion of patients treated with ustekinumab 45 mg or 90 mg alone or in combination with MTX achieved ACR 20 response at week 24 compared to placebo (42.4% and 49.5% vs 22.8%; p < 0.0001 for both comparisons); responses were maintained at week 52 (*McInnes et al 2013*). Similar results were observed in the PSUMMIT 2 trial (n = 312) with 43.8% of ustekinumab-treated patients and 20.2% of placebo-treated patients achieving an ACR 20 response (p < 0.001) (*Ritchlin et al 2014*).
    - In PSUMMIT-1, patients taking placebo or ustekinumab 45 mg could adjust therapy at week 16 if they had an inadequate response, and all remaining patients in the placebo group at week 24 were crossed over to receive treatment with ustekinumab 45 mg (*McInnes et al 2013*). At week 100 (*Kavanaugh et al 2015a*), the ACR 20 responses were 63.6%, 56.7%, and 62.7% in the 90 mg, 45 mg, and placebo crossover groups, respectively. ACR 50 and ACR 70 responses followed a similar pattern and ranged from 37.3% to 46% and 18.6% to 24.7%, respectively. At week 100, the proportions of patients achieving PASI 75 were 71.3%, 72.5%, and 63.9% in the 90 mg, 45 mg, and placebo crossover groups, respectively. Improvements in physical function and HRQoL were sustained over time, with median decreases in HAQ-DI scores from baseline to week 100 of 0.38, 0.25, and 0.38 in the 90 mg, 45 mg, and placebo crossover groups, respectively.
- Cosentyx (secukinumab) gained FDA approval for the treatment of PsA based on 2 multicenter, double-blind, placebo-controlled randomized controlled trials – FUTURE 1 and FUTURE 2 *(Mease et al 2015, McInnes et al 2015*). The FUTURE 1 study randomized patients to secukinumab 75 mg or 150 mg every 4 weeks (following IV loading doses) or placebo and evaluated ACR 20 at week 24. In the FUTURE 2 study, patients were randomized to secukinumab 75 mg, 150 mg, or 300 mg SQ every 4 weeks (following SQ loading doses given at weeks 0, 1, 2, 3, and 4) or placebo and evaluated at week 24 for ACR 20 response.
    - In FUTURE 1 at week 24, both the secukinumab 75 mg and 150 mg doses demonstrated significantly higher ACR 20 responses vs placebo (50.5% and 50.0% vs 17.3%, respectively; p < 0.0001 vs placebo).
    - All pre-specified endpoints including dactylitis, enthesitis, SF-36 PCS, HAQ-DI, DAS28-CRP, ACR 50, PASI 75, PASI 90, and mTSS score were achieved by week 24 and reached statistical significance.
    - At week 104 in a long-term extension study of FUTURE 1, ACR 20 was achieved in 66.8% of patients with secukinumab 150 mg and 58.6% of patients with secukinumab 75 mg (*Kavanaugh et al 2017*).
    - In FUTURE 2 at week 24, ACR 20 response rates were significantly greater with secukinumab than with placebo: 54.0%, 51.0%, and 29.3% vs 15.3% with secukinumab 300 mg, 150 mg, and 75 mg vs placebo, respectively (p < 0.0001 for secukinumab 300 mg and 150 mg; p < 0.05 for 75 mg vs placebo).
    - Improvements were seen with secukinumab 300 mg and 150 mg with regard to PASI 75/90 scores, DAS28-CRP, SF-36 PCS, HAQ-DI, dactylitis, and enthesitis. Efficacy was observed in both TNF-naïve patients and in patients with prior TNF inadequate response or intolerance.
- The efficacy of Otezla (apremilast) was demonstrated in 3 placebo-controlled trials in patients with PsA. At week 16, significantly more patients in the Otezla groups had ≥ 20% improvement in symptoms, as defined by ACR response criteria (*Cutolo et al 2013, Edwards et al 2016, Kavanaugh et al 2014a*). Clinical improvements observed at 16 weeks were sustained at 52 weeks (*Edwards et al 2016, Kavanaugh et al 2015b*).
- Orencia (abatacept) gained FDA approval for the treatment of PsA based on 2 double-blind, placebo-controlled clinical trials in patients with an inadequate response or intolerance to DMARD therapy (*Mease et al 2011, Mease et al 2017[a]*). In a phase 2 dose-finding trial (n = 170), patients received abatacept 3 mg/kg, 10 mg/kg, or 30/10 mg/kg (2 doses of 30 mg/kg then 10 mg/kg) on days 1, 15, 29 and then every 28 days (*Mease et al 2011*). Compared to placebo (19%), the proportion of patients achieving ACR 20 was significantly higher with abatacept 10 mg/kg (48%; p = 0.006) and 30/10 mg/kg (42%; p = 0.022) but not 3 mg/kg (33%). A phase 3 trial (n = 424) randomized patients to abatacept 125 mg weekly or placebo (*Mease et al 2017[a]*). At week 24, the proportion of patients with ACR 20 response was significantly higher with abatacept (39.4%) vs placebo (22.3%; p < 0.001).
- Taltz (ixekizumab) received FDA approval for the treatment of PsA based on 2 double-blind clinical trials, SPIRIT-P1 and SPIRIT-P2 (*Mease et al 2017[b], Nash et al 2017*). SPIRIT-P1 randomized 417 biologic naïve patients to placebo, adalimumab 40 mg every 2 weeks, ixekizumab 80 mg every 2 weeks, or ixekizumab 80 mg every 4 weeks. At week 24, ACR 20 response rates for ixekizumab every 2 weeks and every 4 weeks were 62.1% and 57.9%, respectively, which was significantly greater than the ACR 20 reponse rate with placebo (30.2%; p ≤ 0.001). The active reference treatment, adalimumab, had an ACR 20 at week 24 of 57.4% (*Mease et al 2017[b]*). SPIRIT-P2 randomized 363 patients who had a previous inadequate response to a TNF inhibitor to placebo, ixekizumab 80 mg every 2 weeks, or ixekizumab 80 mg every 4 weeks. At week 24, ACR 20 response rates for ixekizumab every 2 weeks and every 4 weeks were 48% and 53%, respectively, which was significantly greater than the ACR 20 reponse rate with placebo (20%; p < 0.0001) (*Nash et al 2017*).

- An open-label extension of the SPIRIT-P1 trial followed patients through week 52, demonstrating sustained efficacy with ixekizumab. The ACR 20, ACR 50, and ACR 70 response rates for the every 4 week and every 2 weeks groups were 69.1% and 68.8%, 54.6% and 53.1%, and 39.2% and 39.6% at week 52, respectively (*van der Heijde et al 2018[b]*).
- An additional open-label extension of the SPIRIT-P1 trial followed patients through week 156. The ACR 20, ACR 50, and ACR 70 response rate for the every 2 weeks and every 4 weeks groups were 62.5% and 69.8%, 56.1% and 51.8%, and 43.8% and 33.4%, respectively (*Chandran et al 2020*).

- SPIRIT-H2H is a 52-week multicenter, open-label study comparing ixekizumab with adalimumab in patients with PsA and without prior use of biologic DMARDs. At week 52, a higher proportion of patients treated with ixekizumab achieved the combined ACR 50 and PASI 100 response (39% vs 26%, $p < 0.001$) and PASI 100 response (64% vs 41%, $p < 0.001$) compared with the patients treated with adalimumab. Both agents yielded similar outcomes for ACR 50 (49.8% vs 49.8%, $p = 0.924$) (*Smolen et al 2020[b]*).
- Xeljanz (tofacitinib) received FDA approval for the treatment of PsA based on 2 double-blind, placebo-controlled clinical trials in patients with an inadequate response or intolerance to DMARD therapy (*Mease et al 2017[c], Gladman et al 2017*). The OPAL Broaden trial randomized 422 patients to tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, adalimumab 40 mg every 2 weeks, placebo with a blinded switch to tofacitinib 5 mg after 3 months, or placebo with a blinded switch to tofacitinib 10 mg after 3 months. The primary endpoint of the proportion of patients achieving ACR 20 at month 3 occurred in 50% in the tofacitinib 5 mg group, 61% in the tofacitinib 10 mg group, 33% in the placebo group ($p = 0.01$ vs 5 mg; $p < 0.001$ vs 10 mg), and 52% in the adalimumab group (*Mease et al 2017[c]*). The OPAL Beyond trial randomized 395 patients to tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, placebo with a blinded switch to tofacitinib 5 mg after 3 months, or placebo with a blinded switch to tofacitinib 10 mg after 3 months. The primary endpoint of the proportion of patients achieving ACR 20 at month 3 occurred in 50% in the tofacitinib 5 mg group, 47% in the tofacitinib 10 mg group, and 24% in the placebo group ($p < 0.001$ for both comparisons) (*Gladman et al 2017*).
- Tremfya (guselkumab) received FDA approval for the treatment of PsA based on 2 randomized, double-blind, placebo controlled trials (*Deodhar et al 2020[c], Mease et al 2020*). The DISCOVER-1 trial randomized 381 patients with active PsA despite standard therapies to receive guselkumab 100 mg every 4 weeks, guselkumab 100 mg at weeks 0, 4, then every 8 weeks, or placebo. At week 24, ACR 20 response rates for guselkumab every 4 weeks and every 8 weeks were 59% and 52%, respectively, which was significantly greater than the ACR 20 response rate with placebo (22%; $p < 0.0001$) (*Deodhar et al 2020[c]*). The DISCOVER-2 trial randomized 741 biologic-naïve patients with PsA to receive guselkumab 100 mg every 4 weeks, guselkumab 100 mg at weeks 0, 4, then every 8 weeks, or placebo. At week 24, ACR 20 response rates for guselkumab every 4 weeks and every 8 weeks were 64% and 64%, respectively, which was significantly greater than the ACR 20 response rate with placebo (33%; $p < 0.0001$) (*Mease et al 2020*).
- A small, single-center randomized trial (N = 100) compared Remicade (infliximab), Enbrel (etanercept), and Humira (adalimumab) in patients with PsA who had had an inadequate response to DMARDs (*Atteno et al 2010*). The investigators found that each of the agents effectively controlled the signs and symptoms of PsA, and ACR response rates were similar among agents. Patients receiving infliximab and adalimumab showed the greatest improvement in PASI scores, whereas patients receiving etanercept showed the greatest improvement on the tender joint count and HAQ. Limitations of this trial were lack of blinding and lack of a placebo group.
- The multicenter, randomized, double-blind EXCEED study compared Cosentyx (secukinumab) to Humira (adalimumab) in 853 biologic-naïve patients with active PsA and an inadequate response to DMARDs (*McInnes et al 2020*). The ACR 20 response rates at week 52 were 67% with secukinumab and 62% with adalimumab ($p = 0.0719$). Secukinumab did not show statistical superiority over adalimumab.
- A meta-analysis based on both direct and indirect comparisons evaluated the efficacy and safety of Humira (adalimumab), Enbrel (etanercept), Remicade (infliximab), and Simponi (golimumab) over 24 weeks for the treatment of PsA (*Fénix et al 2013*). The investigators found no differences among products for the primary endpoint of ACR 50 or secondary endpoints of ACR 20 and ACR 70, except that etanercept was associated with a lower ACR 70 response. However, low sample sizes limited the power of the analysis.
- A meta-analysis of 9 randomized controlled trials and 6 observational studies evaluated Humira (adalimumab), Enbrel (etanercept), Simponi (golimumab), or placebo in the achievement of ACR 20, ACR 50, and ACR 70 endpoints in patients with moderate to severe PsA (*Lemos et al 2014*). Patients who used adalimumab, etanercept and golimumab were more likely to achieve ACR 20 and ACR 50 after 12 or 24 weeks of treatment. In long-term analysis (after all participants used anti-TNF for at least 24 weeks), there was no difference in ACR 20 and ACR 50 between the anti-TNF and control groups, but patients originally randomized to anti-TNF were more likely to achieve ACR 70.

- A meta-analysis of 8 studies evaluated Cosentyx (secukinumab), Taltz (ixekizumab), Siliq (brodalumab), and Stelara (ustekinumab) in the achievement of ACR 20, ACR 50, and ACR 70 endpoints in patients with PsA (*Bilal et al 2018*). Patients who used these agents were more likely to achieve ACR 20, ACR 50, and ACR70 after 24 weeks of treatment. Another network meta-analysis of 6 studies evaluated Cosentyx (secukinumab), Taltz (ixekizumab), and Stelara (ustekinumab) over 24 weeks in patients with active PsA (*Wu et al 2018*). The investigators found that all agents improved ACR20 and ACR50 at week 24 compared to placebo. A different network meta-analysis of 8 studies evaluated Orencia (abatacept), Otezla (apremilast), Stelara (ustekinumab), and Cosentyx (secukinumab) in the achievement of ACR 20 and ACR 50 in adults with moderate to severe PsA (*Kawalec et al 2018*). The investigators found a significant difference in ACR20 response rate between Cosentyx (secukinumab) 150 mg and Otezla (apremilast) 20 mg (RR, 2.55; 95% CI, 1.24 to 5.23) and Cosentyx (secukinumab) 300 mg and Otezla (apremilast) 20 mg (RR, 3.57; 95% CI, 1.48 to 8.64) or Otezla (apremilast) 30 mg (RR, 2.84; 95% CI, 1.18 to 6.86).
- Two indirect comparison meta-analyses sought to compare the efficacy of biologics for the treatment of PsA in patients with an inadequate response to prior therapies.
  - An analysis of 12 randomized trials compared various biologics in patients having an inadequate response to NSAIDs or traditional DMARDs (*Ungprasert et al 2016a*). The investigators determined that patients receiving older TNF inhibitors (evaluated as a group: Enbrel [etanercept], Remicade [infliximab], Humira [adalimumab], and Simponi [golimumab]) had a statistically significantly higher chance of achieving ACR 20 compared to patients receiving Cimzia (certolizumab), Otezla (apremilast), or Stelara (ustekinumab). Patients receiving Cosentyx (secukinumab) also had a higher chance of achieving ACR 20 compared to certolizumab, ustekinumab, and apremilast, but the relative risk did not always reach statistical significance. There was no statistically significant difference in this endpoint between secukinumab and the older TNF inhibitors, or between apremilast, ustekinumab, and certolizumab.
  - An analysis of 5 randomized trials compared various non-TNF inhibitor biologics (Orencia [abatacept], secukinumab, ustekinumab, and apremilast) in patients having an inadequate response or intolerance to TNF inhibitors (*Ungprasert et al 2016[b]*). The investigators found no difference for any between-agent comparison in the likelihood of achieving an ACR 20 response.
  - These meta-analyses had limitations, notably being based on a small number of trials, and should be interpreted with caution.
- In a network meta-analysis of 8 randomized trials (N = 3086), the efficacy and safety of apremilast were compared with tofacitinib in patients with active PsA, including treatment with tofacitinib 10 mg or 5 mg, apremilast 20 or 30 mg, and placebo *(Song et al 2019)*. Tofacitinib 10 mg and apremilast 30 mg were among the most effective treatments, followed by tofacitinib 5 mg and apremilast 20 mg. Tofacitinib 10 mg was most likely to be most effective in ACR 20 response (SUCRA = 0.785), followed by apremilast 30 mg (SUCRA = 0.670), tofacitinib 5 mg (SUCRA = 0.596), and apremilast 20 mg (SUCRA = 0.448). There were no significant differences in adverse event rates.
- A network meta-analysis of 30 randomized trials (N = 10,191) compared the efficacy of infliximab, apremilast, adalimumab, tofacitinib, ustekinumab, golimumab, abatacept, secukinumab, certolizumab, brodalumab, etanercept, and ixekizumab in PsA (*Qiu et al 2020*). Direct and indirect comparisons were performed. In direct comparisons, most agents were better than placebo in terms of ACR 20 response rate (except adalimumab, tofacitinib, and abatacept), and no agent was significantly different from placebo in terms of serious adverse events. In the network meta-analysis, etanercept and infliximab were more effective than golimumab for ACR 20 response, and infliximab was more effective than certolizumab for PASI 75 response. Etanercept and infliximab were ranked as the most effective treatments.
- A network meta-analysis of 30 randomized trials (only 12 randomized trials for peripheral arthritis outcome) assessed the efficacy of adalimumab, etanercept, infliximab, golimumab, certolizumab, ustekinumab, secukinumab, ixekizumab, guselkumab, brodalumab, risankizumab, and tildrakizumab on peripheral arthritis by using ACR 70 criteria and on skin by reporting PASI 100 (*Torres et al 2021*). Secukinumab and ixekizumab had the highest probability for reaching both ACR 70 and PASI 100 responses.
- A meta-analysis of 11 randomized studies (N = 5382) revealed that TNF inhibitors, IL inhibitors, and abatacept are more likely to achieve radiographic non-progression compared with placebo (*Wu et al 2020*). Ixekizumab and adalimumab had a similar proportion of non-progressors.

Ulcerative colitis (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 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 end points at week 8, i.e., rectal bleeding and 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 1,064 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 2014b*). 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 2014a*).
- 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 Entyvio-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*). 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 Xeljanz (tofacitinib) for UC was evaluated in two 8-week induction trials followed by a 52-week maintance trial. In the induction trials, patients were assigned to tofacitinib 10 mg twice daily or placebo. 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 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 (*Sandborn et al 2017*).
- 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% every 12 weeks vs 43.8% every 8 weeks vs 24% 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 anti-TNF agents (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.

Uveitis (UV)

- The safety and efficacy of Humira (adalimumab) were assessed in adult patients with non-infectious intermediate, posterior, and panuveitis in 2 randomized, double-masked, placebo-controlled studies, VISUAL I and VISUAL II.
  - VISUAL I (n = 217) enrolled adults with active noninfectious intermediate UV, posterior UV, or panuveitis despite having received prednisone treatment for ≥2 weeks (*Jaffe et al 2016*). Patients were randomized to adalimumab (80 mg loading dose then 40 mg every 2 weeks) or placebo; all patients also received a prednisone burst followed by tapering of prednisone over 15 weeks. The primary endpoint was the time to treatment failure (TTF) at or after week 6. TTF was a multicomponent outcome that was based on assessment of new inflammatory lesions, visual acuity, anterior chamber cell grade, and vitreous haze grade. The median TTF was 24 weeks in the adalimumab group and 13 weeks in the placebo group. Patients receiving adalimumab were less likely than those in the placebo group to have treatment failure (hazard ratio, 0.50; 95% CI, 0.36 to 0.70; p < 0.001).
  - VISUAL II (n = 226) had a similar design to VISUAL I; however, VISUAL II enrolled patients with inactive UV on corticosteroids rather than active disease (*Nguyen et al 2016a*). Patients were randomized to adalimumab (80 mg loading dose then 40 mg every 2 weeks) or placebo; all patients tapered prednisone by week 19. TTF was significantly improved in the adalimumab group compared with the placebo group (median not estimable [>18 months] vs 8.3 months; hazard ratio, 0.57, 95% CI, 0.39 to 0.84; p = 0.004). Treatment failure occurred in 61 (55%) of 111 patients in the placebo group compared with 45 (39%) of 115 patients in the adalimumab group.
- The SYCAMORE study established the efficacy and safety of Humira (adalimumab) in pediatric patients with JIA-associated UV. The double-blind trial evaluated 90 children and adolescents ≥ 2 years of age and randomized them to adalimumab or placebo until treatment failure or 18 months had elapsed. The primary endpoint was the time to treatment failure. Sixteen treatment failures (27% of patients) occurred with adalimumab compared to 18 failures (60% of patients) with placebo (HR, 0.25; 95% CI, 0.12 to 0.90). Adverse events occurred more frequently with adalimumab (10.07 events per patient year [PY] vs 6.51 events per PY with placebo) (*Ramanan et al 2017*).

Multiple indications

- The efficacy of infliximab-dyyb (European Union formulation) in patients (n = 481) with CD, UC, RA, PsA, spondyloarthritis, and PsO who were treated with the originator infliximab (European Union formulation) for ≥ 6 months was assessed in the NOR-SWITCH trial (*Jørgensen et al 2017*). Twenty-five percent of patients in the infliximab originator group experienced disease worsening compared to 30% of patients in the infliximab-dyyb group (TD, -4.4%; 95% CI, -12.7% to 3.9%; noninferiority margin, 15%). The authors concluded that infliximab-dyyb was noninferior to originator infliximab.

Behçet disease, CAPS, CRS, DIRA, FMF, GCA, HIDS/MKD, NOMID, NRAS, and TRAPs

- The efficacy of Otezla (apremilast) for Behçet disease was evaluated in a randomized, double-blind, placebo-controlled trial in 207 adults with Behçet disease with active oral ulcers who were previously treated with at least one nonbiologic therapy (*Hatemi et al 2019*). At week 12, apremilast 30 mg twice daily was associated with a 42.7 point mean reduction from baseline in oral ulcer pain on a visual analog scale (VAS), compared with an 18.7 point reduction with placebo. The area under the curve (AUC) of the total mean number of ulcers during the 12 week period was 129.5 in the apremilast vs 222.1 in the placebo group ; p < 0.001). The proportion of patients who were oral ulcer-free at week 12 was 53% and 22% with apremilast vs placebo, respectively. Adverse events with apremilast included diarrhea, nausea, and headache.
- The efficacy of Kineret (anakinra) for NOMID was evaluated in a prospective, open-label, uncontrolled study in 43 patients treated for up to 60 months. The study demonstrated improvements in all disease symptoms comprising the disease-specific Diary Symptom Sum Score (DSSS), as well as in serum markers of inflammation. A subset of patients (n = 11) who went through a withdrawal phase experienced worsening of disease symptoms and inflammatory markers, which promptly responded to reinstitution of treatment (*Kineret prescribing information 2020*). A cohort study of 26 patients followed for 3 to 5 years demonstrated sustained improvement in disease activity and inflammatory markers (*Sibley et al 2012*).

- The efficacy of Kineret (anakinra) for DIRA was evaluated in a long-term natural history study of 9 patients (ages 1 months to 9 years) with genetically-confirmed DIRA who were treated with anakinra for up to 10 years. All patients achieved inflammatory remission (defined as CRP ≤ 5 mg/dL and absence of pustulosis, inflammatory bone disease, or glucocorticosteroid use) (*Kineret prescribing information 2020*).
- The efficacy of Cimzia (certolizumab) was evaluated in a phase 3, randomized, double-blind, placebo-controlled trial in 317 patients with NRAS. Patients were randomized to certolizumab (400 mg at weeks 0, 2, and 4, followed by 200 mg every 2 weeks) or placebo in addition to nonbiologic background medication. At week 52, treatment with certolizumab was associated with a significantly higher proportion of patients achieving major improvement (≥ 2 point decrease in Ankylosing Spondylitis Disease Activity Score; 47.2% vs 7.0%; p < 0.0001) *(Deodhar et al 2019[b]).*
- The efficacy and safety of Taltz (ixekizumab) were evaluated in NRAS in the 52 week, randomized, double-blind, placebo-controlled, parallel-group, multicenter COAST-X trial (*Deodhar et al 2020[a]*). In COAST-X, 303 adults with NRAS and an inadequate response or intolerance to NSAIDs were randomly assigned to ixekizumab 80 mg SQ every 4 weeks (n = 96), every 2 weeks (n = 102), or placebo (n = 105). Both primary endpoints were met with ixekizumab: ASAS 40 at week 16 (35% every 4 weeks vs 40% every 2 weeks vs 19% placebo; p = 0.0094 and p = 0.0016, respectively) and ASAS 40 at week 52 (30% every 4 weeks vs 31% every 2 weeks vs 13% placebo; p = 0.0045 and p = 0.0037, respectively). The most common treatment-emergent adverse events were nasopharyngitis and injection site reaction.
- The efficacy and safety of Cosentyx (secukinumab) were evaluated in NRAS in the randomized, double-blind, placebo-controlled, phase 3 PREVENT study (*Deodhar et al 2020[b]*). In this trial, 555 adults with NRAS were randomized to receive secukinumab with a loading dose, secukinumab without a loading dose, or placebo (secukinumab was dosed as 150 mg at weeks 0, 1, 2, and 3, then every 4 weeks starting at week 4). The primary analyses were performed in TNF inhibitor-naïve patients (n = 501). Both primary endpoints were met. At week 16, more patients in the secukinumab plus loading dose group achieved ASAS 40 compared with placebo (41.5% vs 29.2%; p < 0.05). At week 52, more patients in the secukinumab without loading dose group achieved ASAS 40 compared with placebo (39.8% vs 19.9%; p < 0.05).
- The efficacy and safety of Ilaris (canakinumab) has been evaluated for the treatment of CAPS, TRAPS, HIDS/MKD, FMF, and adult-onset Still's disease.
  - Efficacy and safety in CAPS were evaluated in a trial in patients aged 9 to 74 years with the MWS phenotype and in a trial in patients aged 4 to 74 years with both MWS and FCAS phenotypes. Most of the trial periods were open-label. Trials demonstrated improvements based on physician's assessments of disease activity and assessments of skin disease, CRP, and serum amyloid A (*Ilaris prescribing information 2020*). Published data supports the use of canakinumab for these various CAPS phenotypes (*Koné-Paut et al 2011, Kuemmerle-Deschner et al 2011, Lachmann et al 2009*).
  - Efficacy and safety in TRAPS, HIDS/MKD, and FMF were evaluated in a study in which patients having a disease flare during a screening period were randomized into a 16-week double-blind, placebo-controlled period. For the primary efficacy endpoint, canakinumab was superior to placebo in the proportion of TRAPS, HIDS/MKD, and FMF patients who resolved their index disease flare at day 15 and had no new flare for the duration of the double-blind period (45% vs 8%, 35% vs 6%, and 61% vs 6%, respectively). Resolution of the flare was defined as a PGA score <2 (minimal or no disease) and CRP within normal range (or reduction ≥70% from baseline) (*De Benedetti et al 2018*).
  - Efficacy and safety in adult-onset Still's disease were evaluated in a randomized, double-blind, placebo-controlled study of 36 patients with adult-onset Still's disease and active joint involvement. The primary endpoint, proportion of patients achieving a significant reduction in DAS28 at week 12, was achieved in 67% of canakinumab-treated patients and 41% of placebo-treated patients (p = 0.18). Proportions of patients achieving the secondary endpoints of ACR 30, 50, and 70 were significantly greater in the canakinumab group (61%, 50%, and 28% with canakinumab vs 20%, 6.7%, and 0% with placebo; p = 0.033, 0.009, and 0.049 for canakinumab vs placebo, respectively). The study was terminated prematurely due to recruitment difficulties (*Kedor et al 2020*).
- The efficacy and safety of Actemra (tocilizumab) has been evaluated for treatment of GCA and CRS.
  - Efficacy and safety of tocilizumab in GCA were evaluated in a double-blind, placebo-controlled phase 3 trial (GiACTA) in patients ≥ 50 years old with active GCA and a history of elevated ESR (*Stone et al 2017*). Patients received tocilizumab every week or every other week with a 26-week prednisone taper, or received placebo with a 26-week or 52-week prednisone taper. Patients who received tocilizumab every week and every other week experienced higher sustained remission rates at week 52 compared to placebo (p < 0.01).
  - The efficacy of tocilizumab in CRS was based on the result of a retrospective analysis of pooled outcome data from clinical trials of chimeric antigen receptor (CAR) T-cell therapies for hematological cancers (*Actemra prescribing information 2020*). Patients aged 3 to 23 years received tocilizumab with or without high-dose corticosteroids for

severe or life-threatening CRS. Sixty-nine percent of patients treated with tocilizumab achieved a response. In a second study using a separate study population, CRS resolution within 14 days was confirmed.

- A systematic literature review of 38 studies determined that anakinra, canakinumab, and etanercept are the most commonly studied biologics for treating familial Mediterranean fever, while studies with adalimumab, tocilizumab, rilonacept, and infliximab remain limited (*Kuemmerle-Deschner et al 2020*). The available evidence suggests that anakinra and canakinumab are effective in treating familial Mediterranean fever.

TREATMENT GUIDELINES

- RA:
  - In patients with moderate or high disease activity despite DMARD monotherapy, the ACR recommends the use of combination DMARDs, a TNF inhibitor, or a non-TNF inhibitor biologic (tocilizumab, abatacept, or rituximab); tofacitinib is another option in patients with established RA, mainly in patients failing or intolerant to biologic DMARDs. If disease activity remains moderate or high despite use of a TNF inhibitor, a non-TNF biologic is recommended over another TNF inhibitor or tofacitinib. Anakinra was excluded from the ACR guideline because of its low use and lack of new data (*Singh et al 2016c*). The ACR updated guideline on RA management is currently underway with final publication anticipated in spring 2021.
  - EULAR guidelines for RA management were recently updated (*Smolen et al 2020[a]*). EULAR recommends that therapy with DMARDs should be initiated as soon as the RA diagnosis is made with treatment aimed at reaching a target of sustained remission or low disease activity in every patient. If the treatment target is not achieved with the first conventional synthetic DMARD strategy, in the absence of poor prognostic factors, others should be considered. If poor prognostic factors are present with treatment failure, a biological or targeted synthetic DMARD should be added. If a biological or targeted synthetic DMARD has failed, treatment with another should be considered. If one TNF inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF inhibitor.
  - The ACR released a position statement on biosimilars, which stated that the decision to substitute a biosimilar product for a reference drug should only be made by the prescriber. The ACR does not endorse switching stable patients to a different medication (including a biosimilar) of the same class for cost saving reasons without advance consent from the prescriber and knowledge of the patient (*ACR 2018*). Similarly, the Task Force on the Use of Biosimilars to Treat Rheumatological Disorders recommends that both healthcare providers and patients should take part in the decision-making process for switching amongst biosimilars (*Kay et al 2018*).
  - EULAR has released guidelines for use of antirheumatic drugs in pregnancy, which state that etanercept and certolizumab are among possible treatment options for patients requiring therapy (*Götestam Skorpen et al 2016*).
  - The ACR/Arthritis Foundation guidelines for the management of osteoarthritis of the hand, hip, and knee strongly recommends against the use of biologics (eg, TNF inhibitors, IL-1 receptor antagonists) for any form of osteoarthritis (*Kolasinski et al 2020*).
- JIA:
  - According to the ACR JIA guidelines focusing on the management of SJIA, the inflammatory process in SJIA is likely different from that of other JIA categories, with IL-1 and IL-6 playing a central role. In patients with SJIA and active systemic features, recommendations vary based on the active joint count and the physician global assessment. Anakinra is 1 of the recommended first-line therapies; canakinumab, tocilizumab, and TNF-inhibitors are among the second-line therapies. In patients with SJIA and no active systemic features, treatments vary based on the active joint count. Abatacept, anakinra, tocilizumab, and TNF inhibitors are among the second-line treatments for these patients (*Ringold et al 2013*).
  - The ACR and Arthritis Foundation published a guideline for the treatment of JIA in 2019 focusing on therapy for non-systemic polyarthritis, sacroiliitis, and enthesitis. In children and adolescents with JIA and polyarthritis with moderate to high disease activity, addition of a biologic (TNF inhibitor, abatacept, or tocilizumab) is conditionally recommended. Patients with continued disease activity and primary TNF inhibitor failure are conditionally recommended to receive abatacept or tocilizumab over a second TNF inhibitor. Children and adolescents with JIA and active sacroiliitis despite treatment with NSAIDs are strongly recommended to add TNF inhibitor therapy over continuing NSAID monotherapy. In children and adolescents with JIA and active enthesitis, TNF inhibitor therapy is conditionally recommended over methotrexate or sulfasalazine *(Ringold et al 2019)*. The ACR is developing a new clinical practice guideline for the management of JIA, specifically covering pharmacologic and non-pharmacologic treatments that were not addressed in the 2019 guidelines; final publication is anticipated in summer 2021.
- UC:

- For the treatment of UC, 2019 guidelines from the American College of Gastroenterology (ACG) recommend 5-aminosalicylate (5-ASA) therapy for induction of remission in mildly active UC, and budesonide, systemic corticosteroids, TNF inhibitor therapy (adalimumab, golimumab, or infliximab), vedolizumab, and tofacitinib for induction of remission in moderately to severely active disease. Vedolizumab and tofacitinib are recommended for induction of remission in patients who have failed previous TNF inhibitor therapy. For maintenance of remission in patients with previously mildly active disease, 5-ASA therapy is recommended, and in patients with previously moderately to severely active disease, continuation of anti-TNF therapy, vedolizumab, or tofacitinib is recommended after induction of remission with these agents (*Rubin et al 2019*).
- The American Gastroenterological Association (AGA) recommends standard-dose mesalamine or diazo-bonded 5-aminosalicylates (balsalazide, olsalazine) as first-line options for most patients with mild to moderate disease (*Ko et al 2019*). For adult outpatients with moderate to severe UC, the AGA strongly recommends using infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or ustekinumab over no treatment (*Feuerstein et al 2020*).
- The European Crohn's and Colitis Organisation (ECCO) recommends thiopurine, anti-TNF drugs, vedolizumab, or methotrexate for patients with UC who have active steroid-dependent disease. In the case of further treatment failure, an alternative anti-TNF agent, vedolizumab, or colectomy can be considered. Anti-TNF agents and vedolizumab are also treatment options for patients who have steroid- or immunomodulator-refractory disease (*Harbord et al 2017*).

- CD:
  - The ACG states that the anti-TNF monoclonal antibodies 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 anti-TNF induced remission; due to the potential for immunogenicity and loss of response, combination with azathioprine/6-mercaptopurine or methotrexate should be considered. The combination of infliximab with an immunomodulator (thiopurine) is more effective than monotherapy with individual agents in patients with moderate to severe CD and who are naïve to both agents. Infliximab can also treat fuliminant CD. Vedolizumab with or without an immunomodulator can be used for induction and maintenance of remission in patients with moderate to severe CD. Patients are candidates for ustekinumab therapy, including for the maintenance of remission, if they have moderate to severe CD and have failed corticosteroids, thiopurines, methotrexate, or anti-TNF inhibitors. The guideline acknowledges the effectiveness of biosimilar infliximab and biosimilar adalimumab for the management of moderate to severe CD (*Lichtenstein et al 2018*).
  - The AGA recommends using anti-TNF drugs to induce remission in patients with moderately severe CD (*Terdiman et al 2013*). 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-mercaptopurine, prednisone, MTX, a TNF inhibitor, or certain combinations) based on the patient's risk level (*Sandborn 2014*).
  - In 2020, ECCO released a guideline on medical treatment in CD (*Torres et al 2020*). Regarding immunomodulators, these guidelines recommend 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. 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 anti-TNF therapy.
    - Recommending vedolizumab for induction of response and remission in patients with moderate-to-severe CD with inadequate response to conventional therapy and/or to anti-TNF therapy.
    - 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 anti-TNF therapy.
- Pregnancy in inflammatory bowel disease:
  - Consensus statements for the management of inflammatory bowel disease in pregnancy, coordinated by the Canadian Association of Gastroenterology, state 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[b]*).
  - The AGA pregnancy care pathway for inflammatory bowel disease also recommends that biologics can be continued 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*).
- PsO and PsA:
  - Joint guidelines from the American Academy of Dermatology (AAD)/National Psoriasis Foundation (NPF) state that topical medications (eg, corticosteroids, vitamin D analogues) are the most common agents used to treat mild to moderate PsO. They are commonly used as adjunctive therapy to phototherapy, systemic agents, and biologics (*Elmets et al 2021).* Phototherapy is viewed as a reasonable and effective treatment option for patients requiring more than topical medications and/or those wishing to avoid systemic medications (*Elmets et al 2019*). Although biologic therapies have changed the treatment landscape, non-biologic systemic agents (eg, methotrexate) either as monotherapy or in combination with biologics, are still widely used due to benefit
  - for widespread disease, comparatively low cost, increased availability, and ease of administration (*Menter et al 2020[a])*.
  - Joint guidelines from the AAD/NPF on the treatment of psoriasis with biologics address the effectiveness of these drugs as monotherapy or in combination to treat moderate-to-severe disease in adults. The guideline does not provide relevant ranking for preferences of individual biologics, but does recommend that etanercept, infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, and tildrakizumab can all be recommended as a monotherapy option for patients. Further recommendations on specific presentations of the disease, combination therapy, and dosing recommendations are included in the guidance (*Menter et al 2019*).
  - The AAD/NPF guideline on PsO in pediatric patients states that etanercept, adalimumab, and ustekinumab are effective biologic therapies for moderate to severe pediatric psoriasis. Infliximab can be recommended as monotherapy or in combination with MTX for use in pediatric patients with severe plaque or pustular psoriasis that is unresponsive to other systemic medications, rapidly progressive, unstable, and/or life threatening (*Menter et al 2020[b]*).
  - EULAR 2019 PsA guidelines recommend biologic DMARDs in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, such as MTX. For patients with peripheral arthritis, an inadequate response to at least 1 synthetic DMARD, and relevant skin involvement, biologics targeting IL-12/23 or IL-17 pathways may be considered. In patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD and at least one biologic DMARD, JAK inhibitors may be considered; JAK inhibitors may also be considered in patients for whom biologic DMARD therapy is not appropriate. Apremilast is considered a treatment option in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, in whom biologics and JAK inhibitors are not appropriate (*Gossec et al 2020, Kerschbaumer et al 2020*).
  - The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommendations for PsA vary based on whether the arthritis is peripheral or axial and based on prior therapies, and may include DMARDS, NSAIDs, simple analgesics, a TNF inhibitor, an IL-12/23 inhibitor, or a PDE-4 inhibitor (*Coates et al 2016).*
  - The American College of Rheumatology/National Psoriasis Foundation guideline on PsA recommends that a TNF inhibitor is preferred in treatment-naïve patients with active PsA, although an oral therapy (MTX, sulfasalazine, leflunomide, cyclosporine, or apremilast) can be a first-line option in patients without severe PsA and without severe psoriasis, or if a patient has another compelling reason to avoid a TNF inhibitor. In patients who fail oral therapy, a switch to a TNF inhibitor is preferred and placed ahead of IL-17 biologics (secukinumab, ixekizumab, brodalumab), IL-12/23 biologics (ustekinumab), abatacept, and tofacitinib (*Singh et al 2019*).
- AS:
  - The American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network joint recommendations for treatment of AS and NRAS were updated in 2019. Patients with active AS or NRAS who do not respond to initial NSAID therapy are conditionally recommended to be treated with sulfasalazine, MTX, or tofacitinib; sulfasalazine or methotrexate should be considered only in patients with prominent peripheral arthritis or when TNF inhibitors are not available. Patients who do not respond to NSAID therapy are strongly recommended to receive treatment with a TNF inhibitor, although no particular TNF inhibitor is preferred. Treatment with a TNF inhibitor is conditionally recommended over tofacitinib, secukinumab, and ixekizumab in these patients. In patients with active disease who have primary nonresponse with a TNF inhibitor, treatment with secukinumab or ixekizumab is strongly recommended, and treatment with tofacitinib is conditionally recommended.

Patients with secondary nonresponse to treatment with a TNF inhibitor are conditionally recommended to receive treatment with an alternative TNF inhibitor. In patients with AS and inflammatory bowel disease or recurrent iritis, TNF inhibitors are conditionally recommended over treatment with other biologics. In patients with stable disease who are treated with an originator TNF inhibitor, the guideline strongly recommends continuing the originator TNF inhibitor over mandated switching to its biosimilar *(Ward et al 2019).*

- Joint recommendations for the management of axial spondyloarthritis are available from ASAS and EULAR. (AS is synonymous with radiographic axial spondyloarthritis; these guidelines also include non-radiographic axial spondyloarthritis). The guidelines state that NSAIDs should be used first-line in patients with pain and stiffness; other analgesics might be considered if NSAIDs have failed or are contraindicated or poorly tolerated. Glucocorticoid injections may be considered but patients with axial disease should not receive long-term systemic glucocorticoids. Sulfasalazine may be considered in patients with peripheral arthritis, but patients with purely axial disease should normally not be treated with conventional DMARDs. Biologic DMARDs should be considered in patients with persistently high disease activity despite conventional treatments, and current practice is to start with a TNF inhibitor. If a TNF inhibitor fails, switching to another TNF inhibitor or to an IL-17 inhibitor should be considered (*van der Heijde et al 2017[b]*).

- Ocular inflammatory disorders:
  - Expert panel recommendations for the use of TNF inhibitors in patients with ocular inflammatory disorders are available from the American Uveitis Society (*Levy-Clarke et al 2014*). Infliximab and adalimumab can be considered as first-line immunomodulatory agents for the treatment of ocular manifestations of Behçet's disease and as second-line immunomodulatory agents for the treatment of UV associated with juvenile arthritis. They also can be considered as potential second-line immunomodulatory agents for the treatment of severe ocular inflammatory conditions including posterior UV, panuveitis, severe UV associated with seronegative spondyloarthropathy, and selected patients with scleritis. Etanercept seems to be associated with lower rates of treatment success in these conditions.
  - A 2019 guideline by the ACR and Arthritis foundation focusing on children with JIA-associated UV conditionally recommended starting a monoclonal antibody TNF inhibitor over etanercept in children and adolescents with chronic anterior UV. Children and adolescents with inadequate response to one monoclonal TNF inhibitor are conditionally recommended to be treated with an escalated dose and/or frequency of the TNF inhibitor over switching to another TNF inhibitor; patients failing dose escalation are conditionally recommended to switch to another monoclonal TNF inhibitor. Children and adolescents failing MTX and 2 monoclonal TNF inhibitors are conditionally recommended to receive abatacept or tocilizumab as biologic DMARD options *(Angeles-Han et al 2019).*

- Additional indications:
  - Based upon guidelines from the European Dermatology Forum, adalimumab is recommended among first-line therapies for HS, and infliximab may be considered a second-line option (*Gulliver et al 2016, Zouboulis et al 2015*).
  - For the treatment of FMF, EULAR recommendations state that treatment with colchicine should begin as soon as FMF is diagnosed. Biologic treatment, such as anti-IL-1 therapy, is indicated in patients not responding to the maximum tolerated dose of colchicine. TNF inhibitors have also been used in colchicine-resistant patients, with good responses seen in observational studies (*Ozen et al 2016*).
  - For the management of HS, the US and Canadian Hidradenitis Suppurativa Foundation recommend adalimumab to improve disease severity and QoL in patients with moderate-to-severe disease (*Alikhan et al, 2019*). Additionally, infliximab is recommended for moderate-to-severe disease; however, the optimal dose is not currently known. Anakinra and ustekinumab may be effective agents for HS as well.
  - For the management of GCA, EULAR recommendations state that tocilizumab (or methotrexate as an alternative) should be used as an adjunctive therapy in patients who have refractory or relapsing disease or who are at an increased risk of glucocorticoid-related adverse effects or complications (*Hellmich et al 2020*).
  - No recent guidelines were identified for CAPS, CRS, DIRA, HIDS/MKD, TRAPS, or Still's disease.

SAFETY SUMMARY

- Contraindications:
  - Actemra (tocilizumab), Avsola (infliximab-axxq), Cimzia (certolizumab), Cosentyx (secukinumab), Entyvio (vedolizumab), Ilaris (canakinumab), Ilumya (tildrakizumab-asmn), Inflectra (infliximab-dyyb), Kevzara (sarilumab), Kineret (anakinra), Otezla (apremilast), Remicade (infliximab), Renflexis (infliximab-abda), Stelara (ustekinumab), and Taltz (ixekizumab) use in patients with hypersensitivity to any component of the product.
  - Siliq in patients with CD because Siliq may cause worsening of disease.
  - Enbrel (etanercept) in patients with sepsis.

- Kineret (anakinra) in patients with hypersensitivity to *E coli*-derived proteins.
- Remicade (infliximab), Avsola (infliximab-axxq), Inflectra (infliximab-dyyb), and Renflexis (infliximab-abda) in patients with hypersensitivity to murine proteins; and doses >5 mg/kg in patients with moderate to severe heart failure.

- Boxed Warnings:
  - Actemra (tocilizumab), Avsola (infliximab-axxq), Cimzia (certolizumab), Enbrel (etanercept), Humira (adalimumab), Inflectra (infliximab-dyyb), Kevzara (sarilumab), Olumiant (baricitinib), Remicade (infliximab), Renflexis (infliximab-abda), Rinvoq (upadacitinib), Simponi / Simponi Aria (golimumab), and Xeljanz / Xeljanz XR/Xeljanz oral solution (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), Enbrel (etanercept), Humira (adalimumab), Inflectra (infliximab-dyyb), Olumiant (baricitinib), Remicade (infliximab), Renflexis (infliximab-abda), Rinvoq (upadacitinib), Simponi / Simponi Aria (golimumab), and Xeljanz (tofacitinib) all have warnings for increased risk of malignancies.
  - Xeljanz/Xeljanz XR/Xeljanz oral solution (tofacitinib) have 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. Rinvoq (upadacitinib) and Olumiant (baricitinib), other JAK inhibitors, also carry a boxed warning for this risk.
  - Rituxan (rituximab) and Truxima (rituximab-abbs) can cause fatal infusion reactions, hepatitis B activation, severe mucocutaneous reactions, and progressive multifocal leukoencephalopathy (PML).
  - Siliq has a boxed warning that suicidal ideation and behavior, including completed suicides, have occurred in patients treated with Siliq. The prescriber should weigh potential risks and benefits in patients with a history of depression and/or suicidal ideation or behavior, and patients should seek medical attention if these conditions arise or worsen during treatment.
  - Olumiant (baricitinib) has a boxed warning for thrombosis, including deep venous thrombosis, pulmonary embolism, and arterial thrombosis.
- Warnings/Precautions (applying to some or all of the agents in the class):
  - Reactivation of 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 heart failure
  - 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 Actemra (tocilizumab), Xeljanz/Xeljanz XR/Xeljanz oral solution (tofacitinib) and Kevzara (sarilumab)
  - Increased incidence of CD and UC with Cosentyx (secukinumab) and Taltz (ixekizumab); risk of new-onset CD or exacerbation of CD with Siliq (brodalumab)
  - Infusion-related and hypersensitivity reactions with Entyvio (vedolizumab)
  - Diarrhea, nausea, and vomiting with Otezla (apremilast)
  - Depression with Otezla (apremilast)
  - Gastrointestinal perforations with Xeljanz/Xeljanz XR/Xeljanz oral solution (tofacitinib), Olumiant (baricitinib), Actemra (tocilizumab), Kevzara (sarilumab), Rituxan (rituximab), and Truxima (rituximab-abbs)
  - PML with Entyvio (vedolizumab)
  - Thrombosis with Olumiant (baricitinib)
  - Embryo-fetal toxicity with Rinvoq (upadacitinib)
  - Hepatotoxicity with Actemra (tocilizumab)
  - Cardiovascular and cerebrovascular reactions during and after infusion (infliximab)
  - Macrophage activation syndrome with Ilaris (canakinumab)
  - Posterior reversible encephalopathy syndrome (PRES) with Stelara (ustekinumab)
  - Consult prescribing information for other drug-specific warnings/precautions
- Adverse Reactions:
  - Infusion site reactions, diarrhea, nausea/vomiting, abdominal pain, infections, hypertension, and headache.

- Consult prescribing information for other drug-specific AEs

- Risks of Long-Term Treatment: As it becomes accepted practice to treat patients with these conditions 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.
  - Rheumatoid Arthritis
    - Safety of adalimumab for RA has been supported in a 5-year study in RA and a 10-year study in patients with early RA (*Keystone et al 2014a, Burmester et al 2014b*). In the 5-year extension study, overall rates of serious AEs and serious infections were 13.8 events per 100 PY and 2.8 events per 100 PY, respectively. The rate of serious events was highest in the first 6 months and then declined. No new safety signals were reported in the 10-year study.
    - Certolizumab plus MTX had a consistent safety profile over 5 years in patients with RA (*Keystone et al 2014b*). The most frequently reported AEs included urinary tract infections (rate of 7.9 per 100 patient-years), nasopharyngitis (rate of 7.3 per 100 PY), and upper respiratory infections (rate of 7.3 per 100 PY). Serious AE rates were 5.9 events per 100 patient-years for serious infections and 1.2 events per 100 PY for malignancies.
    - Abatacept has been evaluated in 2 long-term extension studies. Abatacept IV plus MTX demonstrated a similar safety profile between the 7 year follow-up and a 52-week double-blind study (*Westhovens et al 2014*). Serious AEs reported in both the double-blind and long-term follow-up studies were the following: serious infections (17.6 events per 100 PY), malignancies (3.2 events per 100 PY), and autoimmune events (1.2 events per 100 PY). In a 5-year extension trial, rates of serious infections, malignancies, and autoimmune events were 2.8, 1.5, and 0.99 events per 100 patient-years exposure, respectively. Efficacy was demonstrated by ACR 20 with response rates of 82.3% and 83.6% of patients at year 1 and year 5, respectively.
    - Data from 5 RCTs of Actemra (tocilizumab), their open-label extension trials, and a drug interaction study were analyzed for measures of safety. A total of 4,009 patients with moderate to severe RA received at least 1 dose of tocilizumab. Mean duration of tocilizumab treatment was 3.07 years (up to 4.6 years); total duration of observation was 12,293 PY. The most common AEs and serious AEs were infections. A longer-term safety profile from this analysis matches previous observations. No new safety signals were identified (*Genovese et al 2013*).
    - A Cochrane review showed no evidence of a statistically significant difference in the rate of withdrawal because of AEs in the Enbrel (etanercept) plus DMARD group and the DMARD alone group at 6 months, 12 months, and 2 years. At 3 years, withdrawals were significantly reduced in the etanercept 25 mg plus DMARD group compared with the DMARD alone group (RR, 0.7; 95% CI, 0.5 to 1). There was no evidence of statistically significant differences in the rates of breast cancer at 12 months, fever at 6 months, flu-like syndrome at 6 months and 2 years, infection at 6 months and 2 years, malignancy at 12 months and 2 years, pneumonia at 12 months, and serious infection at 12 months and 2 years between the etanercept plus DMARD group and the DMARD group (*Lethaby et al 2013*).
    - A systematic review analyzed 66 randomized controlled trials and 22 long-term extension studies evaluating biologics and tofacitinib for the rate of serious infections in patients with moderate to severe active RA (*Strand et al 2015b*). The estimated incidence rates (unique patients with events/100 patient-years) of serious infections were 3.04 (95% CI, 2.49 to 3.72) for abatacept, 3.72 (95% CI, 2.99 to 4.62) for rituximab, 5.45 (95% CI, 4.26 to 6.96) for tocilizumab, 4.90 (95% CI, 4.41 to 5.44) for TNF inhibitors, and 3.02 (95% CI, 2.25 to 4.05) for tofacitinib 5 mg and 3.00 (95% CI, 2.24 to 4.02) for tofacitinib 10 mg. Authors concluded that the rates of serious infections with tofacitinib in RA patients are within the range of those reported for biologic DMARDs.
    - A meta-analysis analyzed 50 randomized controlled trials and long-term extension studies evaluating biologic DMARDs and tofacitinib to compare the risks of malignancies in patients with RA (*Maneiro et al 2017*). The overall risk of malignancies was 1.01 (95% CI, 0.72 to 1.42) for all TNF antagonists, 1.12 (95% CI, 0.33 to 3.81) for abatacept, 0.54 (95% CI, 0.20 to 1.50) for rituximab, 0.70 (95% CI, 0.20 to 2.41) for tocilizumab, and 2.39 (95% CI, 0.50 to 11.5) for tofacitinib. The authors concluded that treatment with biologic DMARDs or tofacitinib does not increase the risk of malignancies.
    - A pooled analysis of 9 RA trials evaluating baricitinib included 3492 patients (7860 PY exposure). The incidence rate for major adverse cardiovascular events was comparable between placebo (0.5 per 100 PY) and baricitinib 4 mg (0.8 per 100 PY). Incidence rates for arterial thrombotic events and congestive heart failure were also similar between baricitinib and placebo. The occurrence of a deep vein thrombosis or pulmonary embolism occurred more frequently in the baricinitib 4 mg group (6 events in 997 patients) vs placebo (0 events in 1070 patients) (*Taylor et al 2019*).

- PsO
  - A total of 3,117 patients treated with at least 1 dose of Stelara (ustekinumab) for moderate to severe PsO were evaluated for long-term safety. At least 4 years of ustekinumab exposure was seen in 1,482 patients (including 838 patients with ≥ 5 years of exposure). The most commonly reported AEs were nasopharyngitis, upper respiratory tract infection, headache and arthralgia. Infections, malignancies and cardiac disorders were the most commonly reported serious AEs. Twenty deaths were reported through year 5. The causes of death were considered related to cardiovascular events (n = 5), malignancy (n = 5), infection (n = 3) and other causes (n = 7). The observed mortality rate among ustekinumab-treated patients was consistent with that expected in the general U.S. population (SMR = 0.36; 95% CI, 0.22 to 0.55). From year 1 to year 5, rates of overall AEs, and AEs leading to discontinuation generally decreased. Serious AE rates demonstrated year-to-year variability with no increasing trend. The results of this long-term study of AEs are similar to reports of shorter-term studies (*Papp et al 2013*).
  - In a 5-year extension study, a total of 2510 patients on etanercept for the treatment of PsO were evaluated for long-term safety and efficacy (*Kimball et al 2015*). Serious AEs were reported as a cumulative incidence of the entire 5-year observation period. The following incidences were reported: serious infections (6.5%, 95% CI, 5.4 to 7.7%); malignancies excluding nonmelanoma skin cancer (3.2%, 95% CI, 2.3 to 4.1%); nonmelanoma skin cancer (3.6%, 95% CI, 2.7 to 4.1%); coronary artery disease (2.8%, 95% CI, 2 to 3.6%); PsO worsening (0.7%, 95% CI, 0.3 to 1.2%); CNS demyelinating disorder (0.2%, 95%CI, 0 to 0.4%); lymphoma and tuberculosis each (0.1%, 95% CI, 0 to 0.3%); and opportunistic infection and lupus each (0.1%, 95%CI, 0 to 0.2%). A total of 51% of patients reported clear/almost clear rating at month 6 and remained stable through 5 years.
  - In a ≥ 156-week extension study, a total of 1,184 patients treated with apremilast in ESTEEM 1 and 2 were evaluated for long-term safety and tolerability (*Crowley et al 2017*). Serious AEs (≥ 2 patients) were coronary artery disease (n = 6), acute myocardial infarction (n = 4), osteoarthritis (n = 4), and nephrolithiasis (n = 4). The exposure-adjusted incidence rate for major cardiac events was 0.5/100 patients years, for malignancies was 1.2/100 patient years, for serious infections was 0.9/100 patient-years, and for suicide attempts was 0.1/100 patient-years.
  - A multicenter registry called Psoriasis Longitudinal Assessment and Registry (PSOLAR) evaluated the risk of serious infections in patients with PsO (*Kalb et al 2015*). Patients were followed for up to 8 years with a total of 11,466 patients with PsO enrolled, 74.3% of whom were from the U.S. A total of 22,311 patient-years of data were collected. Ustekinumab, infliximab, adalimumab, and etanercept as well as traditional DMARDs were included in the data analysis. During the follow-up period, 323 serious infections were reported. The rates of serious infections per 100 patient-years were 0.83 (secukinumab), 1.47 (etanercept), 1.97 (adalimumab), and 2.49 (infliximab). The most commonly reported serious infection was cellulitis. Risk factors for serious infections were increasing age, diabetes mellitus, smoking, and history of significant infections prior to registry entry. Exposure to infliximab (hazard ratio, 2.51; 95% CI, 1.45 to 4.33; $p < 0.001$) and adalimumab (hazard ratio, 2.13; 95% CI, 1.33 to 3.41; $p = 0.002$) during the registry were independently associated with the risk of serious infections whereas use of ustekinumab or etanercept were not.
- PsA
  - Subcutaneous golimumab for patients with active PsA demonstrated safety and efficacy over 5 years in the long-term extension of the randomized, placebo-controlled GO-REVEAL study (*Kavanaugh et al 2014b*). Approximately one-half of patients also took MTX concurrently. No new safety signals were observed.
- AS
  - A meta-analysis of 25 randomized controlled studies with 2,403 patients with AS or non-radiographic axial spondyloarthritis treated with agents such as adalimumab, certolizumab, etanercept, golimumab, infliximab, sarilumab, tocilizumab, and secukinumab showed no significant increase in the risk of serious infections with biologic agents compared to controls (OR, 1.42; 95% CI, 0.58 to 3.47) (*Wang et al 2018*).
  - Another meta-analysis of 14 randomized controlled trials with 2,032 patients with AS that were treated with adalimumab, certolizumab, etanercept, golimumab, or infliximab revealed no significant difference between TNF inhibitors and placebo for overall serious adverse events (OR, 1.34; 95% CI, 0.87 to 2.05), risk of serious infections (OR, 1.59; 95% CI, 0.63 to 4.01), risk of malignancy (OR, 0.98; 95% CI, 0.25 to 3.85), and discontinuation due to adverse events (OR, 1.55; 95% CI, 0.95 to 2.54) (*Hou et al 2018*).
- Multiple indications
  - One study looked at 23,458 patients who were treated with Humira (adalimumab) for RA, JIA, AS, PsA, PsO and 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 anti-TNF therapies (*Burmester et al 2013b*).

- Pooled data from 5 Phase 3 trials of SQ golimumab over at least 3 years demonstrated a safety profile consistent with other TNF inhibitors (*Kay et al 2015*). A total of 1,179 patients with RA, PsA or AS were treated for at least 156 weeks. Rates of AEs up to week 160 for placebo, golimumab 50 mg and golimumab 100 mg, respectively, were as follows: 0.28, 0.30, 0.41 for death; 5.31, 3.03, 5.09 for serious infection; 0, 0.17, 0.35 for tuberculosis; 0, 0.13, 0.24 for opportunistic infection; 0, 0, 0.12 for demyelination; and 0, 0.04, 0.18 for lymphoma.
- A total of 18 multicenter, placebo-controlled, randomized controlled trials evaluated the safety profile of certolizumab pegol monotherapy or in combination with DMARDs in RA, CD, AS, PsA and PsO (*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), ADRs (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 PsO, PsA, and CD. A total of 5584 patients were evaluated, equating to 4521 PYs. Respective incidences per 100 PY of infections (125.4 vs 129.4), major cardiovascular adverse events (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*).
- Several meta-analyses evaluated the safety of TNF inhibitors.
  - An analysis of TNF inhibitors in RA, PsA, and AS included data from 71 randomized trials (follow-up 1 to 36 months) and 7 open-label extension studies (follow-up 6 to 48 months) (*Minozzi et al 2016*). The data demonstrated that use of TNF inhibitors increases the risk of infectious AEs. Overall, there was a 20% increase of any infections, a 40% increase of serious infections, and a 250% increase of tuberculosis. The tuberculosis incidence rate was higher with infliximab and adalimumab compared to etanercept. There was little data on the incidence of opportunistic infections.
  - An analysis of TNF inhibitors in RA, PsA, and AS included data from 32 randomized trials (follow-up 2 to 36 months) and 6 open-label extension trials (follow-up 6 to 48 months) (*Bonovas et al 2016*). Synthesis of the data did not demonstrate that the use of TNF inhibitors significantly affects cancer risk during this length of treatment. However, few malignancy events were observed and evidence may be insufficient to make definitive conclusions, particularly regarding longer-term risks.

- 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/Xeljanz oral solution (tofacitinib), adjust dose with potent inhibitors of cytochrome P450 (CYP) 3A4 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.
- Risk Evaluation and Mitigation Strategy (REMS)
  - Siliq (brodalumab) is available only through the Siliq REMS program. The goal of the program is to mitigate the risk of suicidal ideation and behavior, including completed suicides, which occurred in clinical trials. Key requirements of the REMS program include:
    - Prescribers must be certified with the program.
    - Patients must enroll in the program.
    - Pharmacies must be certified with the program and must only dispense to patients who are enrolled in the program.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Actemra (tocilizumab)	Vials: 80 mg/4 mL; 200 mg/10 mL; 400 mg/20 mL	**RA:** IV: 4 mg/kg IV every 4 weeks. May increase to 8 mg/kg IV every 4 weeks. Maximum dose = 800	**RA:** Can give with MTX or other DMARDs.	Give as a single 60-minute intravenous infusion. <30 kg, use a 50 mL infusion bag.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
	Prefilled syringe or autoinjector: 162 mg/0.9 mL	mg. SQ: <100 kg, administer 162 mg SQ every other week, followed by an increase to every week based on clinical response; ≥100 kg, 162 mg administered SQ every week. **PJIA:** <30 kg, 10 mg/kg IV every 4 weeks; ≥30 kg, 8 mg/kg IV every 4 weeks. <30 kg, 162 mg SQ every 3 weeks; ≥30 kg, 162 mg SQ every 2 weeks. **SJIA:** <30 kg, 12 mg/kg IV every 2 weeks; ≥30 kg, 8 mg/kg IV every 2 weeks; <30 kg, 162 mg SQ every 2 weeks; ≥30 kg, 162 mg SQ once weekly. **GCA:** 162 mg SQ every week with tapering glucocorticoids. May give every other week depending on clinical considerations. **CRS:** <30 kg, 12 mg/kg IV; ≥30 kg, 8 mg/kg IV; maximum, 800 mg per infusion.	**PJIA and SJIA:** Can give with MTX. **GCA:** Can use alone after discontinuation of glucocorticoids. **CRS:** Can give with corticosteroids. May repeat up to 3 additional doses if no clinical improvement, with at least 8 hours between doses. **RA, PJIA, and SJIA, and GCA**: Adjust dose for liver enzyme abnormalities, low platelet count, infection, and low ANC.	≥30 kg, use a 100 mL infusion bag. Before infusion, allow bag to come to room temperature. Do not administer with other drugs. Patients can self-inject with the prefilled syringe or autoinjector. Rotate injection sites.
Avsola (infliximab-axxq)	Vial: 100 mg	**CD (≥ 6 years old), PsA, PsO and UC (≥ 6 years old)**: 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. **RA:** 3 mg/kg IV at 0, 2, and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase	**RA:** give with MTX. **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. Do not administer with other drugs.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		to 10 mg/kg or give every 4 weeks. **AS:** 5 mg/kg IV at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.		
Cimzia (certolizumab)	Powder for reconstitution: 200 mg Prefilled syringe: 200 mg/mL	**CD:** 400 mg SQ initially and at weeks 2 and 4. Maintenance dose is 400 mg every 4 weeks. **RA, PsA:** 400 mg SQ initially and at weeks 2 and 4. Then 200 mg every 2 weeks. Can consider a maintenance dose of 400 mg every 4 weeks. **PsO:** 400 mg SQ every other week or 400 mg SQ initially and at weeks 2 and 4, followed by 200 mg every other week (for body weight ≤ 90 kg) **AS, NRAS:** 400 mg SQ initially and at weeks 2 and 4. Maintenance dose is 200 mg every 2 weeks or 400 mg every 4 weeks.	Patients can self-inject with the prefilled syringe.	When a 400 mg dose is required, give as 2 200 mg SQ injections in separate sites in the thigh or abdomen.
Cosentyx (secukinumab)	Sensoready pen: 150 mg/1 mL Prefilled syringe: 150 mg/1 mL Vial: 150 mg lyophilized powder	**PsO:** 300 mg by SQ injection at weeks 0, 1, 2, 3 and 4, followed by 300 mg every 4 weeks. **PsA, AS, NRAS:** With a loading dose (not required): 150 mg at weeks 0, 1, 2, 3, and 4, followed by 150 mg every 4 weeks; without loading dose: 150 mg every 4 weeks.	**PsO:** For some patients, a dose of 150 mg may be acceptable. **PsA:** For PsA patients with coexistent moderate to severe PsO, dosing for PsO should be followed. If active PsA or AS continues, consider 300 mg dose every 4 weeks.	Each 300 mg dose is given as 2 subcutaneous injections of 150 mg. Patients may self-administer with the pen or prefilled syringe. The vial is for healthcare professional use only.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Enbrel (etanercept)	Prefilled syringe: 25 mg/0.5 mL and 50 mg/mL Prefilled SureClick autoinjector: 50 mg/mL Multiple-use vial: 25 mg lyophilized powder Solution: 50 mg/mL in Enbrel Mini® cartridge for use with reusable autoinjector only Single-dose vial: 25 mg/0.5 mL	**RA, AS, PsA:** 50 mg SQ weekly. **PsO (adults):** 50 mg SQ twice weekly for 3 months, then 50 mg weekly. **PJIA and PsO (pediatrics):** ≥63 kg, 50 mg SQ weekly; <63 kg, 0.8 mg/kg SQ weekly.	**RA, AS, PsA:** MTX, NSAIDs, glucocorticoids, salicylates, or analgesics may be continued. **JIA:** NSAIDs glucocorticoids, or analgesics may be continued.	Patients may be taught to self-inject. May bring to room temperature prior to injecting.
Entyvio (vedolizumab)	Lyophilized cake for injection in 300 mg single-dose vial	**CD and UC:** 300 mg administered by IV infusion at time 0, 2, and 6 weeks, and then every 8 weeks thereafter. Discontinue therapy if there is no evidence of therapeutic benefit by week 14.	All immunizations should be 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.
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	**RA, AS, PsA**: 40 mg SQ every other week. For RA, may increase to 40 mg every week or 80 mg every other week if not on MTX. **PJIA or pediatric uveitis:** 10 kg to <15 kg: 10 mg SQ every other week; 15 kg to <30 kg: 20 mg SQ every other week; ≥30 kg, 40 mg SQ every other week **CD and UC:** 160 mg SQ on Day 1 (given in 1 day or split over 2 consecutive days), followed by 80 mg SQ 2 weeks later (Day 15). Two weeks later (Day 29) begin a maintenance dose of 40 mg SQ every other week. **HS:** 160 mg SQ on Day 1 (given in 1 day or split	**RA, AS, PsA:** MTX, other non-biologic DMARDS, glucocorticoids, NSAIDs, and/or analgesics may be continued. **JIA:** NSAIDs, MTX, analgesics, and/or glucocorticoids, may be continued. **CD and UC:** aminosalicylates and/or corticosteroids may be continued. Azathioprine, 6-MP or MTX 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.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		over 2 consecutive days), followed by 80 mg SQ 2 weeks later (Day 15). Two weeks later (Day 29), begin 40 mg weekly or 80 mg every other week. **PsO and UV:** initial dose of 80 mg SQ, followed by 40 mg SQ every other week starting 1 week after the initial dose. **CD in pediatric patients ≥ 6 years and older:** 17 kg to < 40 kg: 80 mg on day 1 (given as two 40 mg injections) and 40 mg 2 weeks later (on day 15); maintenance dose is 20 mg every other week starting at week 4. ≥40 kg: 160 mg on day (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. **HS in adolescent patients ≥ 12 years and older:** 30 kg to <60 kg: 80 mg on day 1, 40 mg on day 8; maintenance dose is 40 mg every other week. ≥60 kg: 160 mg on day 1, 80 mg on day 15, 40 mg on day 29; maintenance dose is 40 mg every week.		

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Ilaris (canakinumab)	Single-dose vial: 150 mg injection solution	**SJIA and adult-onset Still's disease:** ≥7.5 kg, 4 mg/kg SQ every 4 weeks (maximum dose of 300 mg). **CAPS**: ≥15 to ≤40 kg, 2 mg/kg SQ; >40 kg, 150 mg SQ; frequency every 8 weeks. **TRAPS, HIDS/MKD, and FMF**: ≤40 kg, 2 mg/kg SQ; >40 kg, 150 mg SQ; frequency every 4 weeks.	For CAPS: children 15 to 40 kg with an inadequate response can be increased to 3 mg/kg. For TRAPS, HIDS/MKD, and FMF: If the clinical response is inadequate, the dose may be increased to 4 mg/kg (weight ≤40 kg) or 300 mg (weight >40 kg).	Do not inject into scar tissue.
Ilumya (tildrakizumab-asmn)	Prefilled syringe: 100 mg/mL	**PsO:** 100 mg SQ at weeks 0 and 4, and then every 12 weeks.		Should be administered only by a healthcare provider. Bring to room temperature (30 minutes) prior to injecting.
Inflectra (infliximab-dyyb)	Vial: 100 mg	**CD (≥ 6 years old), PsA, PsO and UC (≥6 years old)**: 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. **RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg or give every 4 weeks. **AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.	**RA:** give with MTX. **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. Do not administer with other drugs.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Kevzara (sarilumab)	Prefilled syringe: 150 mg/1.14 mL 200 mg/1.14 mL Prefilled pen: 150 mg/1.14 mL 200 mg/1.14 mL	**RA:** 200 mg SQ every 2 weeks.	**RA:** give with or without MTX or other conventional DMARDs Reduce dose for neutropenia, thrombocytopenia, and elevated liver enzymes.	Patients may be taught to self-inject. Bring to room temperature (30 minutes [pre-filled syringe] or 60 minutes [pre-filled pen]) prior to injecting. Rotate injection sites.
Kineret (anakinra)	Prefilled syringe: 100 mg/0.67 mL	**RA:** 100 mg SQ once daily. **CAPS (NOMID) and DIRA:** 1 to 2 mg/kg SQ once daily. Maximum dose is 8 mg/kg/day.	**NOMID**: dose can be given once or twice daily.	Patients may be taught to self-inject. A new syringe must be used for each dose.
Olumiant (baricitinib)	Tablet: 1 mg, 2 mg	**RA:** 2 mg once daily.	Avoid use in combination with other JAK inhibitiors, biologic DMARDs, or potent immunosuppressants such as azathioprine and cyclosporine.	May be taken with or without food.
Orencia (abatacept)	Vial: 250 mg Prefilled syringe: 50 mg/0.4 mL 87.5 mg/0.7 mL 125 mg/1 mL ClickJect autoinjector: 125 mg/mL	**RA:** IV: <60kg, 500 mg IV; 60 to 100 kg, 750 mg IV; >100 kg, 1,000 mg IV initially, then 2 and 4 weeks after the first infusion and every 4 weeks thereafter SQ: 125 mg SQ once weekly initiated with or without an IV loading dose. With IV loading dose, use single IV infusion as per body weight listed above, followed by the first 125 mg SQ injection within a day of the IV infusion and then once weekly. **PJIA:** IV: 6 to 17 years and <75 kg: 10 mg/kg IV initially, then 2 and 4 weeks after the first infusion and every 4		IV infusion should be over 30 minutes. Use 100 mL bag for IV infusion. Do not administer with other drugs. Patients may be taught to self-inject the SQ dose. For SQ, injection sites should be rotated.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		weeks thereafter. >75 kg, follow adult RA IV schedule; maximum dose = 1,000 kg. SQ: 2 to 17 years, 10 to <25 kg, 50 mg once weekly; 25 to < 50 kg, 87.5 mg once weekly, ≥ 50 kg, 125 mg once weekly. **PsA:** IV: follow adult RA IV schedule. SQ: 125 mg once weekly without IV dose.		
Otezla (apremilast)	Tablet: 10 mg, 20 mg, and 30 mg	**PsA, PsO, Behçet's:** Day 1: 10 mg in the morning Day 2: 10 mg in the morning and in the evening Day 3: 10 mg in the morning and 20 mg in evening Day 4: 20 mg in the morning and evening Day 5: 20 mg in the morning and 30 mg in the evening Day 6 and thereafter: 30 mg twice daily.	Titrate according to the labeling when initiating therapy to reduce gastrointestinal symptoms. Dosage should be reduced to 30 mg once daily in patients with severe renal impairment (CrCl <30 mL/min as estimated by the Cockcroft-Gault equation). For initial dosing in these patients, use only the morning titration schedule listed above (evening doses should be excluded).	May be taken with or without food. Do not crush, split, or chew the tablets.
Remicade (infliximab)	Vial: 100 mg	**CD (≥ 6 years old), PsA, PsO and UC (≥ 6 years old)**: 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.	**RA:** give with MTX. **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.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		RA: 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg or give every 4 weeks. **AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.		Do not administer with other drugs.
Renflexis (infliximab-abda)	Vial: 100 mg	**CD (≥ 6 years old), PsA, PsO and UC (≥ 6 years old)**: 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. **RA:** 3 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 3 mg/kg every 8 weeks. Can increase to 10 mg/kg or give every 4 weeks. **AS:** 5 mg/kg IV at 0, 2 and 6 weeks followed by a maintenance regimen of 5 mg/kg every 6 weeks.	**RA:** give with MTX. **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. Do not administer with other drugs.
Rinvoq (upadacitinib)	Extended release tablet: 15 mg	**RA:** 15 mg once daily.		May be administered with or without food.
Rituxan (rituximab)	Vial: 100 mg/10 mL 500 mg/50 mL	**RA:** Two 1000 mg IV infusions separated by 2 weeks (one course). Additional doses should be given every 24 weeks or based on clinical evaluation but no sooner than every 16 weeks.	Give with MTX.	Give methyl-prednisolone 100 mg IV 30 minutes prior to each infusion to reduce the incidence and severity of infusion reactions.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
Siliq (brodalumab)	Prefilled syringe: 210 mg/1.5 mL	**PsO:** 210 mg SQ at weeks 0, 1, and 2 followed by every 2 weeks.	**PsO**: If an adequate response has not been achieved after 12 to 16 weeks, consider discontinuation.	Patients may self-inject when appropriate and after proper training. The syringe should be allowed to reach room temperature before injecting.
Simponi/Simponi Aria (golimumab)	SmartJect® autoinjector: 50 mg/0.5 mL and 100 mg/mL Prefilled syringe: 50 mg/0.5 mL and 100 mg/mL Aria, Vial: 50 mg/4 mL	**RA, PsA, and AS**: 50 mg SQ once monthly **UC:** 200 mg SQ at week 0; then 100 mg at week 2; then 100 mg every 4 weeks. **Aria (RA, PsA, and AS)**: 2 mg/kg IV at weeks 0 and 4, then every 8 weeks. **Aria (PJIA):** 80 mg/m^2 IV at weeks 0 and 4, and then every 8 weeks.	**RA:** give with MTX. **PsA and AS**: may give with or without MTX or other DMARDs. Needle cover of the syringe contains dry rubber (latex). **Aria (RA)**: give with MTX (**PsA, AS)**: give with or without MTX or other non-biologic DMARDs. Corticosteroids, NSAIDs, and/or analgesics may be continued. Efficacy and safety of switching between IV and SQ formulations have not been established.	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. **Aria**: IV infusion should be over 30 minutes. Dilute with 0.9% sodium chloride or 0.45% sodium chloride for a final volume of 100 mL. Do not administer with other drugs.
Skyrizi (risankizumab-rzaa)	Prefilled syringe: 75 mg/0.83 mL	**PsO:** 150 mg (two 75 mg injections) SQ at week 0, week 4, and every 12 weeks thereafter.	Product is not made with natural rubber latex.	Each dose must be administered in different anatomic locations. Patients may be taught to self-inject using the prefilled syringes.
Stelara (ustekinumab)	Prefilled syringe: 45mg/0.5 mL and 90 mg/mL Vial: 45 mg/0.5 mL and 130 mg/26 mL	**PsO**: ≤100 kg, 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. >100 kg, 90 mg SQ initially and 4 weeks	**Co-existent moderate-to-severe PsO with PsA weighing >100 kg**: 90 mg SQ initially and 4 weeks later,	Patients may be taught to self-inject using the prefilled syringes. In pediatric patients, it is recommended that Stelara be administered by a

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		later, followed by 90 mg every 12 weeks. **PsO (≥ 6 years):** <60 kg, 0.75 mg/kg (injection volume based on weight) 60 to 100 kg, 45 mg >100 kg, 90 mg; administer recommended dose initially, 4 weeks later, than every 12 weeks. **PsA:** 45 mg SQ initially and 4 weeks later, followed by 45 mg every 12 weeks. **CD and UC**: 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).	followed by 90 mg every 12 weeks. Needle cover of the syringe contains dry rubber (latex).	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.
Taltz (ixekizumab)	Prefilled syringe: 80 mg/mL Autoinjector: 80 mg/mL	**PsO:** 160 mg by SQ injection at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks. **PsO (6 to <18 years old):** <25 kg, 40 mg SQ at week 0 then 20 mg every 4 weeks; 25 to 50 kg, 80 mg SQ at week 0 then 40 mg every 4 weeks; >50 kg, 160 mg SQ at week 0, then 80 mg every 4 weeks. **PsA, AS:** 160 mg by SQ injection at week 0, followed by 80 mg every 4 weeks. **NRAS:** 80 mg by SQ injection every 4 weeks.		Patients weighing >50 kg may be taught to self-inject with either the prefilled syringe or the autoinjector. Bring to room temperature prior to injecting. Rotate injection sites. Doses for patients weighing ≤50 kg must be administered by a healthcare professional. Contents of a prefilled syringe should be transferred to a sterile vial, and the appropriate dose drawn out of the vial into a new syringe.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		NOTE: For patients with PsA with coexistent moderate-to-severe PsO, use dosing regimen for PsO.		
Tremfya (guselkumab)	Prefilled syringe or single-dose patient-controlled autoinjector: 100 mg/mL	**PsO, PsA:** 100 mg by SQ injection at week 0, week 4, and then every 8 weeks	For PsA, Tremfya may be used alone or in combination with MTX.	Patients may be taught to self-inject. Bring to room temperature (30 minutes) prior to injecting.
Truxima (rituximab-abbs)	Vial: 100 mg/10 mL 500 mg/50 mL	**RA:** Two 1000 mg IV infusions separated by 2 weeks (one course). Additional doses should be given every 24 weeks or based on clinical evaluation but no sooner than every 16 weeks.	Give with MTX.	Give methyl-prednisolone 100 mg IV 30 minutes prior to each infusion to reduce the incidence and severity of infusion reactions.
Xeljanz/Xeljanz XR (tofacitinib)	Tablet: 5 mg, 10 mg Extended-release Tablet: 11 mg, 22 mg Oral solution: 1 mg/mL	**RA:** 5 mg PO twice daily or 11 mg PO once daily **PsA:** 5 mg PO twice daily or 11 mg once daily used in combination with nonbiologic DMARDs **UC (induction):** 10 mg PO twice daily or 22 mg PO 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. **UC (maintenance):** 5 mg PO twice daily or 11 mg PO once daily; for patients with loss of response during maintenance, 10 mg twice daily or 22 mg once daily may be	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. Use as monotherapy or in combination with MTX or other nonbiologic DMARDs in RA.	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.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing Considerations	Administration Considerations
		considered and limited to the shortest duration. **PJIA:** 3.2 mg (3.2 mL oral solution) twice daily if weight ≥ 10 kg but < 20 kg, 4 mg (4 mL oral solution) twice daily if weight ≥ 20 kg but < 40 kg, and 5 mg (tablet or 5 mL oral solution) twice daily if weight ≥ 40 kg.	Dose adjustment needed in patients taking CYP450 inhibitors and in lymphopenia, neutropenia, and anemia.	

ANC=absolute neutrophil count; AS=ankylosing spondylitis; CRS=cytokine release syndrome; DIRA=deficiency of interleukin-1 receptor antagonist; DMARD=disease-modifying anti-rheumatic drug; GCA=giant cell arteritis; HS=hidradenitis suppurative; IV=intravenous infusion; JAK=Janus kinase; JIA=juvenile idiopathic arthritis; MTX=methotrexate; NOMID=neonatal-onset multisystem inflammatory disease; NRAS=nonradiographic axia spondyloarthritis; NSAID=non-steroidal anti-inflammatory drug; PJIA=polyarticular juvenile idiopathic arthritis; PO=orally; PsA=psoriatic arthritis; PsO=plaque psoriasis; RA=rheumatoid arthritis; SJIA=systemic juvenile idiopathic arthritis; SQ=subcutaneously; UC=ulcerative colitis.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Actemra (tocilizumab)	Frequency of serious infection greater in ≥65 years. Use caution.	Not studied in children <2 years. Safety and efficacy only established in SJIA, PJIA, and CRS.	No dose adjustment in mild or moderate impairment. Not studied in severe impair-ment.	Not studied in patients with impairment.	Unclassified† Limited data in pregnant women not sufficient to determine risks. Unknown whether excreted in breast milk; risks and benefits should be considered.
Avsola (infliximab-axxq)	Frequency of serious infection is greater in ≥65 years. Use caution.	Not recom-mended in children <6 years with CD or UC.	No data	No data	Unclassified† Available data have not reported a clear association with adverse pregnancy outcomes. Unknown whether excreted in breast milk; consider risks and benefits.
Cimzia (certolizumab)	The number of subjects ≥65 years in clinical trials was not sufficient to determine	Safety and effectiveness have not been established.	No data	No data	Unclassified† Limited data from ongoing pregnancy

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	whether they responded differently from younger subjects. Use caution.				registry not sufficient to inform risks. Minimal excretion in breast milk; risks and benefits should be considered.
Cosentyx (secukinumab)	The number of subjects ≥65 years in clinical trials was not sufficient to determine whether they responded differently from younger subjects.	Safety and efficacy have not been established.	No data	No data	Unclassified† Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk; use with caution.
Entyvio (vedolizumab)	The number of patients ≥65 years in clinical trials was not sufficient to determine whether they responded differently from younger subjects.	Safety and efficacy have not been established.	No data	No data	Unclassified† Available and ongoing data have not identified a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Available data suggest presence in milk; use with caution.
Enbrel (etanercept)	The number of patients ≥65 years in clinical trials was not sufficient to determine whether they responded differently from younger subjects. Use caution.	Not studied in children <2 years with PJIA or <4 years with PsO.	No data	No data	Unclassified† Available studies do not reliably support association with major birth defects. Present in low levels in breast milk; consider risks and benefits.
Humira (adalimumab)	Frequency of serious infection and malignancies is greater in ≥65 years. Use caution.	Only studied in PJIA, pediatric uveitis (ages 2 years and older), CD (6 years and older), and HS	No data	No data	Unclassified† Available studies do not reliably support association with major birth defects.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
		(12 years and older).			Present in low levels in breast milk; consider risks and benefits.
Ilaris (canakinumab)	The number of patients ≥65 years in clinical trials was not sufficient to determine whether they responded differently from younger subjects.	Not studied in children <2 years (SJIA, TRAPS, HIDS/ MKD, and FMF) or <4 years (CAPS).	No data	No data	Unclassified† Limited data from postmarketing reports not sufficient to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.
Ilumya (tildrakizumab-asmn)	The number of patients ≥65 years in clinical trials was not sufficient to determine whether they responded differently from younger subjects.	Safety and efficacy have not been established.	No data	No data	Unclassified† Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.
Inflectra (infliximab-dyyb)	Frequency of serious infection is greater in ≥65 years. Use caution.	Not recom-mended in <6 years in children with CD or UC.	No data	No data	Unclassified† Available data have not reported a clear association with adverse pregnancy outcomes. Unknown whether excreted in breast milk; consider risks and benefits.
Kevzara (sarilumab)	Frequency of serious infection is greater in ≥ 65 years. Use caution.	Safety and efficacy have not been established.	Dosage adjustment not required in mild to moderate renal impairment. Kevzara has not been studied in severe renal impairment.	No data	Unclassified† Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.
Kineret (anakinra)	Use caution as there is a higher	For NOMID, has been used in all	CrCl <30 mL/min: give	No data	Unclassified†

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	incidence of infections in the elderly in general.	ages. For DIRA, has been used in ages from 1 month to 9 years. Safety and efficacy have not been established in pediatric patients with juvenile RA. Not possible to give a dose <20 mg.	dose every other day.		Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk; use caution.
Olumiant (baricitinib)	No overall differences were observed in the safety and efficacy profiles of elderly patients.	Safety and efficacy have not been established.	Use not recommended in patients with estimated glomerular filtration rate < 30 mL/min/1.73 m^2; for estimated glomerular filtration rate between 30 and 60 mL/min/1.73m^2: administer 1 mg once daily.	No dose adjustment for mild or moderate impairment; not recommended in patients with severe hepatic impairment.	Unclassified† Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk; avoid use.
Orencia (abatacept)	Frequency of serious infection and malignancies is greater in ≥65 years. Use caution.	Not recom-mended in <2 years old. IV dosing has not been studied in patients < 6 years old. ClickJect autoinjector subcutaneous injection has not been studied in patients < 18 years.	No data	No data	Unclassified† Data on use in pregnant women insufficient to inform risks. Unknown whether excreted in breast milk.
Otezla (apremilast)	No overall differences were observed in the	Safety and efficacy have not been established.	The dose of Otezla should be reduced to 30 mg once	No dosage adjustment necessary.	Unclassified† Available data have not established a

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	safety profile of elderly patients.		daily in patients with severe renal impairment (CrCl<30 mL/min).		drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Unknown whether excreted in breast milk; consider risks and benefits.
Remicade (infliximab)	Frequency of serious infection is greater in ≥65 years. Use caution.	Not recom-mended in <6 years in children with CD or UC.	No data	No data	Unclassified† Available data do not report clear association with adverse outcomes. Present in low levels in breast milk; systemic exposure thought to be low; consider risks and benefits.
Renflexis (infliximab-abda)	Frequency of serious infection is greater in ≥ 65 years. Use caution.	Not recom-mended in < 6 years in children with CD or UC.	No data	No data	Unclassified† Available data do not report clear association with adverse outcomes. Unknown whether excreted in breast milk; consider risks and benefits.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
Rinvoq (upadacitinib)	No differences in safety or efficacy were observed between older and younger patients; however, there was a higher rate of overall adverse events in elderly patients.	Safety and efficacy have not been established.	No dose adjustment required.	No dose adjustment required in mild or moderate hepatic impairment; not recommended in severe hepatic impairment.	Unclassified† Animal data suggest potential for fetal harm; females of reproductive potential should use effective contraception during treatment and for 4 weeks following completion of therapy. Unknown whether excreted in human breast milk, but excreted in animal milk; breastfeeding not recommended during treatment and for 6 days after last dose.
Rituxan (rituximab)	Rates of serious infections, malignancies, and cardiovascular events were higher in older patients.	Indicated for the treatment of GPA and MPA in children ≥2 years of age; safety and efficacy not established in children with NHL, CLL, PV, or RA.	No data	No data	Unclassified† May potentially cause B-cell lymphocytopenia due to in-utero exposure; advise women to use effective contraception during treatment and for at least 12 months after the last dose. Unknown whether excreted in breast milk; advise women not to breastfeed during treatment and for at least 6 months after the last dose.
Siliq (brodalumab)	No differences in safety or efficacy were observed between older and younger patients, but the number of patients ≥65 years	Safety and effectiveness in <18 years have not been established.	No data	No data	Unclassified† There are no human data in pregnant women to inform risks.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	in clinical trials was insufficient to determine any differences in response.				Unknown whether excreted in breast milk; risks and benefits should be weighed before use.
Simponi/ Simponi Aria (golimumab)	SQ: No differences in AEs observed between older and younger patients. Use caution. IV Aria: Use caution.	Effectiveness in <18 years has not been established (Simponi). Safety and effectiveness established for PJIA and PsA in pediatric patients 2 years and older but not established for other conditions (Aria).	No data	No data	Unclassified† No adequate and well-controlled trials in pregnant women. Unknown whether excreted in breast milk. Consider risks and benefits.
Skyrizi (risankizumab-rzaa)	No differences observed between older and younger patients. Use caution.	Safety and efficacy have not been established.	No data	No data	Unclassified† Limited data in pregnant women are insufficient to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.
Stelara (ustekinumab)	No differences observed between older and younger patients; however, the number of patients ≥65 years in clinical trials was not sufficient to determine differences.	Safety and effectiveness have been established in children 6 to 17 years with moderate to severe PsO; safety and effectiveness not established in children with PsA, CD, or UC.	No data	No data	Unclassified† Limited data in pregnant women are insufficient to inform risks. Unknown whether excreted in breast milk; systemic exposure to breastfed infant expected to be low; consider risks and benefits.
Taltz (ixekizumab)	No differences observed between older and younger	Safety and effectiveness have been	No data	No data	Unclassified†

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
	patients; however, the number of patients ≥65 years in clinical trials was not sufficient to determine differences.	established in children 6 to <18 years with moderate to severe PsO; safety and effectiveness not established in children <6 years with PsO or children of any age with PsA, AS, or NRAS.			There are no available data in pregnant women to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.
Tremfya (guselkumab)	No differences observed between older and younger patients; however, the number of patients ≥ 65 years in clinical trials was not sufficient to determine differences.	Safety and efficacy have not been established.	No data	No data	Unclassified† No available data in pregnant women to inform risks. Unknown whether excreted in breast milk; consider risks and benefits.
Truxima (rituximab-abbs)	Rates of serious infections, malignancies, and cardiovascular events were higher in older patients.	Safety and efficacy have not been established.	No data	No data	Unclassified† May potentially cause B-cell lymphocytopenia due to in-utero exposure; advise women to use effective contraception during treatment and for at least 12 months after the last dose. Unknown whether excreted in breast milk; advise women not to breastfeed during treatment and for at least 6 months after the last dose.

Xeljanz/Xeljanz XR (tofacitinib)	Frequency of serious infection is greater in ≥65 years. Use caution.	Safety and effectiveness established for PJIA in pediatric patients 2 years to 17 years old but not established for other conditions.	Moderate to severe impairment: Patients with RA or PsA receiving Xeljanz XR should switch to Xeljanz and reduce dose to 5 mg once daily and those receiving Xeljanz 5 mg twice daily should reduce to 5 mg once daily. Patients with UC on Xeljanz should switch to 5 mg twice daily (if on 10 mg twice daily) or 5 mg once daily (if on 5 mg twice daily). Patients with UC on Xeljanz XR 22 mg once daily, should reduce to 11 mg once daily; if taking 11 mg once daily, reduce to Xeljanz 5 mg once daily. Patients with PJIA on Xeljanz tablets or oral solution should reduce dosing to once daily if taking 3.2 mg, 4 mg, or 5 mg twice daily. For patients on hemodialysis, administer	Moderate impairment: Patients with RA or PsA receiving Xeljanz XR should switch to Xeljanz and reduce dose to 5 mg once daily and those receiving Xeljanz 5 mg twice daily should reduce to 5 mg once daily. Patients with UC on Xeljanz should switch to 5 mg twice daily (if on 10 mg twice daily) or 5 mg once daily (if on 5 mg twice daily). Patients with UC on Xeljanz XR 22 mg once daily, should reduce to 11 mg once daily; if taking 11 mg once daily, reduce to Xeljanz 5 mg once daily. Patients with PJIA on Xeljanz tablets or oral solution should reduce dosing to once daily if taking 3.2 mg, 4 mg, or 5 mg twice daily. Not recom-mended in	Unclassified† Available data are insufficient to inform a drug-associated risk; consider pregnancy planning and prevention for females of reproductive potential. Unknown whether excreted in breast milk; advise women to avoid breastfeeding during treatment and for at least 18 hours after the last dose of Xeljanz or 36 hours after the last dose of Xeljanz XR.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy and Nursing
			doses after the dialysis session. Do not take supplemental doses if a dose was taken before dialysis.	severe hepatic impairment.	

AS=ankylosing spondylitis; CLL=chronic lymphocytic leukemia; CrCl=creatinine clearance; CD=Crohn's disease; CAPS=cryopyrin-associated periodic syndromes; CRS=cytokine release syndrome; DIRA=deficiency of interleukin-1 receptor antagonist; FMF=familial Mediterranean fever; GPA=granulomatosis with polyangiitis; HS=hidradenitis suppurative; HIDS/MKD=hyperimmunoglobulin D syndrome/mevalonate kinase deficiency; MPA=microscopic polyangiitis; NHL=non-Hodgkin's lymphoma; NOMID= Neonatal-Onset Multisystem Inflammatory Disease; NRAS=non-radiographic axial spondyloarthritis; PJIA=polyarticular juvenile idiopathic arthritis; PsA=psoriatic arthritis; PsO=plaque psoriasis; PV=pemphigus vulgaris; RA=rheumatoid arthritis; SJIA=systemic juvenile idiopathic arthritis; TRAPS=tumor necrosis factor receptor associated periodic syndrome; UC=ulcerative colitis; XR=extended-release.
†In accordance with the FDA's Pregnancy and Lactation Labeling Rule (PLLR), this product is not currently assigned a Pregnancy Category. Consult product prescribing information for details.

CONCLUSION

- Immunomodulators for a variety of conditions associated with inflammation are available. Mechanisms of action and indications vary among the products. Products in this class have clinical trial data supporting efficacy for their FDA-approved indications.
- Limited head-to-head clinical trials between the agents have been completed.
  - In patients with RA, abatacept and infliximab showed comparable efficacy at 6 months, but abatacept demonstrated greater efficacy after 1 year on some endpoints such as DAS28-ESR, EULAR response, LDAS, and ACR 20 responses (*Schiff et al 2008*).
  - In patients with RA, abatacept and adalimumab were comparable for ACR 20 and ACR 50 responses over 2 years in a single-blind study (*Schiff et al 2014*).
  - In patients with RA, upadacitinib was superior to abatacept for changes in the DAS28-CRP and the achievement of remission (*Rubbert-Roth et al 2020*).
  - In patients with RA and an inadequate response or intolerance to MTX, sarilumab significantly improved change from baseline in DAS28-ESR over adalimumab (*Burmester et al 2017*). DAS28-ESR remission, ACR 20/50/70 response rates, and improvements in HAQ-DI scores were also more likely with sarilumab.
  - Patients with severe arthritis who could not take MTX were randomized to monotherapy with tocilizumab or adalimumab for 24 weeks in a randomized, double-blind study (*Gabay et al 2013*). The patients in the tocilizumab group had a significantly greater improvement in DAS28 at week 24 than patients in the adalimumab group.
  - In patients with RA and inadequate response or intolerance to MTX, upadacitinib was associated with significantly greater ACR 20 response compared with adalimumab at weeks 12 and 26 *(Fleischman et al 2018).*
  - In biologic-naïve patients with RA and an inadequate response to DMARDs, initial treatment with rituximab was demonstrated to have non-inferior efficacy to initial TNF inhibitor treatment (*Porter et al 2016*).
  - A randomized, open-label trial evaluated biologic treatments in patients with RA who had had an inadequate response to a TNF inhibitor. In this population, a non-TNF biologic (tocilizumab, rituximab, or abatacept) was more effective in achieving a good or moderate disease activity response at 24 weeks than use of a second TNF inhibitor. However, a second TNF inhibitor was also often effective in producing clinical improvement (*Gottenberg et al 2016*). Another recent randomized trial did not demonstrate clinical efficacy differences between abatacept, rituximab, and use of a second TNF inhibitor in this patient population *(Manders et al 2015*).
  - Secukinumab and ustekinumab were compared for safety and efficacy in the CLEAR and CLARITY studies, which were double-blind, randomized controlled trials in 676 and 1102 patients, respectively, with moderate to severe PsO (*Bagel et al 2018, Thaçi et al 2015*). In both studies, the proportion of patients achieving PASI 90 was significantly higher with secukinumab compared to ustekinumab (CLEAR: 79% vs 57.6%, $p < 0.0001$; CLARITY: 66.5% vs 47.9%, $p < 0.0001$) at week 16 in CLEAR and at week 12 in CLARITY.
  - In the IXORA-S study, the proportion of patients achieving PASI 90 at week 12 was significantly higher with ixekizumab compared to ustekinumab (72.8% vs 42.2%, respectively; $p < 0.001$) (*Reich et al 2017[b]).*

- A greater proportion of PsO patients achieved the primary outcome, PASI 75 at week 12, with ustekinumab 45 mg (67.5%) and 90 mg (73.8%) compared to etanercept 50 mg (56.8%; p = 0.01 vs ustekinumab 45 mg; p < 0.001 vs ustekinumab 90 mg). In this trial, etanercept therapy was associated with a greater risk of injection site erythema than ustekinumab (14.7% vs 0.7%) (*Griffiths et al 2010*).
- In the FIXTURE study in patient with moderate to severe PsO, 77.1%, 67%, 44%, and 4.9% of patients achieved PASI 75 with secukinumab 300 mg, secukinumab 150 mg, etanercept at FDA-recommended dosing, and placebo, respectively (*Langley et al 2014*).
- In the UNCOVER-2 and UNCOVER-3 studies, the proportions of patients achieving PASI 75 and achieving PGA 0 or 1 were higher in patients treated with ixekizumab compared to those treated with etanercept.
- In the AMAGINE-2 and AMAGINE-3 studies, the proportions of patients achieving PASI 100 were higher in patients treated with brodalumab compared to those treated with ustekinumab (*Lebwohl et al 2015*).
- In the VOYAGE 1 and VOYAGE 2 studies, the proportions of patients with moderate to severe PsO achieving IGA 0 or 1 and PASI 90 were higher with guselkumab compared to those treated with adalimumab *(Blauvelt et al 2017, Reich et al 2017[a]*).
- In two trials of patients with moderate to severe chronic PsO, risankizumab was associated with significant improvement in PASI 90 response at week 16 vs ustekinumab *(Gordon et al 2018)*.
- In ECLIPSE, patients with moderate-to-severe plaque PsO were randomly assigned to Tremfya (guselkumab) or Cosentyx (secukinumab) (*Reich et al 2019[a]*). Results revealed that the proportion of patients with a PASI 90 response at week 48 was greater in the guselkumab group as compared to the secukinumab group (84% vs 70%; p < 0.0001).
- No meaningful differences were shown in the treatment of RA and PsA in comparisons of infliximab and infliximab-dyyb conducted to establish biosimilarity between these agents (*Park et al 2013, Park et al 2016, Park et al 2017, Yoo et al 2013, Yoo et al 2016, Yoo et al 2017*). Similarly, no meaningful differences between infliximab and infliximab-abda were found in treatment of RA in clinical studies to establish biosimilarity (*Choe et al 2017, Shin et al 2015*).
- In patients with CD, UC, RA, PsA, spondyloarthritis, and PsO who were treated with the originator infliximab for ≥ 6 months, infliximab-dyyb was noninferior to infliximab originator group for disease worsening (*Jørgensen et al 2017*).
- In the SPIRIT-H2H study, ixekizumab led to a higher proportion of patients with PsA achieving the combined ACR 50 and PASI 100 and PASI 100 alone compared with adalimumab (*Smolen et al 2020[b]*)
- Entyvio (vedolizumab) was directly compared to Humira (adalimumab) in the VARSITY trial (*Sands et al 2019*). 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).
- More comparative studies are needed.

- For RA, patients not responding to initial DMARD treatment may be treated with combination DMARDs, TNF inhibitors, non-TNF inhibitor biologics, and/or tofacitinib per ACR guidance (*Singh et al 2016c*). EULAR guidelines for RA management were recently updated (*Smolen et al 2020[a]*). EULAR recommends that therapy with DMARDs should be initiated as soon as the RA diagnosis is made with treatment aimed at reaching a target of sustained remission or low disease activity in every patient. If the treatment target is not achieved with the first conventional synthetic DMARD strategy, in the absence of poor prognostic factors, others should be considered. If poor prognostic factors are present with treatment failure, a biological or targeted synthetic DMARD should be added. If a biological or targeted synthetic DMARD has failed, treatment with another should be considered. If one TNF inhibitor therapy has failed, patients may receive an agent with another mode of action or a second TNF inhibitor. EULAR has also released guidelines for use of antirheumatic drugs in pregnancy, which state that the TNF inhibitors etanercept and certolizumab are among possible treatment options for patients requiring therapy (*Götestam Skorpen et al 2016*).
- EULAR 2019 PsA guidelines recommend biologic DMARDs in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, such as MTX (*Gossec et al 2020, Kerschbaumer et al 2020*). For patients with peripheral arthritis, an inadequate response to at least 1 synthetic DMARD, and relevant skin involvement, biologics targeting IL-12/23 or IL-17 pathways may be considered. In patients with peripheral arthritis and an inadequate response to at least one synthetic DMARD and at least one biologic DMARD, JAK inhibitors may be considered; JAK inhibitors may also be considered in patients for whom biologic DMARD therapy is not appropriate. Apremilast is considered a

treatment option in patients with peripheral arthritis and an inadequate response to at least 1 synthetic DMARD, in whom biologics and JAK inhibitors are not appropriate.

- Guidelines from GRAPPA recommend various biologics for the treatment of PsO and PsA based on patient-specific factors, including TNF inhibitors, IL-17 and IL-12/23 inhibitors, and PDE-4 inhibitors (*Coates et al 2016*). Joint guidelines from the AAD/NPF on the treatment of PsO with biologics do not provide ranking for preferences of individual biologics, but do note that etanercept, infliximab, adalimumab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, risankizumab, and tildrakizumab can be recommended as a monotherapy option for patients with moderate to severe PsO (*Menter et al 2019*).
- The ACR/NPF guideline on PsA recommends that a TNF inhibitor is preferred in treatment-naïve patients with active PsA, although an oral therapy can be a first-line option in patients without severe PsA and without severe psoriasis, or if a patient has another compelling reason to avoid a TNF inhibitor. In patients who fail oral therapy, a switch to a TNF inhibitor is preferred and placed ahead of IL-17 biologics, IL-12/23 biologics, abatacept, and tofacitinib (*Singh et al 2019*).
- The ACR guideline for SJIA notes that IL-1 and IL-6 play a central role in the inflammatory process for this condition, and recommend agents such as anakinra, canakinumab, tocilizumab, abatacept, and TNF inhibitors among either first- or second-line treatments (*Ringold et al 2013*). Patients with JIA and active sacroiliitis or enthesitis are recommended to receive TNF inhibitor therapy, and patients with non-systemic polyarthritis are recommended to receive TNF inhibitor therapy, abatacept, or tocilizumab. Patients with continued disease activity and primary TNF inhibitor failure are recommended to receive abatacept or tocilizumab *(Ringold et al 2019)*.
- According to the ACG, for induction of remission in moderately to severely active UC, TNF inhibitor therapy, vedolizumab, or tofacitinib are recommended, and should be continued to maintain remission. Vedolizumab and tofacitinib are recommended in patients with previous failure to TNF inhibitor therapy (*Rubin et al 2019*). For adult outpatients with moderate to severe UC, the AGA strongly recommends using infliximab, adalimumab, golimumab, vedolizumab, tofacitinib, or ustekinumab over no treatment (*Feuerstein et al 2020*). The AGA recommends that for patients at high risk for colectomy, anti-TNF drugs and vedolizumab can be considered for induction and maintenance therapy (*Dassopoulos et al 2014*). ECCO guidelines recommend thiopurine, anti-TNF drugs, vedolizumab, or methotrexate for patients with UC who have active steroid-dependent disease and anti-TNF agents or vedolizumab for patients who have steroid- or immunomodulator-refractory disease (*Harbord et al 2017*).
- The ACG states that the anti-TNF monoclonal antibodies 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 anti-TNF induced remission as monotherapy or in combination with azathioprine/6-mercaptopurine or methotrexate. The combination of infliximab with an immunomodulator (thiopurine) is more effective than monotherapy with individual agents in patients with moderate to severe CD and who are naïve to both agents. Infliximab can also treat fuliminant CD. Vedolizumab with or without an immunomodulator can be used for induction and maintenance of remission in patients with moderate to severe CD. Patients are candidates for ustekinumab therapy, including for the maintenance of remission, if they have moderate to severe CD and have failed corticosteroids, thiopurines, methotrexate, or anti-TNF inhibitors. The guideline acknowledges the effectiveness of biosimilar infliximab and biosimilar adalimumab for the management of moderate to severe CD (*Lichtenstein et al 2018*). The AGA recommends using anti-TNF drugs to induce remission in patients with moderately severe CD (*Terdiman et al 2013*). In 2020, ECCO released a guideline on medical treatment in CD (*Torres et al 2020*). Regarding immunomodulators, these guidelines recommend 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, among other recommendations.
- Consensus statements for the management of inflammatory bowel disease in pregnancy, from the Canadian Association of Gastroenterology and from the AGA, recommend that biologics can be continued during pregnancy and delivery as the benefits of maintaining disease remission outweigh any risks associated with biologic maintenance therapy (*Mahadevan et al 2019, Nguyen et al 2016[bj]*).
- Based upon guidelines from the European Dermatology Forum, adalimumab is recommended among first-line therapies for HS, with infliximab a potential second-line option (*Gulliver et al 2016, Zouboulis et al 2015*).
- Joint guidelines from ASAS and EULAR state that biologic DMARDs should be considered in patients with AS and persistently high disease activity despite conventional treatments (*van der Heijde et al 2017[bj]*). The 2019 ACR, Spondylitis Association of America, and Spondyloarthritis Research and Treatment Network guidelines strongly recommend TNF inhibitors for patients who have active disease despite NSAIDs; no TNF inhibitor is preferred over

another for AS for most patients. Secukinumab or ixekizumab are recommended in patients with active disease who have primary nonresponse with a TNF inhibitor (*Ward et al 2019*).

- Infliximab and adalimumab are recommended over etanercept for various ocular inflammatory disorders (*Levy-Clarke et al 2016*).
- Caution is warranted with these biologic agents due to severe infections and malignancies that can occur with their use. Tocilizumab, TNF inhibitors, tofacitinib, sarilumab, baricitinib, and upadacitinib have boxed warnings regarding a risk of serious infections. TNF inhibitors, tofacitinib, baricitinib, and upadacitinib also have boxed warnings regarding an increased risk of malignancies. Brodalumab has a boxed warning regarding the risk of suicidal ideation and behavior. Tofacitinib (10 mg twice daily dose), upadacitinib, and baricitinib also have boxed warnings regarding thrombosis risk.
- Warnings, precautions, and AE profiles vary in this class.
- All of the biologic agents with the exception of apremilast, baricitinib, tofacitinib, and upadacitinib are given by subcutaneous injection and/or intravenous infusion. Administration schedule varies among the injectable agents in the class. Apremilast, baricitinib, tofacitinib, and upadacitinib are given orally.
- Selection of an agent for a patient is determined by approved indications, response, administration method, tolerability, AE profile, and cost of the agent.

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Publication Date: March 15, 2021

Prior Authorization Guideline

Guideline Name Growth Hormones

1 . Criteria

Product Name: **Genotropin, Norditropin**	
Approval Length	6 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - For recipients with open epiphyses and remaining growth potential, all of the following:

1.1 The recipient has had an evaluation by a pediatric endocrinologist or pediatric nephrologist with a recommendation for growth hormone therapy

AND

1.2 The recipient has had an evaluation ruling out all other causes for short stature

AND

1.3 If there are any other pituitary hormone deficiencies, such as thyroid, glucocorticoids, or gonadotropic hormones, the recipient is receiving adequate replacement therapy

AND

1.4 One of the following:

1.4.1 Diagnosis of Prader-Willi Syndrome

OR

1.4.2 Diagnosis of Noonan Syndrome and both of the following:

- Height is at least two standard deviations below the mean or below the fifth percentile for the patient's age and gender
- Bone age is less than 16 years for males or less than 14 years for females

OR

1.4.3 Diagnosis of Turner Syndrome and recipient is a female with a bone age of less than 14 years

OR

1.4.4 Diagnosis of chronic renal insufficiency (< 75 mL/min) and height is at least two standard deviations below the mean or below the third percentile for the recipient's age and gender

OR

1.4.5 Diagnosis of small for gestational age and both of the following:

- Age of 2 years of older
- Height is at least two standard deviations below the mean or below the third percentile for the patient's age and gender

OR

1.4.6 Recipient is a newborn with evidence of hypoglycemia and one of the following:

- Low growth hormone level (< 20 ng/nL)
- Low insulin like growth factor (IGH)-1 for age
- Low IGF binding protein 3 (IGFBP-3) for age (no stimulation test required for infants)

OR

1.4.7 Diagnosis of growth hormone deficiency or hypothalamic pituitary disease (e.g., hypopituitarism due to structure lesions/trauma to the pituitary including pituitary tumor, pituitary surgical damage, trauma, or cranial irradiation) and all of the following:

1.4.7.1 Height is at least two standard deviations below the mean or below the third percentile for the patient's age and gender

AND

1.4.7.2 Bone age is less than 16 years for males or less than 14 years for females

AND

1.4.7.3 One of the following:

- Two failed growth hormone stimulation tests (< 10 ng/mL)
- One failed growth hormone stimulation test (< 10 ng/mL) and one failed IGF-1 or IGFBP-3 test
- One failed growth hormone stimulation test (<10 ng/mL) OR one failed IGF-1 or IGFBP-3 test, and there are deficiencies in three or more pituitary axes (e.g., thyroid stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), adrenocorticotropic hormone (ACTH), or antidiuretic hormone (ADH))

OR

2 - For recipients with closed epiphyses and no remaining growth potential, all of the following:

2.1 The recipient is being evaluated by an endocrinologist

AND

2.2 If there are any other pituitary hormone deficiencies, such as thyroid, glucocorticoids, or gonadotropic hormones, the recipient is receiving adequate replacement therapy

AND

2.3 Diagnosis of growth hormone deficiency or hypothalamic pituitary disease (e.g., hypopituitarism due to structure lesions/trauma to the pituitary including pituitary tumor, pituitary surgical damage, trauma or cranial irradiation)

AND

2.4 One of the following:

2.4.1 Two failed growth hormone stimulation tests (< 5 ng/mL)

OR

2.4.2 One failed growth hormone stimulation test (< 5 ng/mL) and one failed IGF-1 or IGFBP-3 test

OR

2.4.3 Both of the following:

- One failed growth hormone stimulation test (<10 ng/mL) OR one failed IGF-1 or IGFBP-3 test, and there are deficiencies in three or more pituitary axes (e.g., thyroid stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), adrenocorticotropic hormone (ACTH), or antidiuretic hormone (ADH))
- Severe clinical manifestations of growth hormone deficiency as evident by alterations in body composition (e.g., decreased lean body mass, increased body fat), cardiovascular function (e.g., reduced cardiac output, lipid abnormalities) or bone mineral density

Product Name: **Genotropin, Norditropin**	
Approval Length	1 year(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - For recipients with open epiphyses and remaining growth potential, all of the following:

1.1 One of the following diagnoses:

- Chronic renal insufficiency
- Growth hormone deficiency
- Hypothalamic pituitary disease
- Newborn infant with evidence of hypoglycemia
- Noonan Syndrome
- Prader-Willi Syndrome
- Small for gestational age
- Turner Syndrome

AND

1.2 Recipient's growth rate is at least 2.5 cm/year

AND

1.3 Recipient does not have evidence of an expanding lesion or tumor formation

AND

1.4 The recipient has not undergone a renal transplant

OR

2 - For recipients with closed epiphyses and no remaining growth potential, all of the following:

2.1 Diagnosis of growth hormone deficiency or hypothalamic pituitary disease

AND

2.2 There is documentation of improvement in clinical manifestations associated with growth hormone deficiency

Product Name: **Humatrope, Nutropin AQ NuSpin, Omnitrope, Saizen, Zomacton**	
Approval Length	6 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - For recipients with open epiphyses and remaining growth potential, all of the following:

1.1 The recipient has had an evaluation by a pediatric endocrinologist or pediatric nephrologist with a recommendation for growth hormone therapy

AND

1.2 The recipient has had an evaluation ruling out all other causes for short stature

AND

1.3 If there are any other pituitary hormone deficiencies, such as thyroid, glucocorticoids, or gonadotropic hormones, the recipient is receiving adequate replacement therapy

AND

1.4 One of the following:

1.4.1 Diagnosis of Prader-Willi Syndrome

OR

1.4.2 Diagnosis of Noonan Syndrome and both of the following:

- Height is at least two standard deviations below the mean or below the fifth percentile for the patient's age and gender
- Bone age is less than 16 years for males or less than 14 years for females

OR

1.4.3 Diagnosis of Turner Syndrome and recipient is a female with a bone age of less than 14 years

OR

1.4.4 Diagnosis of chronic renal insufficiency (< 75 mL/min) and height is at least two standard deviations below the mean or below the third percentile for the recipient's age and gender

OR

1.4.5 Diagnosis of small for gestational age and both of the following:

- Age of 2 years of older
- Height is at least two standard deviations below the mean or below the third percentile for the patient's age and gender

OR

1.4.6 Recipient is a newborn with evidence of hypoglycemia and one of the following:

- Low growth hormone level (< 20 ng/nL)
- Low insulin like growth factor (IGH)-1 for age
- Low IGF binding protein 3 (IGFBP-3) for age (no stimulation test required for infants)

OR

1.4.7 Diagnosis of growth hormone deficiency or hypothalamic pituitary disease (e.g., hypopituitarism due to structure lesions/trauma to the pituitary including pituitary tumor, pituitary surgical damage, trauma, or cranial irradiation) and all of the following:

1.4.7.1 Height is at least two standard deviations below the mean or below the third percentile for the patient's age and gender

AND

1.4.7.2 Bone age is less than 16 years for males or less than 14 years for females

AND

1.4.7.3 One of the following:

- Two failed growth hormone stimulation tests (< 10 ng/mL)
- One failed growth hormone stimulation test (< 10 ng/mL) and one failed IGF-1 or IGFBP-3 test
- One failed growth hormone stimulation test (<10 ng/mL) OR one failed IGF-1 or IGFBP-3 test, and there are deficiencies in three or more pituitary axes (e.g., thyroid stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), adrenocorticotropic hormone (ACTH), or antidiuretic hormone (ADH))

AND

1.5 One of the following:

1.5.1 Patient experienced therapeutic failure of two different preferred medications within the same drug class

OR

1.5.2 Patient has an allergy, contraindication, drug-to-drug interaction, or a history of unacceptable/toxic side effects with ALL preferred medications within the same drug class

OR

1.5.3 The non-preferred medication is being requested for the use of a unique indication that is supported by peer-reviewed literature or an FDA-approved indication

OR

2 - For recipients with closed epiphyses and no remaining growth potential, all of the following:

2.1 The recipient is being evaluated by an endocrinologist

AND

2.2 If there are any other pituitary hormone deficiencies, such as thyroid, glucocorticoids, or gonadotropic hormones, the recipient is receiving adequate replacement therapy

AND

2.3 Diagnosis of growth hormone deficiency or hypothalamic pituitary disease (e.g., hypopituitarism due to structure lesions/trauma to the pituitary including pituitary tumor, pituitary surgical damage, trauma or cranial irradiation)

AND

2.4 One of the following:

2.4.1 Two failed growth hormone stimulation tests (< 5 ng/mL)

OR

2.4.2 One failed growth hormone stimulation test (< 5 ng/mL) and one failed IGF-1 or IGFBP-3 test

OR

2.4.3 Both of the following:

- One failed growth hormone stimulation test (<10 ng/mL) OR one failed IGF-1 or IGFBP-3 test, and there are deficiencies in three or more pituitary axes (e.g., thyroid stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), adrenocorticotropic hormone (ACTH), or antidiuretic hormone (ADH))
- Severe clinical manifestations of growth hormone deficiency as evident by alterations in body composition (e.g., decreased lean body mass, increased body fat), cardiovascular function (e.g., reduced cardiac output, lipid abnormalities) or bone mineral density

AND

2.5 One of the following:

2.5.1 Patient experienced therapeutic failure of two different preferred medications within the same drug class

OR

2.5.2 Patient has an allergy, contraindication, drug-to-drug interaction, or a history of unacceptable/toxic side effects with ALL preferred medications within the same drug class

OR

2.5.3 The non-preferred medication is being requested for the use of a unique indication that is supported by peer-reviewed literature or an FDA-approved indication

Product Name: **Humatrope, Nutropin AQ NuSpin, Omnitrope, Saizen, Zomacton**	
Approval Length	1 year(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - For recipients with open epiphyses and remaining growth potential, all of the following:

1.1 One of the following diagnoses:

- Chronic renal insufficiency
- Growth hormone deficiency
- Hypothalamic pituitary disease
- Newborn infant with evidence of hypoglycemia
- Noonan Syndrome
- Prader-Willi Syndrome
- Small for gestational age
- Turner Syndrome

AND

1.2 Recipient's growth rate is at least 2.5 cm/year

AND

1.3 Recipient does not have evidence of an expanding lesion or tumor formation

AND

1.4 The recipient has not undergone a renal transplant

AND

1.5 One of the following:

1.5.1 Patient experienced therapeutic failure of two different preferred medications within the same drug class

OR

1.5.2 Patient has an allergy, contraindication, drug-to-drug interaction, or a history of unacceptable/toxic side effects with ALL preferred medications within the same drug class

OR

1.5.3 The non-preferred medication is being requested for the use of a unique indication that is supported by peer-reviewed literature or an FDA-approved indication

OR

2 - For recipients with closed epiphyses and no remaining growth potential, all of the following:

2.1 Diagnosis of growth hormone deficiency or hypothalamic pituitary disease

AND

2.2 There is documentation of improvement in clinical manifestations associated with growth hormone deficiency

AND

2.3 One of the following:

2.3.1 Patient experienced therapeutic failure of two different preferred medications within the same drug class

OR

2.3.2 Patient has an allergy, contraindication, drug-to-drug interaction, or a history of unacceptable/toxic side effects with ALL preferred medications within the same drug class

OR

2.3.3 The non-preferred medication is being requested for the use of a unique indication that is supported by peer-reviewed literature or an FDA-approved indication

Product Name: **Serostim**	
Approval Length	12 Week(s)
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of Human Immune Deficiency Virus (HIV) with wasting or cachexia

AND

2 - The medication is indicated to increase lean body mass, body weight, and physical endurance

AND

3 - The recipient is receiving and is compliant with antiretroviral therapy

AND

4 - The recipient has experienced an involuntary weight loss of >10% pre-illness baseline or they have a body mass index of < 20 kg/m²

AND

5 - The recipient has experienced an adverse event, allergy, or inadequate response to megestrol acetate, or the recipient has a contraindication to treatment with this agent

AND

6 - The recipient has experienced an adverse event, allergy, or inadequate response to an anabolic steroid (e.g., testosterone, oxandrolone, nandrolone), or the recipient has a contraindication to treatment with these agents

Product Name: **Somavert**	
Approval Length	12 Week(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of acromegaly

AND

2 - Recipient is 18 years of age or older

AND

3 - One of the following:

3.1 The recipient has an inadequate response to one of the following:

- Surgery
- Radiation therapy
- Dopamine agonist (e.g., bromocriptine, cabergoline) therapy

OR

3.2 The recipient is not a candidate for surgery, radiation therapy, AND dopamine agonist (e.g., bromocriptine, cabergoline) therapy

AND

4 - The recipient has tried and failed, or has a contraindication or intolerance, to generic octreotide (a somatostatin analogue)

AND

5 - The medication is prescribed by or in consultation with an endocrinologist

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

Approval Criteria

1 - The recipient must have a documented positive clinical response to Somavert therapy (e.g., biochemical control; decrease or normalization of IGF-1 levels)

Product Name: **Zorbtive**	
Approval Length	6 Months for initial authorization, 1 year for reauthorization/continuing treatment
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of short bowel syndrome

AND

2 - Recipient is 18 years of age or older

AND

3 - The medication is being prescribed by or following a consultation with a gastroenterologist

AND

4 - The recipient is receiving specialized nutritional support (e.g., high carbohydrate, low-fat diets via enteral or parenteral nutrition)

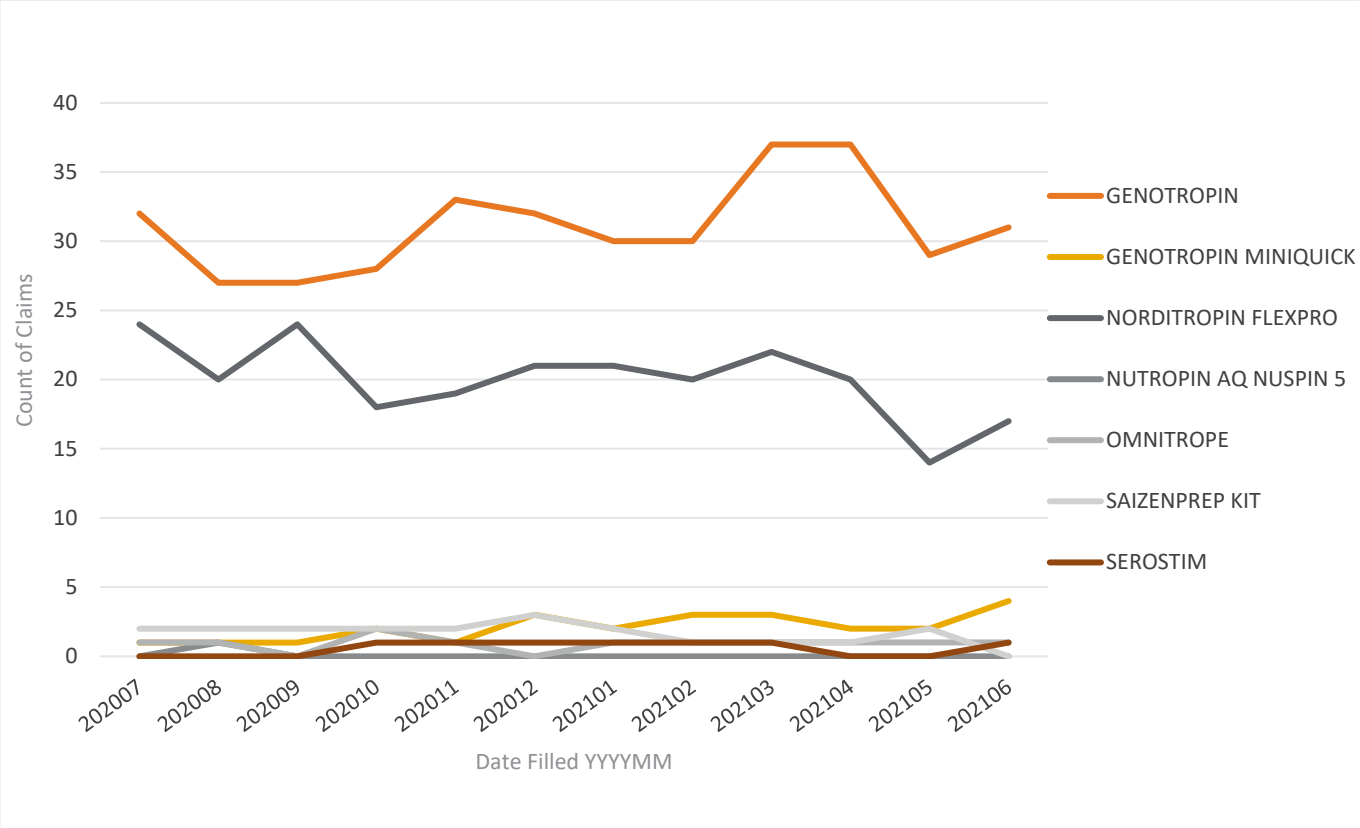
Nevada Medicaid

Top Ten Therapeutic Classes

Fee for Service

July 1, 2020 - June 30, 2021

Drug Name	Members	Claims	Total Days Supply	Total Quantity
GENOTROPIN	42	373	10,960	1,353
NORDITROPIN FLEXPRO	30	240	6,970	1,178
OMNITROPE	1	11	330	50
GENOTROPIN MINIQUICK	3	25	700	700
SAIZENPREP RECONSTITUTIONKIT	2	20	552	105
SEROSTIM	1	7	198	196
NUTROPIN AQ NUSPIN 5	1	1	30	8



D. Growth Hormones

Therapeutic Class: Growth Hormone
Last Reviewed by the DUR Board: July 23,2020

Growth Hormones are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the SSA Act and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

a. Approval will be given if the following criteria are met and documented:

1. Children (with open epiphyses and with remaining growth potential) must meet all of the following:

a. The recipient has had an evaluation by a pediatric endocrinologist or pediatric nephrologist with a recommendation for growth hormone therapy; and

b. The recipient has had an evaluation ruling out all other causes for short stature; and

c. The recipient is receiving adequate replacement therapy for any other pituitary hormone deficiencies, such as thyroid, glucocorticoids or gonadotropic hormones.

The recipient must then meet one of the following:

1. The recipient has a diagnosis of Noonan Syndrome, Prader-Willi Syndrome or Turner Syndrome and their height is at least two standard deviations below the mean or below the fifth percentile for the patient's age and gender and the bone age is less than 16 years for male recipients or less than 14 years for female recipients; or

2. The recipient has a diagnosis of Prader-Willi Syndrome; or

3. The recipient has a diagnosis of Turner Syndrome, is female and has a bone age of less than 14 years; or

4. The recipient has a diagnosis of chronic renal insufficiency (<75 mL/minute), and their height is at least two standard deviations below the mean or below the third percentile for the recipient's age and gender; or

5. The recipient has a diagnosis of being small for gestational age, the recipient is two years of age or older, and the height is at least two standard deviations below the mean or below the third percentile for the recipient's age and gender; or

6. The recipient is a newborn infant with evidence of hypoglycemia, and has low growth hormone level (<20 ng/mL), low for age insulin like growth factor (IGF)-1 or IGF binding protein (BP) 3 (no stimulation test required for infants); or

7. The recipient has a diagnosis of growth hormone deficiency or hypothalamic pituitary disease (e.g., hypopituitarism due to structure lesions/trauma to the pituitary including pituitary tumor, pituitary surgical damage, trauma or cranial irradiation), and their height is at least two standard deviations below the mean or below the third percentile for the patient's age and gender and their bone age is less than 16 years for male or less than 14 years for female.

   And recipient must meet one of the following:

   a. The recipient has failed two growth hormone stimulation tests (<10 ng/mL); or

   b. The recipient has failed one growth hormone stimulation test (<10 ng/mL) and one IGF-1 or IGFBP-3 test; or

   c. The recipient has failed one growth hormone stimulation test (<10 ng/mL) or IGF-1 or IGFBP-3 test and they have deficiencies in three or more pituitary axes (e.g., thyroid stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), adrenocorticotropic hormone (ACTH) or antidiuretic hormone (ADH)).

2. Adults (with closed epiphyses, and no remaining growth potential) must meet all of the following:

   a. The recipient is being evaluated by an endocrinologist; and

   b. The recipient is receiving adequate replacement therapy for any other pituitary hormone deficiencies, such as thyroid, glucocorticoids or gonadotropic hormones; and

   c. The recipient has a diagnosis of growth hormone deficiency or hypothalamic pituitary disease (e.g., hypopituitarism due to

structure lesions/trauma to the pituitary including pituitary tumor, pituitary surgical damage, trauma or cranial irradiation); and

The recipient must then meet one of the following:

1. The recipient has failed two growth hormone stimulation tests (<5 ng/mL); or

2. The recipient has failed one growth hormone stimulation test (<5 ng/mL) and one IGF-1 or IGFBP-3 test; or

3. The recipient has failed one growth hormone stimulation test (<5 ng/mL) or IGFBP-3 test and has deficiencies in three or more pituitary axes (i.e., TSH, LH, FSH, ACTH, ADH), and has severe clinical manifestations of growth hormone deficiency as evident by alterations in body composition (e.g., decreased lean body mass, increased body fat), cardiovascular function (e.g., reduced cardiac output, lipid abnormalities) or bone mineral density.

3. Continued authorization will be given for recipients (up to age 21, with remaining growth potential) who meet all of the following:

a. The recipient has a diagnosis of chronic renal insufficiency, growth hormone deficiency, hypothalamic pituitary disease, newborn infant with evidence of hypoglycemia, Noonan Syndrome, Prader-Willi Syndrome, small for gestational age or Turner Syndrome; and

b. The recipient's epiphyses are open; and

c. The recipient's growth rate on treatment is at least 2.5 cm/year; and

d. The recipient does not have evidence of an expanding lesion or tumor formation; and

e. The recipient has not undergone a renal transplant.

4. Continued authorization will be given for recipients (age 21 years and older, with closed epiphyses and no remaining growth potential) who meet all of the following:

a. The recipient has a diagnosis of growth hormone deficiency or hypothalamic pituitary disease; and

b. There is documentation of improvement in clinical manifestations associated with growth hormone deficiency

5. Prior Authorization Guidelines

a. Initial prior authorization will be for six months.

b. Recertification approval will be for 12 months.

c. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx.

b. Serostim® (somatropin)

1. Approval will be given if the following criteria are met and documented:

a. The recipient has a diagnosis of Human Immune Deficiency Virus (HIV) with wasting or cachexia; and

b. The medication is indicated to increase lean body mass, body weight and physical endurance; and

c. The recipient is receiving and is compliant with antiretroviral therapy; and

d. The recipient has experienced an involuntary weight loss of >10% pre-illness baseline or they have a body mass index of <20 kg/m^2; and

e. The recipient has experienced an adverse event, allergy or inadequate response to megestrol acetate, or the recipient has a contraindication to treatment with this agent; and

f. The recipient has experienced an adverse event, allergy or inadequate response to an anabolic steroid (e.g., testosterone, oxandrolone, nandrolone) or the recipient has a contraindication to treatment with these agents.

2. Prior Authorization Guidelines:

a. Prior authorization approval will be for 12 weeks.

b. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx.

c. Zorbtive® (somatropin)

1. Approval will be given if all the following criteria are met and documented:

a. The recipient has a diagnosis of short bowel syndrome; and

b. The recipient is age 18 years or older; and

c. The medication is being prescribed by or following a consultation with a gastroenterologist; and

d. The recipient is receiving specialized nutritional support (e.g., high carbohydrate, low-fat diets via enteral or parenteral nutrition).

2. Prior Authorization Guidelines

a. Initial authorization will be approved for six months.

b. Recertification request will be approved for 12 months.

c. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx.

d. Somavert® (pegvisomant)

1. Approval will be given if all the following criteria are met and documented:

a. The recipient has a diagnosis of acromegaly; and

b. The recipient is 18 years age or older; and

c. One of the following:

1. The recipient has an inadequate response to one of the following:

a. Surgery; or

b. Radiation Therapy; or

c. Dopamine agonist (e.g. bromocriptine, cabergoline) therapy; or

2. The recipient is not a candidate for all the following:

a. Surgery; and

b. Radiation Therapy; and

c. Dopamine agonist (e.g. bromocriptine, cabergoline) therapy; and

d. The recipient has tried and failed, a contraindication, or intolerance to generic octreotide (a somatostatin analogue); and

e. The medication is prescribed by or in consultation with an endocrinologist.

2. Recertification Criteria:

a. The recipient must meet the following:

1. The recipient must have a documented positive clinical response to Somavert® therapy (e.g. biochemical control; decrease or normalization of IGF-1 levels).

3. Prior Authorization Guidelines:

a. Initial authorization will be approved for 12 weeks.

b. Recertification approval will be approved for 12 months.

c. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx.

Therapeutic Class Overview
Growth Hormone

INTRODUCTION

- Growth hormone (GH) affects many of the metabolic processes carried out by somatic cells, most notably increasing body mass. Overall growth is stimulated by GH therapy; however, the effects are not evenly distributed among protein, lipid, and carbohydrate compartments. Specifically, body protein content and bone mass increase, total body fat content decreases, and there is an increase in plasma and liver lipid content due to the mobilization of free fatty acids from peripheral fat stores. Another physiological effect of GH is stimulation of cartilage growth (*Molitch et al 2011*).
- Growth hormone deficiency (GHD) in pediatric patients is a clinical diagnosis that is confirmed by biochemical testing. A patient's growth patterns are compared to the established norms. The clinical manifestations of GHD vary depending on whether a patient has complete or partial deficiency. In complete deficiency, pediatric patients present with early severe growth failure, delayed bone age, central disposition of body fat and very low serum concentrations of GH, insulin-like growth factor-1 (IGF-1) and IGF binding protein-3. These patients are also more prone to hypoglycemia, prolonged jaundice, microphallus in males, and giant cell hepatitis. GHD in pediatric patients with partial deficiency may be more difficult to diagnose, as these manifestations may not be as obvious (*Molitch et al 2011*).
- Once a diagnosis of GHD is confirmed in pediatric patients, GH therapy should be initiated and continued until cessation of linear growth. Therapy should be initiated as soon as possible, as evidence demonstrates that growth response is more robust when GH therapy is started at a younger age (*Molitch et al 2011*).
- Several preparations of GH are currently available for use in pediatric patients. Recombinant GH preparations, administered by subcutaneous (SC) injection, are currently the most widely utilized. Due to the variability in individual response to therapy, after initial dosing, the dose of GH is adjusted based on growth response and IGF-1 level. While not universally supported, the therapeutic goal of therapy is to achieve a level of IGF-1 that is slightly higher than average, because growth velocity is typically greatest at these levels. A patient's growth velocity, as compared to a similar population, should also be monitored to determine if the growth response is adequate (*Molitch et al 2011*).
- Possible explanations for an inadequate response to GH therapy include poor adherence, incorrect diagnosis of GHD, subtherapeutic dose of GH, or concurrent mild GH insensitivity. In pediatric patients, GH therapy is typically continued at least until linear growth is nearly complete (eg, decreased to less than 2.5 centimeters per year). At this point, retesting for GHD should occur to determine if GH therapy should be continued into adulthood (*Molitch et al 2011*).
- The majority of pediatric patients with idiopathic, isolated GHD in their childhood have normal GH secretion during late adolescence and young adulthood. In contrast, pediatric patients with genetic GHD, multiple pituitary hormone deficiencies, and/or those with structural defects in the hypothalamic-pituitary region rarely recover the ability to secrete GH as an adult. Therefore, retesting may not be required (*Molitch et al 2011*).
- GHD may also occur in adult patients. Approximately 15% to 20% of adult-onset GHD represents the continuation of childhood-onset GHD into maturity; the remainder is adult-onset acquired from damage to the pituitary gland or hypothalamus. GHD is associated with increased metabolic syndrome, increased cardiovascular morbidity and mortality rates, reduced lean body mass, increased abdominal adiposity, early atherosclerosis, dyslipidemia, coagulation abnormalities, insulin resistance, decreased bone mineral density, and a decreased quality of life (*Reed et al 2013*). The role of GH therapy in adults is not as clear as it is in pediatric patients in whom therapy is required for normal growth. There is evidence to demonstrate that when used in adult patients with GHD, GH therapy increases muscle mass and decreases body fat. Evidence of other potential beneficial effects of GH therapy in adults is not as well established and includes improvement in bone mineral density, sense of well-being, muscle strength, and lipid profile. GH therapy can be considered in adult patients with severe clinical manifestations and unequivocal evidence of GHD due to organic disease of childhood- or adult-onset (*Molitch et al 2011*).
- Most of the GH preparations contain somatropin, otherwise known as recombinant human GH. The various preparations are Food and Drug Administration (FDA)-approved for use in a variety of pediatric conditions associated with a failure in growth, including chronic kidney disease (CKD), Turner syndrome, being born small for gestational age, Prader-Willi syndrome, mutations in the Short Stature Homeobox gene, Noonan syndrome, and idiopathic short stature.
- The majority of preparations are also indicated for the treatment of GHD in adults. Of note, Serostim is FDA-approved solely for the treatment of human immunodeficiency virus-associated wasting or cachexia in adults, while Zorbtive is

approved for the treatment of short bowel syndrome in patients receiving specialized nutritional support. Specific FDA-approved indications for the various GH preparations are outlined in Table 2. All of the GH preparations are available for SC injection, and there are currently no generics available within the class.

- In 2020, the first long-acting GH derivative, somapacitan-beco (Sogroya), was FDA-approved for the treatment of GHD in adults (*FDA 2020*). Somapacitan-beco reversibly binds to circulating albumin, thus prolonging the product's half-life (*Johannsson et al 2020*). This is the first GH therapy to be administered once weekly instead of once daily for adult GHD (*FDA 2020*).
- GH preparations are available in various formulations, and several delivery devices are available. The dosing device may be a factor in patient adherence with the prescribed regimen.
- Medispan Class: Growth Hormones

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Genotropin (somatropin)	-
Humatrope (somatropin)	-
Norditropin Flexpro (somatropin)	-
Nutropin AQ (somatropin)	-
Omnitrope (somatropin)	-
Saizen (somatropin)	-
Serostim (somatropin)	-
Sogroya (somapacitan-beco)*	-
Zomacton (somatropin)	-
Zorbtive (somatropin)	-

*Sogroya was FDA-approved on August 28, 2020 but has not yet been launched by its manufacturer.

(*Drugs@FDA 2021, Purple Book: Database of Licensed Biological Products 2021*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Genotropin	Humatrope	Norditropin Flexpro	Nutropin AQ	Omnitrope	Saizen	Serostim	Sogroya	Zomacton	Zorbtive
Growth failure associated with chronic renal insufficiency before renal transplant				✔						
Growth failure associated with Noonan syndrome			✔							
Growth failure associated with Prader-Willi syndrome	✔		✔		✔					
Growth failure associated with short-stature homeobox-containing gene deficiency		✔							✔	
Growth failure associated with Turner syndrome	✔	✔	✔	✔	✔				✔	
Growth failure in children born small for gestational age	✔	✔	✔		✔				✔	
Growth failure due to GH deficiency	✔	✔	✔	✔	✔	✔			✔	
Adults with GH deficiency	✔	✔	✔	✔	✔	✔		✔	✔	
Idiopathic short stature	✔	✔	✔	✔	✔				✔	
Human immunodeficiency virus-associated wasting or cachexia							✔			

Indication	Genotropin	Humatrope	Norditropin Flexpro	Nutropin AQ	Omnitrope	Saizen	Serostim	Sogroya	Zomacton	Zorbtive
Treatment of short bowel syndrome in patients receiving specialized nutritional support										✔

(Prescribing information: *Genotropin 2019, Humatrope 2019, Norditropin Flexpro 2020, Nutropin AQ 2016, Omnitrope 2019, Saizen 2020, Serostim 2019, Sogroya 2020, Zomacton 2018, Zorbtive 2019*)

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

CLINICAL EFFICACY SUMMARY

- There are limited head-to-head clinical trials comparing different GH preparations to one another.
- One phase 3, randomized controlled trial (RCT) compared weekly somapacitan-beco to placebo in adults with GHD (REAL 1) (*Johannsson et al 2020*). Daily GH therapy was also included as an active comparator. A total of 301 patients were randomized 2:1:2 to once-weekly somapacitan-beco (blinded), once-weekly placebo (blinded), or daily GH (open-label). At 34 weeks, somapacitan-beco reduced truncal fat percentage when compared to placebo (primary outcome), with an estimated difference of -1.53% (95% confidence interval [CI], -2.68 to -0.38; p = 0.0090). The between-group estimated difference for reduction in truncal fat percentage for somapacitan-beco vs daily GH therapy (secondary analysis) was 1.17% (95% CI, 0.23 to 2.11); this endpoint was not designed as a confirmatory test and no p-value was calculated. Improvements were maintained with both somapacitan-beco and daily GH throughout a 52-week open-label extension period.
- Clinical data support the use of GH for the treatment of growth failure associated with chronic renal insufficiency. A meta-analysis of 16 RCTs (N = 809) evaluating the effects of GH in children with CKD found that patients who were treated with GH had a greater increase in mean height velocity (3.88 cm) than those who received either no treatment or placebo after 1 year (*Hodson et al 2012*). A retrospective, matched control cohort study found that long-term therapy with GH (mean 4.2 years) reduced linear growth deceleration in children with CKD and improved final height (*Bizzarri et al 2018*).
- Clinical trials have demonstrated efficacy of GH for the treatment of growth failure in patients with Noonan syndrome. An RCT evaluating GH in patients with Noonan syndrome found a positive effect of GH on linear growth. Specifically, there was a significantly greater change in height standard deviation score, and bone maturation was accelerated with GH compared to no treatment. In this trial, data also suggest that once treatment with GH is discontinued, “catch-down” (artificially stimulated growth declines once GH is discontinued) growth can occur (*Noordam et al 2001*). In a follow-up analysis of 29 patients treated with GH for a median of 6.4 years, a total of 22 children reached an adult height in the normal range (*Noordam et al 2008*). In a study of 65 patients enrolled in the National Cooperative Growth Study (NCGS) database, it was found that treatment with GH led to gains over predicted height of 9.2 cm in females and 10.9 cm in males (*Romano et al 2009*).
- Clinical trials and a 2020 meta-analysis have demonstrated the significant benefits of GH in pediatric patients with Prader-Willi syndrome in accelerating growth and in improving body composition. Benefits were also observed in improving bone mineral density, lipid profiles, energy expenditure, strength and agility, and pulmonary function (*Carrel et al 1999, Carrel et al 2004, Festen et al 2008, Lindgren et al 1997, Lindgren et al 1998, Lindgren et al 1999, Myers et al 1999, Myers et al, 2007, Passone et al 2020*). Data from 1 trial suggested that growth velocity declines dramatically once treatment is discontinued (*Lindgren et al 1997*).
- Humatrope demonstrated efficacy in increasing first-year height velocity in patients with Short Stature Homeobox-containing gene deficiency when compared to no treatment (p < 0.0001) (*Blum et al 2007*).
- Several clinical trials have demonstrated that GH significantly increases the growth rate of pediatric patients with Turner syndrome. Overall, various dose ranging trials did not consistently demonstrate a superior weight-based GH dosing regimen over another; all doses of GH were beneficial. In addition, data suggested that increases in height are greatest

during the first year of therapy (*Baxter et al 2007, Bertrand et al 1996, Massa et al 1995, Nienhuis et al 1993, Sas et al 1999a, Takano et al 1989a, Takano et al 1989b, Takano et al 1989c, Takano et al 1993, Takano 1995, van Pareren et al 2003, van Teunenbroek et al 1996*). A Cochrane Review of 4 RCTs demonstrated that GH (0.3 to 0.375 mg/kg/week) increased short-term growth in patients with Turner syndrome by approximately 3 cm during the first year of treatment. Despite the increase, the final height achieved was still below the normal range (*Baxter et al 2007*).

- For the treatment of growth failure in pediatric patients born small for gestational age, clinical trials have demonstrated the significant benefits of GH on increasing growth rates (*Arends et al 2003, Bannink et al 2010, Boguszewski et al 1998, Bozzola et al 2004, Chatelain et al 1994, De Schepper et al 2008, de Zegher et al 1996, de Zegher et al 2005, Jung et al 2009, Maiorana et al 2009, Sas et al 1999b*). Data from individual clinical trials and 3 meta-analyses found that response to GH therapy is dose-dependent, and higher doses of GH resulted in additional gain (*de Zegher et al 1996, de Zegher et al 2005*).
- Treatment with GH has been shown to increase height velocity in both prepubertal and pubertal pediatric patients with GHD (*Coelho et al 2008, Cohen et al 2002, de Muinck Keizer-Schrama et al 1992, Kriström et al 2009, MacGillivray et al 1996, Mauras et al 2000, Romer et al 2009, Sas et al 2010, Shih et al 1994, Wilson et al 1985*). Two head-to-head trials demonstrated no differences in safety and efficacy with different GH preparations for the treatment of pediatric GHD. One of the trials compared 3 GH preparations (Genotropin, Humatrope, and Saizen), while the second evaluated 2 preparations (Genotropin and Omnitrope) (*Romer et al 2009, Shih et al 1994*).
- In pediatric patients with idiopathic short stature, somatropin has been shown to increase first-year growth velocity and final height (*Albertsson-Wikland et al 2008, Bryant et al 2007, Deodati et al 2011, Finkelstein et al 2002, Hopwood et al 1993, Kriström et al 2009, van Gool et al 2010, Wit et al 2005*). Additionally, once daily compared to 3 times weekly dosing and higher compared to lower dosing demonstrated a greater increase in growth velocity (*Bryant et al 2007, Finkelstein et al 2002*).
- A registry study evaluated the long-term effectiveness and safety of GH in South Korean pediatric patients ≥ 2 years of age with GHD, idiopathic short stature, Turner syndrome, small for gestational age, and chronic renal failure. Interim analysis of 5-year data for 2024 patients (7324 patient-years) found that most patients showed a beneficial effect on height standard deviation score for up to 4 years, with the most prominent effect observed within 1 year of treatment initiation. The incidence of adverse events was low, and most cases of neoplasm were benign and/or unrelated to GH therapy (*Rhie et al 2019*).
- A systematic review and meta-analysis of 54 placebo-controlled, RCTs enrolling over 3400 patients found that GH therapy was associated with reduced body fat and increased lean mass in adults with GHD (*Hazem et al 2012*). Eleven of 16 trials that assessed quality of life outcomes reported positive outcomes, but a meta-analysis was not possible. Furthermore, results from meta-analyses and RCTs have demonstrated that treatment with GH was associated with improved cardiac function and bone mineral density (*Barake et al 2014, Davidson et al 2004, Maison et al 2003*). However, there are currently conflicting data with regard to the effect of GH on cognitive function, quality of life, and exercise capacity (*Arwert et al 2005, Falleti et al 2006, Rubeck et al 2009, Widdowson, 2010*).
- In patients with human immunodeficiency virus-associated wasting, Serostim has been shown to increase body weight, lean body mass, and work output. However, effects on quality of life were variable (*Moyle et al 2004, Schambelan et al 1996*).
- A meta-analysis assessed the safety and efficacy of GH with or without glutamine supplementation for adult patients with short bowel syndrome; 5 studies were included in the review. Human GH with or without glutamine appeared to provide benefit in terms of increased weight (mean difference [MD] 1.66 kg; 95% CI, 0.69 to 2.63; p = 0.0008), lean body mass (MD 1.93 kg; 95% CI, 0.97 to 2.9; p = 0.0001), energy absorption (MD 4.42 Kcal; 95% CI, 0.26 to 8.58; p = 0.04) and nitrogen absorption (MD 44.85 g; 95% CI, 0.2 to 9.49; p = 0.04) for patients with short bowel syndrome. One RCT, which focused on parenteral nutrition (PN) requirements, demonstrated decreased PN volume, calories, and number of infusions in patients who received GH with or without glutamine supplementation. Only patients who received GH with glutamine maintained statistically significant PN reductions at 3-month follow-up. The results suggested a positive effect of GH on weight gain and energy absorption. However, after cessation of therapy, the effects returned to baseline in the majority of the trials (*Wales et al 2010*).

CLINICAL GUIDELINES

- For pediatric patients, treatment guidelines recommend the use of GH therapy with somatropin as a treatment option for children with growth failure associated with any of the following: GHD, GHD in childhood cancer survivors, Noonan

syndrome, Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency, born small for gestational age, and short stature homeobox-containing gene deficiency (*Cohen et al 2008, Deal et al 2013, Gravholt et al 2017, Grimberg et al 2016, Ketteler et al 2018, Sklar et al 2018*). Routine use of GH in every child with idiopathic short stature is not recommended; decisions about GH therapy should take into account physical and psychological burdens as well as risks and benefits (*Grimberg et al 2016*). Guidelines do not prefer one GH agent over another. Choice of preparation should be individualized based on potential advantages and disadvantages of therapy, therapeutic need, and the likelihood of adherence.

- Treatment guidelines recommend offering GH therapy to adult patients with proven GHD and no contraindications (*Fleseriu et al 2016*). Therapy should be individualized independent of body weight. The dose of GH should be low initially and gradually increased to the minimally effective dose that normalizes IGF-1 levels without side effects (*Fleseriu et al 2016, Yuen et al 2019).* The 2019 American Association of Clinical Endocrinologists/American College of Endocrinology guidelines, which focus on adults and patients transitioning from pediatric to adult care, state that no evidence exists to support any specific GH product over another (*Yuen et al 2019*).
- Small studies evaluating the use of GH in short bowel syndrome have yielded conflicting results; methodological differences limit definitive conclusions on the efficacy of GH. In carefully selected patients who are candidates for growth factor treatment, the glucagon-like peptide-2 analog, teduglutide, is recommended as first-line therapy (*Pironi et al 2016*).

SAFETY SUMMARY

- Contraindications to GH products include active malignancy, diabetic retinopathy, hypersensitivity to the agent or any of its excipients, acute critical illness, and use for growth promotion in children with closed epiphyses. Somatropin is also contraindicated in children with Prader-Willi syndrome who are severely obese, have severe respiratory impairment, or have a history of upper airway obstruction or sleep apnea (Genotropin, Humatrope, Norditropin Flexpro, Nutropin AQ, Omnitrope, Saizen, Zomacton).
- Key Warnings/Precautions (applicable to all GH products unless otherwise noted):
  - Therapy may contribute to increased mortality in patients with acute critical illness due to complications from open heart surgery, abdominal surgery, accidental trauma, or respiratory failure.
  - Somatropin may increase progression or recurrence of intracranial neoplasms, particularly meningiomas in patients treated with radiation to the head for their first neoplasm.
    - The Safety and Appropriateness of GH treatments in Europe (SAGhE) study, which followed almost 24,000 patients for an average of 14.8 years per patient, found that GH therapy does not increase the risk for leukemia or other cancers in patients with isolated growth failure as compared with the age-matched general population. GH was associated with a modest increase in risk for a secondary cancer in patients with a primary cancer diagnosis. In patients with other non-cancer primary diagnoses, there was a modest increase in cancer risk, primarily bone or bladder cancer (*Swerdlow et al 2017*).
  - Malignancy:
    - In childhood cancer survivors who were treated with radiation to the brain/head for their first neoplasm and were later treated with somatropin, an increased risk of a second neoplasm has been reported. Patients with a history of GHD secondary to an intracranial neoplasm who are treated with somatropin should be monitored routinely for progression or recurrence of the tumor.
    - Because children with certain rare genetic causes of short stature have an increased risk of developing malignancies, practitioners should thoroughly consider the risks and benefits of starting somatropin in these patients. If treatment with somatropin is initiated, these patients should be carefully monitored for development of neoplasms.
    - Patients on somatropin should be carefully monitored for increased growth, or potential malignant changes, of preexisting nevi.
    - Somapacitan-beco increases the risk of malignancy progression in patients with active malignancy. There is also a potential risk of new skin malignancy during treatment, including malignant changes of preexisting nevi.
  - Undiagnosed or untreated hypothyroidism may impair optimal response to therapy.
  - A decrease in insulin sensitivity and previously undiagnosed diabetes mellitus may be unmasked during treatment.
  - Intracranial hypertension and pancreatitis have been reported with therapy.
  - Slipped capital femoral epiphyses and scoliosis can occur in pediatric patients.
  - Fluid retention has been associated with treatment in adult patients.

- Increases in serum levels of inorganic phosphorous, alkaline phosphatase, parathyroid hormone and IGF-1 may occur.
- Tissue atrophy may occur when therapy is administered via SC injection at the same site over a long period of time.
- Therapy may reduce serum cortisol levels or unmask central hypoadrenalism in patients at risk for pituitary hormone deficiency.

- Adverse drug events: Arthralgia, back pain, dyspepsia, myalgia, edema, carpal tunnel syndrome, paresthesia, hyperglycemia, headaches, lipoatrophy, and injection site reactions.
- Drug Interactions: Estrogens, glucocorticoids, insulin or other hypoglycemic agents, and drugs metabolized by cytochrome P450 enzymes.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Genotropin (somatropin)	Injection	SC	Weekly dose divided into 6 or 7 injections to Daily	Injections should be rotated to help prevent lipoatrophy.
Humatrope (somatropin)	Injection	SC	Weekly dose divided into 6 or 7 injections to Daily	Injections should be rotated to help prevent lipoatrophy.
Norditropin Flexpro (somatropin)	Injection	SC	Weekly dose divided into 6 or 7 injections to Daily	Injections should be rotated to help prevent lipoatrophy.
Nutropin AQ (somatropin)	Injection	SC	Weekly dose divided into 3 to 7 injections to Daily	Injections should be rotated to help prevent lipoatrophy.
Omnitrope (somatropin)	Injection	SC	Weekly dose divided into 6 or 7 injections to Daily	Injections should be rotated to help prevent lipoatrophy.
Saizen (somatropin)	Injection	SC	Weekly dose divided into 3, 6, or 7 injections to Daily	Injections should be rotated to help prevent lipoatrophy.
Serostim (somatropin)	Injection	SC	Daily	Injections should be rotated to avoid local irritation.
Sogroya (somapacitan-beco)	Injection	SC	Once weekly	Injections should be rotated to help prevent lipoatrophy
Zomacton (somatropin)	Injection	SC	Weekly dose divided into 3, 6, or 7 injections to Daily	Injections should be rotated to help prevent lipoatrophy.
Zorbtive (somatropin)	Injection	SC	Daily	Injections should be rotated to help prevent lipoatrophy. Dosage titration is recommended for fluid retention and arthralgia/carpal tunnel syndrome.

See the current prescribing information for full details.

CONCLUSION

- The safety and efficacy of GH therapy in pediatric patients with growth failure are well established. Treatment guidelines recommend the use of somatropin as a treatment option for children with growth failure associated with any of the following: GHD, GHD in childhood cancer survivors, Turner syndrome, Prader-Willi syndrome, chronic renal insufficiency, born small for gestational age, and short stature homeobox-containing gene deficiency (*Clayton et al 2007*, *Cohen et al 2008, Deal et al 2013, Gravholt et al 2017, Grimberg et al 2016, Ketteler et al 2018, Sklar et al 2018*). Routine use of GH in every child with idiopathic short stature is not recommended; decisions about GH therapy should take into account physical and psychological burdens as well as risks and benefits (*Grimberg et al 2016*). Guidelines do not prefer one GH agent over another. Choice of preparation should be individualized based on potential advantages and disadvantages of therapy, therapeutic need, and the likelihood of adherence.

- For adult patients, guidelines recommend offering GH therapy to those with proven GHD and no contraindications. (*Fleseriu et al 2016).* No evidence exists to support any specific GH product over another (*Yuen et al 2019*).
- There are several GH preparations currently available, most of which contain somatropin (recombinant human GH). These preparations are equally biopotent and have the same natural sequence structure (*Rogol et al 2020*).
- In addition to the somatropin products, somapacitan-beco has been approved by the FDA as a longer-acting GH derivative with once-weekly dosing for adult GHD.
- Differences between GH products such as device features, dose increments, requirement for reconstitution, and requirement for refrigeration may influence individual patient preferences. All of the available GH preparations are available for SC injection, and there are currently no generics available within the class.
- Common adverse reactions that may be observed with GH therapy include arthralgia, back pain, dyspepsia, myalgia, edema, carpal tunnel syndrome, paresthesia, hyperglycemia, headaches, lipoatrophy, and injection site reactions.

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Publication Date: February 16, 2021

Prior Authorization Guideline

Guideline Name Gimoti (metoclopramide) nasal spray

1 . Indications

Drug Name: Gimoti (metoclopramide)
Diabetic Gastroparesis Indicated for the relief of symptoms in adults with acute and recurrent diabetic gastroparesis. Limitations of use: Gimoti is not recommended for use in: 1) pediatric patients due to the risk of tardive dyskinesia (TD) and other extrapyramidal symptoms as well as the risk of methemoglobinemia in neonates and 2) moderate or severe hepatic impairment (Child-Pugh B or C), moderate or severe renal impairment (creatinine clearance less than 60 mL/minute), and patients concurrently using strong CYP2D6 inhibitors due to the risk of increased drug exposure and adverse reactions.

2 . Criteria

Product Name: **Gimoti**	
Approval Length	8 Week(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Diagnosis of acute diabetic gastroparesis

AND

2 - Patient is 18 years of age or older

AND

3 - Patient does NOT have ANY of the following:

- History of signs or symptoms of tardive dyskinesia (TD)
- History of a dystonic reaction to metoclopramide
- Known or suspected circumstances where stimulation of gastrointestinal (GI) motility could be dangerous (e.g., GI hemorrhage, mechanical obstruction, or perforation)
- Known or suspected pheochromocytoma or other catecholamine-releasing paraganglioma
- Diagnosis of epilepsy or any other seizure disorder
- Hypersensitivity to metoclopramide (e.g., angioedema, bronchospasm)
- Moderate or severe renal impairment (creatinine clearance [CrCl] < 60 mL/minute)
- Moderate or severe hepatic impairment (Child-Pugh B or C)

AND

4 - ONE of the following:

- Adequate (e.g., 2-4 week) trial and failure of oral (e.g., tablet, solution, orally disintegrating tablet) or injectable (e.g., intramuscular) metoclopramide
- The patient is NOT a candidate for oral metoclopramide (e.g., demonstrated or documented erratic absorption of oral medications)

Product Name: **Gimoti**	
Approval Length	8 Week(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

1 - Patient continues to meet all initial authorization criteria

AND

2 - At least 2 weeks have passed (i.e., drug holiday) since completion of a previous course of metoclopramide treatment of any dosage form

AND

3 - Demonstrated improvement in signs and symptoms of diabetic gastroparesis (e.g., nausea, vomiting, early satiety, postprandial fullness, bloating, upper abdominal pain)

AND

4 - Prescriber attestation that the patient is being monitored for extrapyramidal symptoms (e.g., tardive dyskinesia, dystonia) or other serious adverse events (e.g., suicidal ideation, fluid retention).

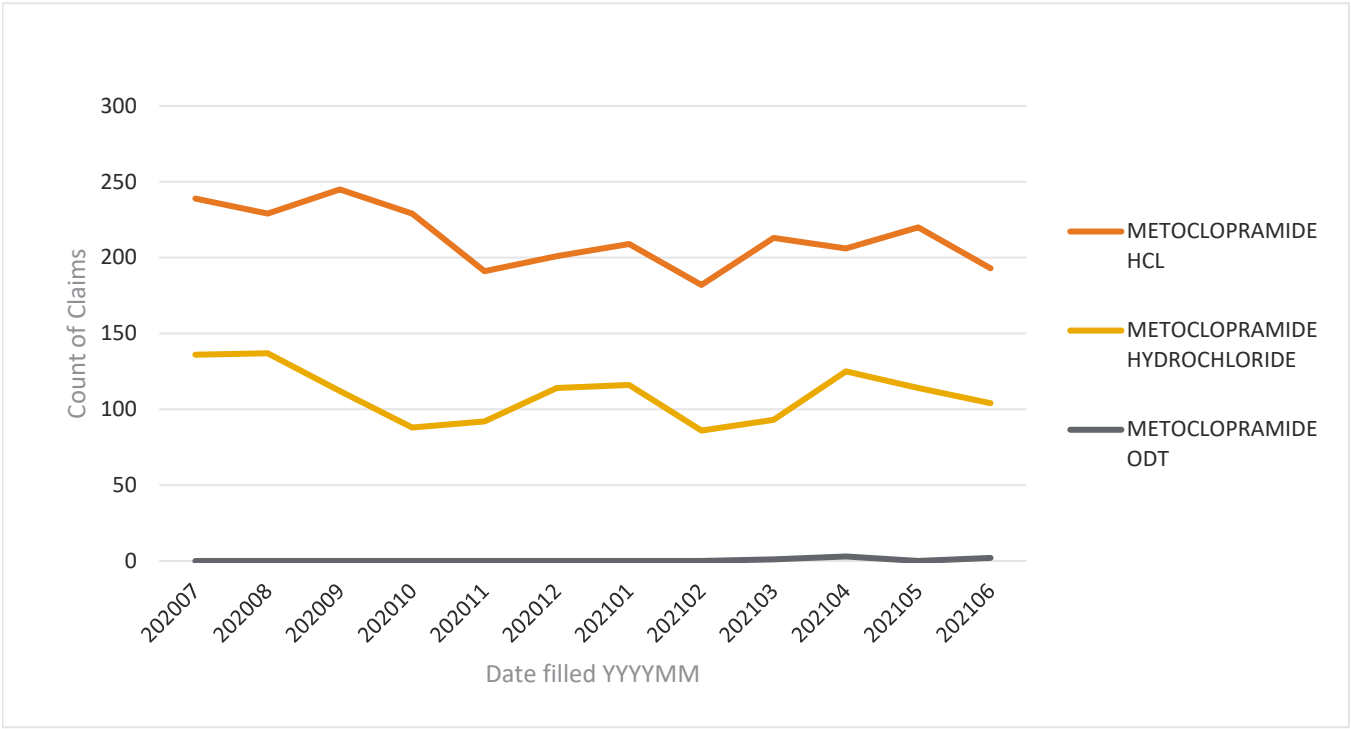
Nevada Medicaid

Top Ten Therapeutic Classes

Fee for Service

July 1, 2020 - June 30, 2021

Drug Name	Members	Claims	Total Days Supply	Total Quantity
METOCLOPRAMIDE HYDROCHLORIDE	732	1,317	23,837	70,375
METOCLOPRAMIDE HCL	1,718	2,557	16,116	74,251
METOCLOPRAMIDE ODT	5	6	229	310



Therapeutic Class Overview
Antiemetics

INTRODUCTION

- Nausea, the sensation of anticipating vomiting, may occur with or without concomitant dyspepsia, other gastrointestinal (GI) symptoms, or vomiting, which is the forceful expulsion of gastric contents (*Longstreth et al 2021*).
- Chemotherapy-induced nausea and vomiting (CINV) is often viewed as the most severe and distressing form of nausea and vomiting (n/v) that occurs in patients with cancer. Additional causes of n/v in this population include surgery, opioid therapy, and radiation (*Hesketh, 2021; Hesketh 2019*).
- Normal function of the upper GI tract involves interactions between the gut and the central nervous system (CNS), with the motor function of the GI tract being controlled at the level of the parasympathetic and sympathetic nervous systems, enteric brain neurons, and smooth muscle cells (*Longstreth et al 2021*).
- Three distinct types of CINV have been defined, including (*Hesketh 2021, Hesketh 2019*):
  - Acute emesis, which most commonly begins within 1 to 2 hours of chemotherapy and usually peaks in the first 4 to 6 hours
  - Delayed emesis, occurring beyond 24 hours after chemotherapy
  - Anticipatory emesis, occurring prior to treatment as a conditioned response in patients who have developed significant n/v during previous cycles of chemotherapy
- Approximately one-third of surgical patients have nausea, vomiting, or both after receiving general anesthesia, with increased risk associated with the female gender, nonsmoker status, previous history of postoperative n/v (PONV), and use of postoperative opioids (*Longstreth et al 2021*).
- Nausea and/or vomiting caused by radiation therapy (RT) is generally less severe than that caused by chemotherapy. The pathophysiology of radiation-induced n/v (RINV) remains unclear, but it is thought to be similar to that caused by chemotherapy (*Feyer et al 2020)*.
- Nausea with or without vomiting is common in early pregnancy. Severe vomiting resulting in dehydration and weight loss is termed hyperemesis gravidarum and occurs less frequently. The treatment goals in patients with nausea and vomiting of pregnancy (NVP) are to reduce symptoms through changes in diet/environment and by medication, to correct consequences or complications of n/v such as dehydration, and to minimize the fetal effects of NVP treatment (*American College of Obstetrics and Gynecologists [ACOG] 2018 [reaffirmed in 2019], Smith et al 2021*).
- Nausea is common in motion sickness and symptoms may also include vomiting and headache. Motion sickness is thought to result from incongruent vestibular, visual, and somatosensory sensory cues *(Priesol 2020)*.
- The mechanism of action for the 5-hydroxytryptamine (5-HT3, or serotonin) agents results from the blockade of 5-HT3 receptors in both the gastric area and the chemoreceptor trigger zone in the CNS. By blocking these receptors, these medications disrupt the signal to vomit and reduce the sensation of nausea (*Mannix et al 2006*).
- The substance P/neurokinin 1 (NK1) receptor antagonists cross the blood brain barrier and occupy the NK1 receptors in the brain, leading to reduced symptoms of n/v.
- Synthetic delta-9-tetrahydrocannabinol (THC) is the active ingredient in the THC derivative agents, also known as the cannabinoids. Cannabinoid receptors have been discovered in neural tissues, and these receptors may play a role in mediating the antiemetic effects of cannabinoids such as dronabinol and nabilone. These agents, like other cannabinoids, have the potential to be abused and produce psychological dependence. Both dronabinol and nabilone may produce alterations in mood (euphoria, detachment, depression, anxiety) and alterations in reality (distorted perceptions of objects and time and hallucinations).
- The mechanism of action of Diclegis and Bonjesta (doxylamine succinate/pyridoxine hydrochloride [HCl]) are unknown (*Diclegis and Bonjesta prescribing information 2018*).
- Dopamine receptor antagonists, such as prochlorperazine (a phenothiazine) and trimethobenzamide (a benzamide), primarily work by blocking D_2-dopamine receptors in the postrema area of the midbrain. They also have M1-muscarinic and H1-histamine antagonizing effects *(Longstreth 2020)*. Scopolamine, an anticholinergic drug, is an M1-muscarinic receptor antagonist. Antihistamines are used for motion sickness *(Longstreth 2020).*

- The 5-HT3 receptor antagonists are Food and Drug Administration (FDA)-approved for the treatment of CINV, PONV, and/or RINV, although the medications and various dosage forms of each agent differ slightly with respect to these indications.
- The D_2 antagonist Barhemsys (amisulpride) is FDA-approved for treatment and prevention of PONV.
- The substance P/NK1 receptor antagonists are currently FDA-approved for the prevention of CINV. In addition, aprepitant is approved for the prevention of PONV.
- The combination product, Akynzeo, contains palonosetron, a 5-HT3 receptor antagonist, and a substance P/NK1 receptor antagonist: netupitant in the oral formulation and fosnetupitant in the injectable formulation. This agent is approved for prevention of acute and delayed n/v associated with initial and repeat courses of cancer chemotherapy.
- Diclegis and Bonjesta are fixed-dose combination products of doxylamine succinate, an antihistamine, and pyridoxine HCl, a vitamin B6 analog. Diclegis and Bonjesta are indicated for the treatment of NVP in women who do not respond to conservative management. It should be noted that these agents have not been studied in hyperemesis gravidarum.
  - The combination of doxylamine and pyridoxine was previously available in the United States under the brand name Bendectin. However, this product was removed from the market in 1983 due to lawsuits alleging teratogenicity despite scientific evidence of the safety and efficacy of the medication. A meta-analysis (MA) of controlled studies on outcome of pregnancies exposed to Bendectin reported no increase in the incidence of birth defects (*Smith et al 2021*).
- Prescription meclizine is FDA-approved for vertigo; however, over-the-counter products are used for n/v and dizziness associated with motion sickness. Transdermal scopolamine is FDA-approved for n/v associated with motion sickness and for PONV. Prochlorperazine is FDA-approved for treatment of severe n/v, promethazine is approved for motion sickness and n/v associated with certain anesthesia and surgery, and trimethobenzamide is approved for PONV and nausea related to gastroenteritis.
- The scope of this review will focus on the agents outlined in Table 1 for their respective FDA-approved indications as related to CINV, PONV, or n/v associated with other conditions such as pregnancy and motion sickness, with a focus on CINV. Other agents including glucocorticoids may also be effective antiemetics; however, they have been excluded from this review. Although certain agents are FDA-approved for other indications, only those related to n/v are included in this review.
- Medispan Therapeutic Class: 5-HT3 Receptor Antagonists; Dopamine Antagonist; Substance P/NK1 Receptor Antagonists; Antiemetics – Miscellaneous; Antiemetic Combinations – Two Ingredient.

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Akynzeo (palonosetron/netupitant) capsule	–
Akynzeo (palonosetron/fosnetupitant) IV solution	–
Aloxi (palonosetron) IV solution	✔
Anzemet (dolasetron) tablets*	
Barhemsys (amisulpride) IV solution	–
Bonjesta (doxylamine succinate/pyridoxine HCl) 20 mg extended-release tablets	–
Cesamet (nabilone) capsule*	–
Cinvanti (aprepitant) IV emulsion	–
Compro (prochlorperazine) rectal suppository	✔
Diclegis (doxylamine succinate/pyridoxine HCl) 10 mg delayed-release tablets	✔
Emend (aprepitant) oral suspension	–
Emend (aprepitant) capsule, combination pack	✔
Emend (fosaprepitant) IV solution	✔
granisetron injection, tablets	✔ ‡
Marinol (dronabinol) capsule‖	✔
meclizine over-the-counter products	✔
ondansetron injection	✔ ‡
Phenergan (promethazine) injection	✔
prochlorperazine injection, tablet	✔
Promethegan (promethazine) rectal suppository	✔

Drug	Generic Availability
promethazine injection, tablet, syrup, oral solution	✔
Sancuso (granisetron) transdermal patch	–
Sustol (granisetron) extended-release subcutaneous injection	–
Syndros (dronabinol) oral solution	–
Tigan (trimethobenzamide) capsule	✔
Tigan (trimethobenzamide) injection	-
Transderm Scop (scopolamine) transdermal film	✔
Varubi (rolapitant) tablet†	–
Zofran (ondansetron) oral solution, tablet	✔ ‡
Zofran (ondansetron) ODT	✔ ‡
Zuplenz (ondansetron) oral soluble film	–

Abbrv: IV=intravenous, ODT=orally disintegrating tablet
*This product has been discontinued in most, but not all strengths.
‡Generic available in at least 1 dosage form and/or strength.
†The FDA website shows the IV rolapitant product as discontinued. The manufacturer of IV rolapitant suspended further distribution of the product in February 2018 due to reports of anaphylaxis, anaphylactic shock, and other serious hypersensitivity reactions associated with its use.
‖Marinol brand has been discontinued, but generic dronabinol is available.

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	5-HT$_3$ Receptor Antagonists				D_2 antagonist	Substance P/NK$_1$ Receptor Antagonists			THC Derivatives		Combination Products	
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Amisulpride	Aprepitant	Fosaprepitant	Rolapitant	Dronabinol	Nabilone	Palonosetron/ netupitant (oral) fosnetupitant (IV)	Doxylamine succinate/ pyridoxine HCl
	Anorexia in patients with AIDS											
Anorexia associated with weight loss in adults with AIDS									✔			
	CINV											
N/V associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments									✔	✔		
Highly emetogenic cancer chemotherapy (HEC) – prevention of acute n/v associated with initial and repeat courses in adults				✔								
Prevention of acute and delayed n/v associated with initial and repeat courses of HEC including high-dose cisplatin in patients ≥ 6 months of age						✔ * (oral suspension)	✔ *					
Prevention of acute n/v associated with initial and repeat courses of emetogenic chemotherapy, including HEC in pediatric patients aged 1 month to < 17 years				✔								
Prevention of acute and delayed n/v associated with initial and repeat courses of HEC, including high-dose cisplatin as a single dose regimen, in adults						✔ * (IV emulsion)						
Prevention of acute and delayed n/v associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, HEC in combination with dexamethasone											✔ (capsule)	

Indication	5-HT$_3$ Receptor Antagonists				D_2 antagonist	Substance P/NK$_1$ Receptor Antagonists			THC Derivatives		Combination Products	
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Amisulpride	Aprepitant	Fosaprepitant	Rolapitant	Dronabinol	Nabilone	Palonosetron/ netupitant (oral) fosnetupitant (IV)	Doxylamine succinate/ pyridoxine HCl
Prevention of acute and delayed n/v associated with initial and repeat courses of HEC in combination with dexamethasone											✔ ¥ (IV)	
Prevention of acute and delayed n/v associated with initial and repeat courses of HEC, including high-dose cisplatin, in patients ≥ 12 years of age						✔ * (capsule)						
Prevention of delayed n/v associated with initial and repeat courses of emetogenic cancer chemotherapy, including, but not limited to, HEC								✔ *				
Prevention of n/v associated with HEC including cisplatin ≥ 50 mg/m^2			✔ (tablet, ODT, oral solution, oral soluble film)									
Prevention of n/v associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin		✔ (injection, tablets)										
Prevention of n/v associated with initial and repeat courses of emetogenic cancer chemotherapy, including high-dose cisplatin, in patients ≥ 6 months of age			✔ (injection)									
Moderately emetogenic cancer (MEC) chemotherapy – prevention of n/v associated with initial and repeat courses in adults				✔								
Prevention of n/v in patients receiving MEC and/or HEC for up to 5 consecutive days		✔ (TD)										
Prevention of n/v associated with initial and repeat courses of MEC			✔									

Indication	5-HT$_3$ Receptor Antagonists				D_2 antagonist	Substance P/NK$_1$ Receptor Antagonists			THC Derivatives		Combination Products	
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Amisulpride	Aprepitant	Fosaprepitant	Rolapitant	Dronabinol	Nabilone	Palonosetron/ netupitant (oral) fosnetupitant (IV)	Doxylamine succinate/ pyridoxine HCl
			(tablet, ODT, oral solution, oral soluble film)									
Prevention of n/v associated with MEC, including initial and repeat courses in ages ≥ 2 years	✔											
Prevention of n/v associated with initial and repeat courses of MEC, in patients ≥ 6 months of age						✔ (oral suspension)						
Prevention of acute and delayed n/v associated with initial and repeat courses of MEC or anthracycline and cyclophosphamide combination chemotherapy regimens.		✔ * (ER injection)										
Prevention of delayed n/v associated with initial and repeat courses of MEC in patients ≥ 6 months of age							✔ *					
Prevention of n/v associated with initial and repeat courses of MEC in patients ≥ 12 years of age						✔ * (capsule)						
Prevention of n/v associated with initial and repeat courses of MEC as a 3 day regimen, in adults						✔ * (IV emulsion)						
Prevention of delayed n/v associated with initial and repeat courses of MEC as a single dose regimen, in adults						✔ * (IV emulsion)						
	NVP											
Treatment of NVP in women who do not respond to conservative management												✔
	PONV											
Prevention of PONV for up to 24 hours following surgery; efficacy beyond 24 hours has not been				✔								

Indication	5-HT$_3$ Receptor Antagonists				D_2 antagonist	Substance P/NK$_1$ Receptor Antagonists			THC Derivatives		Combination Products	
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Amisulpride	Aprepitant	Fosaprepitant	Rolapitant	Dronabinol	Nabilone	Palonosetron/ netupitant (oral) fosnetupitant (IV)	Doxylamine succinate/ pyridoxine HCl
demonstrated; as with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that n/v will occur post-operatively. In patients where n/v must be avoided postoperatively, Aloxi injection is recommended even where the incidence of PONV is low												
Prevention of PONV in adults			✔ (tablet, ODT, oral solution)			✔ (generic aprepitant only)						
Prevention and treatment of PONV; as with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that n/v will occur post-operatively. In patients where n/v must be avoided postoperatively, this drug is recommended even where the incidence of PONV is low.		✔ (injection)			✔							
Prevention of PONV; as with other antiemetics, routine prophylaxis is not recommended for patients in whom there is little expectation that n/v will occur post-operatively. In patients where n/v must be avoided postoperatively, this drug is recommended even where the incidence of PONV is low.			✔ (injection†, oral soluble film)									
	RINV											
Prevention of n/v associated with RT, including TBI and fractionated abdominal RT		✔ (tablets)										
Prevention of n/v associated with radiotherapy in patients receiving either TBI, single high-dose			✔ (tablet, ODT, oral solution,									

Indication	5-HT$_3$ Receptor Antagonists				D_2 antagonist	Substance P/NK$_1$ Receptor Antagonists			THC Derivatives		Combination Products	
	Dolasetron	Granisetron	Ondansetron	Palonosetron	Amisulpride	Aprepitant	Fosaprepitant	Rolapitant	Dronabinol	Nabilone	Palonosetron/ netupitant (oral) fosnetupitant (IV)	Doxylamine succinate/ pyridoxine HCl
fraction to the abdomen, or daily fractions to the abdomen			oral soluble film)									

Abbrv: 5-HT3 = serotonin (5-hydroxytryptamine) 3 receptor, AIDS = acquired immunodeficiency syndrome, ER = extended release, HEC = highly emetogenic cancer chemotherapy, MEC = moderately emetogenic cancer chemotherapy, n/v = nausea/vomiting, NVP = nausea and vomiting of pregnancy, NK1 = neurokinin 1, ODT = orally disintegrating tablet, PONV = postoperative nausea and vomiting, RINV = radiation-induced nausea and vomiting, RT = radiation therapy, TBI = total body irradiation, TD = transdermal patch, THC = delta-9-tetrahydrocannabinol

* When used in combination with other antiemetic agents.

† For patients who do not receive prophylactic ondansetron injection and experience n/v postoperatively, ondansetron injection may be given to prevent further episodes.

¥ Not studied for prevention of n/v associated with anthracycline plus cyclophosphamide chemotherapy.

Table 2 (cont.) Food and Drug Administration Approved Indications.

Indication	Antihistamine	Phenothiazines		Anticholinergic	Benzamide
	Meclizine	Promethazine	Prochlorperazine	Scopolamine	Trimethobenzamide
PONV					
Treatment of PONV					✔ † (capsules, injection)
Prevention and control of n/v associated with certain types of anesthesia and surgery		✔ ¥ (injection, suppository,			

		solution, syrup, tablet)			
Antiemetic therapy in postoperative patients		✔ ¥ (suppository, solution, syrup, tablet)			
Prevention of PONV associated with recovery from anesthesia and/or opiate analgesia and surgery				✔	
Motion Sickness					
Prevents and treats n/v or dizziness associated with motion sickness	✔ *				
Prevention of n/v associated with motion sickness				✔	
Active treatment of motion sickness		✔ ¥ (injection)			
Active and prophylactic treatment of motion sickness		✔ ¥ (suppository, solution, syrup, tablet)			
Nausea associated with gastroenteritis					
Nausea associated with gastroenteritis					✔ † (capsules, injection)
Severe nausea and vomiting					
Control of severe n/v			✔ ** (tablets, injection, suppository)		

Abbrv: n/v = nausea and vomiting, FDA = Food and Drug Administration; ODT = orally disintegrating tablets, PONV = postoperative nausea and vomiting
*Antivert (meclizine) is FDA-approved for treatment of vertigo; however, over-the-counter meclizine prevents and treats nausea, vomiting or dizziness associated with motion sickness.
†Tigan not recommended to use in pediatric patients due to risk of extrapyramidal signs and symptoms, other CNS effects, and risk of exacerbating underlying disease in patients with Reye's syndrome or other hepatic impairment.
¥Promethazine is also FDA-approved for multiple indications including those related to allergic conditions, surgical analgesia, and sedation.
**Prochlorperazine is also FDA-approved for treatment of schizophrenia and anxiety.

(*Prescribing information: Akynzeo 2020, Aloxi 2020, Antivert 2019, Anzemet tablets 2019, Barhemsys 2020, Bonjesta 2018, Cesamet 2020, Cinvanti 2019, Compro 2016, Diclegis tablets 2018, Emend capsules and oral suspension 2021, Emend for injection 2020, granisetron injection 2020, granisetron tablets 2019, Marinol 2017, meclizine chewable tablets 2020, meclizine soluble film 2021, meclizine tablets ODT 2020, ondansetron injection 2019, Promethegan suppository 2014, prochlorperazine injection 2020, prochlorperazine tablets 2018, promethazine injection 2016, promethazine oral solution 2019, promethazine syrup 2018, promethazine tablets 2019, Sancuso 2020, Sustol 2017, Syndros 2020, Tigan capsules 2017, Tigan injection 2016, Transderm Scop 2020, Varubi 2020, Zofran tablets ODT oral solution 2017, Zuplenz 2019*)

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

CLINICAL EFFICACY SUMMARY

Anorexia in patients with AIDS

- A 2015 MA (N = 6,462; 79 trials) evaluated the efficacy and safety of cannabinoids in various conditions, including appetite stimulation in HIV/AIDS. Most trials were of low to moderate quality and compared cannabinoids to usual care, placebo, or no treatment across trials. Compared with placebo, cannabinoids were associated with a higher proportion of patients demonstrating a complete n/v response (47% vs 20%; odds ratio [OR], 3.82; 95% confidence interval [CI], 1.55 to 9.42; 3 trials), reduction in pain (37% vs 31%; OR, 1.41; 95% CI, 0.99 to 2.00; 8 trials), and a greater average reduction in numerical rating scale pain assessment (on a 0 to 10 point scale; weighted mean difference [WMD], -0.46; 95% CI, -0.80 to -0.11; 6 trials). A total of 4 trials evaluated dronabinol for appetite stimulation in 255 patients with HIV infection or AIDS, key outcomes are outlined below (*Abrams et al 2003, Timpone et al 1997, Whiting et al 2015):*
  - Data from 1 small study (n = 139, of which only 88 were evaluable) demonstrated that a large proportion of patients experienced weight gain of ≥ 2 kg within 6 weeks vs placebo (OR, 2.2; 95% CI, 0.68 to 7.27). An active comparison trial found that megestrol acetate was associated with greater weight gain than dronabinol and that combining dronabinol with megestrol acetate did not lead to additional weight gain.
- A 2013 MA of 7 trials, mostly of poor quality, found similar results as *Whiting et al*. Randomized controlled trials (RCTs) included any cannabis intervention and were of a short duration, ranging from 21 to 84 days. Patients had a mean weight gain in the dronabinol group of 0.1 kg, compared with a weight loss of 0.4 kg in the placebo group (*Lutge et al 2013*).

CINV

- For the management of CINV, MAs and head-to-head trials have demonstrated that the cannabinoids, dronabinol and nabilone, are more effective compared to placebo and may be more effective than prochlorperazine and metoclopramide. There are no published clinical trials comparing dronabinol to nabilone for CINV. The effectiveness of Syndros (dronabinol) oral solution for its FDA-approved indications was based on studies of dronabinol capsules.
- In a study by *Lane et al,* the combination of dronabinol plus prochlorperazine significantly reduced the mean duration of vomiting per episode compared to either agent administered with placebo (*Lane et al 1991*).
- Dolasetron has been shown to be an effective therapy in the treatment of CINV in comparative studies with palonosetron, ondansetron, and placebo (*Eberhart et al 2004, Eisenberg et al 2003, Karamanlioglu et al 2003, Lofters et al 1997, Meyer et al 2005, Walker et al 2001*).
- Granisetron and ondansetron are generally recognized as equally efficacious in treating CINV and PONV. Various studies may show slight benefits of 1 over another, but this has not been a consistently proven outcome (*Billio et al 2010, Dabbous et al 2010, del Giglio et al 2000, Dempsey et al 2004, Gan et al 2005, Jaing et al 2004, Kalaycio et al 1998, Lacerda et al 2000, Orchard et al 1999, White et al 2006*).
- Sancuso (granisetron) patch was noninferior to orally administered granisetron for CINV in a randomized trial (*Boccia et al 2011*). However, a MA of 3 studies found oral granisetron significantly reduced the odds of CINV compared with transdermal granisetron *(Chua et al 2020)*.
- Palonosetron was reported to be more effective than other medications in the class as well as placebo, particularly at preventing delayed emesis (*Aapro et al 2005, Billio et al 2010, Botrel et al 2011, Dong et al 2011, Eisenberg et al 2003, Gralla et al 2003, Kaushal et al 2010, Likun et al 2011, Massa et al 2009, Suzuki et al 2016, Chow et al 2018, Matsumoto et al 2020*).
- The safety and efficacy of Sustol (granisetron) were evaluated in a pivotal Phase 3, double-blind (DB), double-dummy, multicenter (MC), RCT in adults receiving HEC or MEC (*Raftopoulos et al 2015[a], Raftopoulos et al 2015[b]*). In the modified intention-to-treat population, both granisetron ER 5 mg and 10 mg were noninferior to palonosetron in preventing acute CINV after HEC and MEC. The FDA-approved dose of granisetron ER 10 mg was noninferior to palonosetron in preventing delayed CINV after MEC and was not superior in preventing delayed CINV after HEC (*Raftopoulos et al 2015[a], Raftopoulos et al 2015[b]*).
- All of the 5-HT3 receptor antagonists have been shown to be equally effective in preventing acute CINV in separate MAs and are superior to placebo (*Billio et al 2010, del Giglio et al 2000, George et al 2009, Singhal et al 2012, Tang et al 2012*). A 2016 MA comparing ondansetron to other 5-HT3 receptor antagonists used for CINV found that ondansetron exhibited similar efficacy to granisetron, but greater efficacy than dolasetron for acute vomiting; palonosetron exhibited greater efficacy than ondansetron for delayed nausea and acute and delayed vomiting (*Simino et al 2016*).

- A 2016 Cochrane review found that 5-HT3 receptor antagonists are effective in children who receive emetogenic chemotherapy. Granisetron or palonosetron may be more effective than ondansetron, and the addition of dexamethasone improves vomiting symptoms (*Phillips et al 2016*).
- A randomized, DB, noninferiority study comparing single-dose palonosetron 20 mcg/kg to multi-dose ondansetron 150 mcg/kg x 3 doses for the prevention of CINV in pediatric patients, aged 0 to 17 years, receiving MEC or HEC found that palonosetron was noninferior to ondansetron in the acute phase (0 to 24 hours post chemotherapy) (*Kovacs et al 2016*). A randomized, DB study in pediatric patients, aged 0 to 18 years, receiving HEC found complete response rates were not significantly different during the acute phase between palonosetron 5 mcg/kg, 10 mcg/kg and ondansetron 150 mcg/kg x 3 doses *(Tan et al 2018).* Palonosetron 10 mcg/kg was superior to ondansetron and palonosetron 5 mcg/kg in the delayed phase. In a randomized, open-label study, palonosetron was found to be noninferior and cost-effective in comparison to ondansetron for the prevention of acute CINV in children (2 to 18 years of age) with cancer (*Jain et al* 2018).
- A randomized, DB study in patients receiving HEC found that when used as part of combination therapy with dexamethasone and aprepitant, palonosetron IV was not more efficacious than granisetron IV at overall prevention of CINV. Combination therapy with palonosetron was, however, more efficacious than granisetron in controlling CINV in the delayed phase (24 to 120 hours post chemotherapy) (*Suzuki et al 2016*).
- A phase 3, randomized, DB trial compared oral with IV palonosetron in cancer patients receiving MEC *(Cui et al 2020)*. The primary endpoint, complete response rate in the acute phase, was not significantly different between treatment arms, and the authors concluded oral palonosetron was noninferior to IV palonosetron.
- One MC, DB, RCT evaluated dexamethasone compared to aprepitant in the prophylaxis of delayed CINV in patients with breast cancer who received chemotherapy containing anthracyclines and cyclophosphamide and the same antiemetic prophylaxis regimen. The primary endpoint was rate of complete response (ie, no vomiting or rescue treatment) from days 2 to 5 after chemotherapy. The results showed similar efficacy and toxicity between dexamethasone and aprepitant in the prevention of delayed emesis (*Roila et al 2014*).
- Aprepitant has been shown to be effective for the treatment of CINV as monotherapy and in combination with various 5-HT3 antagonists and/or dexamethasone (*Herrington et al 2008, Rapoport et al 2010, Yeo et al 2009, Herrstedt et al 2005, Warr et al 2005, Gralla et al 2005, De Wit et al 2004, Poli-Bigelli et al 2003, Hesketh et al 2003, Martin et al 2003, Gore et al 2009, Jordan et al 2009, Grunberg et al 2009*).
- Oral aprepitant- and IV fosaprepitant-based regimens were compared in a phase 3, randomized, DB trial for the prevention of CINV in patients treated with cisplatin-based chemotherapy *(Zhang et al 2020)*. The primary endpoint, complete response during the overall phase, was not significantly different between treatment arms, and the authors concluded the IV fosaprepitant-based regimen was noninferior to the oral aprepitant-based regimen.
- In combination regimens with granisetron and dexamethasone, rolapitant has been shown to be more effective than placebo for the prevention of CINV due to MEC and HEC in clinical trials (*Rapoport et al 2015, Schwartzberg et al 2015*). In combinations with 5-HT3 antagonists and dexamethasone, addition of rolapitant has also been shown to be more effective at preventing CINV over multiple cycles of MEC or HEC, when compared to similar combinations without rolapitant (*Rapoport et al 2016*).
- The fixed-dose combination palonosetron and netupitant + dexamethasone has been shown to be significantly superior to each agent administered individually for CINV prevention following MEC (*Aapro et al 2014*); however, results from another study for CINV prevention revealed similar efficacy between the fixed-dose combination and each agent administered individually with dexamethasone (*Gralla et al 2014*). In a small pilot study, palonosetron/netupitant was no better than placebo in treating chronic nausea in patients with cancer (*Hui et al 2021*).
- In a small study, *Meiri et al* reported that dronabinol and ondansetron were similarly effective for the management of delayed CINV, but combination therapy with these 2 agents was not more effective than either agent alone (*Meiri et al 2007*).
- Trimethobenzamide has limited data supporting its use in CINV *(Hurley and Eshelman 1980).*
- In a large MA (13 dronabinol studies and 16 nabilone studies), treatment with cannabinoids was more effective for complete control of nausea in the first 24 hours of chemotherapy compared to alizapride, chlorpromazine, domperidone, haloperidol, metoclopramide, prochlorperazine, or thiethylperazine (relative risk [RR], 1.38; 95% confidence interval [CI], 1.18 to 1.62; number needed to treat [NNT] = 6) and for complete control of vomiting (RR, 1.28; 95% CI, 1.08 to 1.51; NNT = 8). Of note, cannabinoids were not more effective compared to other agents when the chemotherapy regimen was of very high- or very low-emetogenic risk (*Tramèr et al 2001*).

- In a second MA, authors concluded that with regard to antiemetic efficacy, dronabinol was no more effective compared to placebo (RR, 0.47; 95% CI, 0.19 to 1.16; p = 0.1) but was more effective compared to neuroleptics (RR, 0.67; 95% CI, 0.47 to 0.96; NNT = 3.4). Nabilone was not more effective than neuroleptics (RR, 0.88; 95% CI, 0.72 to 1.08; p = 0.21). With regard to patient preference and tolerability, cannabinoids were preferred over other study agents (RR, 0.33; 95% CI, 0.24 to 0.44; p < 0.00001; NNT = 1.8) (*Machado Rocha et al 2008*).
- In a MA of 23 RCTs (11 dronabinol studies and 12 nabilone studies), compared to placebo, treatment with cannabinoids resulted in a higher chance of reporting complete absence of n/v (RR, 2.9; 95% CI, 1.8 to 4.7; 3 studies); however, patients were more likely to withdraw due to an adverse event compared to placebo (2 trials; RR, 6.9; 95% CI, 1.96 to 24) and compared to prochlorperazine (RR, 3.9; 95% CI, 1.3 to 12; 5 studies). The proportion of patients who reported absence of n/v was not different between cannabinoids and prochlorperazine (*Smith et al 2015*).

NVP

- In a MA on interventions for hyperemesis gravidarum, drowsiness, dizziness, and dystonia were experienced by more women treated with promethazine compared to metoclopramide in a single study. In another study, duration of hospital admission was not different between promethazine and ondansetron, but sedation was more common with promethazine *(Boelig et al 2016).*
- FDA-approvals of Diclegis and Bonjesta (doxylamine succinate/pyridoxine HCl) were based on 1 DB, randomized, multi-center, placebo-controlled study that evaluated the safety and efficacy of doxylamine succinate/pyridoxine HCl in pregnant adult women in the gestational age range of 7 to 14 weeks with n/v. Patients (N = 298) were randomized to 14 days of placebo or 2 tablets daily at bedtime and up to a maximum dose of 4 tablets of doxylamine succinate/pyridoxine HCl. Doxylamine succinate/pyridoxine hydrochloride treatment resulted in a statistically significant improvement in both the symptom and quality of life domains of the Pregnancy Unique-Quantification of Emesis (PUQE) score. There was a 4.8 point mean decrease from baseline in the symptom domain PUQE score at day 15 in the doxylamine succinate/pyridoxine HCl group compared to 3.9 point decrease in the placebo group (p = 0.006). For quality of life, there was also a 2.8 point mean increase from baseline in the score at day 15 in the Diclegis group compared to a 1.8 point decrease in the placebo group (p = 0.005) (*Koren et al 2010*).
  - A follow-up analysis of this trial was conducted in 2015 to evaluate the maternal safety of doxylamine/pyridoxine as compared to placebo. Based on the results of this analysis, doxylamine/pyridoxine was not associated with an overall increased in rate of adverse effects as compared to placebo (*Koren et al 2015*).

PONV

- A Cochrane network meta-analysis of drugs for PONV concluded with high certainty that aprepitant (RR, 0.26; 95% CI, 0.18 to 0.38), granisetron (RR, 0.45; 95% CI, 0.38 to 0.54), and ondansetron (RR, 0.55; 95% CI, 0.51 to 0.60) effectively reduce vomiting, and with moderate certainty that fosaprepitant (RR, 0.06; 95% CI, 0.51 to 0.60) and droperidol (RR, 0.61, 95% CI, 0.54 to 0.69) also effectively reduce vomiting. Monotherapy with NK1 receptor antagonists was found to be as effective as other drugs used in combination, but in general, combination therapy was more effective than monotherapy in preventing vomiting. There was a lack of certainty in safety analyses with the individual drugs that were found to be effective, although the authors concluded that droperidol probably reduces headache compared to placebo (RR, 0.76; 95% CI, 0.67 to 0.86) (*Weibel et al 2020*).
- In a MA, palonosetron was shown to be more effective for prevention of early and late postoperative nausea and late postoperative vomiting compared to ondansetron (*Xiong et al 2015*).
- A 2016 MA found that when compared to other 5-HT3 antagonists and NK1 antagonists, aprepitant reduces incidence of PONV, and need for rescue medications (*Singh et al 2016*).
- In prevention of PONV, amisulpride was studied in 2 randomized, DB, placebo-controlled trials *(Barhemsys prescribing information 2020, Gan et al 2017, Kranke et al 2018)*. In one study, patients received amisulpride monotherapy; in another, patients received amisulpride in combination with IV ondansetron, dexamethasone, or betamethasone. The primary endpoint, complete response within the first 24 postoperative hours, was significantly improved with amisulpride in both trials.
- In treatment of PONV, amisulpride was studied in 2 unpublished randomized, DB, placebo-controlled trials *(Barhemsys prescribing information 2020, Candiotti et al 2020, Habib et al 2020)*. In one study, patients received no PONV prophylaxis; in another, patients received and failed PONV prophylaxis with an antiemetic of another class. The primary

endpoint, complete response within the first 24 postoperative hours, was significantly improved with amisulpride in both trials.

RINV

- There are very few trials evaluating the prevention of RINV, and trials generally include patients with moderate to high risk RINV. The 5-HT3 receptor antagonists are the only agents in class which have demonstrated efficacy, and of these, only ondansetron and granisetron are FDA-approved.
- One DB, active-comparator trial compared oral ondansetron 8 mg to oral granisetron 2 mg in 34 bone marrow transplant patients receiving TBI, which is associated with high emetogenic risks. The study was only powered to demonstrate a difference between each active treatment groups and historical controls. In the intention-to-treat population, significantly more patients given granisetron (33.3%) or ondansetron (26.7%) had zero emetic episodes over 4 days, the primary efficacy end point, than those within the historical control group (0%) ($p < 0.01$) (*Spitzer et al 2000).*
- In a MA of 9 trials, fewer patients had residual emesis with 5-HT3 receptor antagonists compared with placebo (40% vs 57%; RR, 0.7; 95% CI, 0.57 to 0.86), and fewer required rescue medication (6.5% vs 36%; RR, 0.18; 95% CI, 0.05 to 0.60). Despite treatment, most patients did develop RT-induced nausea (70% vs 83%; RR 0.84; 95% CI, 0.73 to 0.96) (*Salvo et al 2012*).

Motion Sickness

- In a MA of 14 studies, scopolamine prevented symptoms of motion sickness more effectively than placebo (RR 0.48; 95% CI, 0.32 to 0.73), but conclusions could not be made regarding its efficacy compared to antihistamines and calcium channel blockers *(Spinks and Wasiak 2011).*

CLINICAL GUIDELINES

- The 5-HT3 receptor antagonists are considered part of the standard of care in the management of CINV due to chemotherapeutic agents with moderate-to-high emetic risk, RINV, and PONV. Treatment of CINV, RINV or PONV generally involves the use of multiple agents that affect different receptor types (*American Gastroentrological Association [AGA] 2001, Herrstedt et al 2017, Hesketh et al 2021, Gan et al 2020, Gupta et al 2016, NCCN 2021, Roila et al 2010).*
- The 2016 expert opinion statement from the American Society for Enhanced Recovery (ASER) for the prophylaxis and management of PONV provides the following recommendations (*Gupta et al 2016*):
  - All patients should receive PONV prophylaxis during the perioperative period.
  - The number of risk factors should determine the number of medications used for treatment and prophylaxis for PONV.
- The 2021 American Society of Clinical Oncology (ASCO) antiemetic guidelines recommend the following for CINV (*Hesketh et al 2021*):
  - For the prevention of n/v induced by HEC, a 4 drug combination of an NK1 receptor antagonist, a 5-HT3 receptor antagonist, dexamethasone, and olanzapine is recommended as first-line therapy.
  - For MEC, other than carboplatin area under the curve (AUC) ≥ 4 mg/mL/min, a 2-drug combination of a 5-HT3 receptor antagonist and dexamethasone is recommended.
  - For MEC that includes carboplatin AUC ≥ 4 mg/mL/min, a 3-drug combination of a NK1 receptor antagonist, a 5-HT3 receptor antagonist, and dexamethasone is recommended.
  - For children receiving HEC, a 3-drug combination of a 5-HT3 receptor antagonist, dexamethasone, and aprepitant or fosaprepitant is recommended. A 2-drug regimen of a 5-HT3 receptor antagonist and dexamethasone can be used if aprepitant or fosaprepitant cannot be given; palonosetron and aprepitant or fosaprepitant can be used if dexamethasone cannot be given.
  - For children receiving MEC, a 2-drug combination of a 5-HT3 receptor antagonist and dexamethasone. If dexamethasone cannot be used, a 2-drug combination of a 5-HT3 receptor antagonist and aprepitant or fosaprepitant is recommended.
  - Cannabinoids (eg, nabilone, dronabinol) are not listed as appropriate first-line antiemetics for any group of patients receiving chemotherapy of high to low emetic risk. These agents can be used in conjunction with standard regimens for patients who continue to have symptoms despite optimal prophylaxis (including use of olanzapine).
  - Dopamine receptor antagonists (eg, prochlorperazine, metoclopramide) are included as agents that may be added on to regimens for patients who experience n/v despite optimal prophylaxis.

- The 2021 National Comprehensive Cancer Network (NCCN) antiemesis guideline recommends the following regimens for prevention of CINV depending on emetic risk (order does not imply preference) *(NCCN 2021):*
  - For high emetic risk IV chemotherapy on day 1: 1) NK-1 receptor antagonist, 5-HT3 receptor antagonist, plus dexamethasone; 2) olanzapine, palonosetron, plus dexamethasone; 3) olanzapine, NK-1 receptor antagonist, 5-HT3 receptor antagonist, and dexamethasone. Additional agents depending on the regimen are used on days 2, 3, and 4.
  - For moderate emetic risk IV chemotherapy on day 1: 1) 5-HT3 receptor antagonist plus dexamethasone; 2) olanzapine, palonosetron, plus dexamethasone; 3) NK-1 receptor antagonist, 5-HT3 receptor antagonist, plus dexamethasone. Additional agents depending on the regimen are used on days 2 and 3.
  - For low emetic risk IV chemotherapy: dexamethasone, metoclopramide, prochlorperazine, or a 5-HT3 receptor antagonist started before chemotherapy and continued daily.
  - For high to moderate emetic risk oral chemotherapy: 5-HT3 receptor antagonist started before chemotherapy and continued daily.
  - For low to minimal emetic risk oral chemotherapy: metoclopramide, prochlorperazine, or a 5-HT3 receptor antagonist started before chemotherapy and continued daily.
  - For breakthrough treatment for CINV (add an agent for a different drug class to the current regimen): olanzapine, lorazepam, dronabinol or nabilone, haloperidol, metoclopramide, scopolamine, prochlorperazine or promethazine, 5-HT3 receptor antagonist, or dexamethasone.
- The NCCN guideline recommends granisetron ± dexamethasone or ondansetron ± dexamethasone for pretreatment for RINV in patients receiving radiation therapy (upper abdomen/localized site) or total body irradiation *(NCCN 2021).*
- The 2018 ACOG Practice Bulletin for NVP recommends the following algorithm (*ACOG 2018 [reaffirmed 2019]*):
  - First-line nonpharmacologic options: Change the prenatal vitamin to 1 that contains only folic acid, ginger capsules, and P6 acupressure with wrist bands.
  - If symptoms persist, escalate to first-line pharmacologic interventions: pyridoxine (vitamin B6) monotherapy or pyridoxine in combination with doxylamine in various doses.
  - If symptoms persist, oral dimenhydrinate, oral diphenhydramine, rectal prochlorperazine, or oral/rectal promethazine may be added.
  - If there is no dehydration and symptoms persist, oral/intramuscular (IM) metoclopramide, oral ondansetron, oral/rectal/IM promethazine, or IM trimethobenzamide may be added.
  - If there is dehydration, patients should receive IV fluid replacement. If symptoms persist, IV dimenhydrinate, IV metoclopramide, IV ondansetron, or IV promethazine may be added.
    - If symptoms continue to persist, IM/IV chlorpromazine or oral/IV methylprednisolone may be added.

SAFETY SUMMARY

- The 5-HT3 receptor antagonists and substance P/NK1 receptor antagonists are contraindicated with hypersensitivity, and overall these agents are generally well-tolerated. Ondansetron is also contraindicated with apomorphine.
- The 5-HT3 receptor antagonists are generally very well-tolerated. There is a warning and general precaution for dolasetron regarding the risk of arrhythmias. Ondansetron and granisetron have QTc prolongation as a general precaution. In addition, the development of serotonin syndrome has been reported with 5-HT3 receptor antagonists. Ondansetron and granisetron may mask progressive ileus or gastric distention following abdominal surgery or in patients with CINV.
- The D_2 antagonist amisulpride carries a warning for QT prolongation, and it should be avoided in patients with congenital long QT syndrome and patients taking droperidol. Electrocardiogram (ECG) monitoring is recommended in patients with pre-existing arrhythmia, electrolyte abnormalities, congestive heart failure, and patients taking other drugs or with other conditions that prolong the QT interval.
- Aprepitant and fosaprepitant are weak-to-moderate inhibitors of CYP3A4 and aprepitant is an inducer of CYP2C9. Netupitant is a substrate and moderate inhibitor of CYP3A4. Rolapitant inhibits CYP2D6; therefore, dose reductions may be warranted with these agents. Aprepitant, fosaprepitant, and rolapitant are contraindicated in patients taking CYP substrates of the respective enzymes that have a narrow therapeutic index, pimozide and thioridazine. Increased plasma concentrations may result in QT prolongation and torsades de pointes. Aprepitant has a warning regarding concurrent therapy with warfarin, a CYP2C9 substrate, and with hormonal contraceptives (during and for 28 days after stopping therapy) due to decreased exposure of the interacting medication.
- Fosaprepitant, aprepitant, and rolapitant can cause serious hypersensitivity reactions, including anaphylaxis and anaphylactic shock, during or soon after infusion. If hypersensitivity reactions occur, discontinue the infusion and

administer appropriate medical therapy. Do not reinitiate aprepitant or fosaprepitant, or rolapitant IV in patients who experience hypersensitivity symptoms with first-time use. Infusion site reactions have been reported with fosaprepitant IV; avoid infusion into small veins or through a butterfly catheter.

- Dronabinol and nabilone have the potential to be abused and produce psychological dependence. Both dronabinol and nabilone may produce alterations in mood and alterations in reality (distorted perceptions of objects and time and hallucinations).
- Dronabinol and nabilone are contraindicated in individuals who are allergic to cannabinoids. Syndros (dronabinol oral solution) is contraindicated in patients with hypersensitivity to alcohol and in patients who have received products containing disulfiram or metronidazole within 14 days. Syndros contains dehydrated alcohol (50%, w/w) and propylene glycol (5.5%, w/w). Disulfiram- and metronidazole-containing products should not be administered within 7 days of completing Syndros treatment.
- Consider risks and benefits of using dronabinol in patients with a history of seizures. Patients with cardiac disorders may experience cardiac effects such as hypotension, hypertension, syncope, or tachycardia with cannabinoids.
- Dronabinol and nabilone may exacerbate or unmask symptoms of mania, depression, or schizophrenia.
- Common adverse events with cannabinoids were dizziness, drowsiness, dry mouth, euphoria, and coordination disturbance.
- Syndros and Marinol both contain the same active ingredient, dronabinol, and the safety of Syndros oral solution was based on studies using dronabinol capsules. Additional warnings and precautions include:
  - Avoid dronabinol in patients with a psychiatric history or monitor patients for new or worsening psychiatric symptoms if use of dronabinol cannot be avoided.
  - Reduce the dose or discontinue if signs and symptoms of cognitive impairment occur.
  - Consider a dose reduction or discontinue in patients who develop worsening nausea, vomiting, or abdominal pain while taking dronabinol.
- Meclizine may cause drowsiness and should be used with caution in patients with asthma, glaucoma, or an enlarged prostate due to its anticholinergic effects. Headache, fatigue, and vomiting are other common adverse events.
- Promethazine has a boxed warning that it should not be used in patients < 2 years old because of the risk of fatal respiratory depression. It should be used with caution in pediatric patients 2 years and older. The injection has a boxed warning for severe tissue injury. Promethazine is also contraindicated in comatose states, hypersensitivity, or for treatment of lower respiratory tract symptoms including asthma. Promethazine injection should not be administered by intra-arterial injection or subcutaneously. Warnings related to promethazine include CNS depression, respiratory depression, lower seizure threshold, bone-marrow depression, and neuroleptic malignant syndrome (NMS).
- Prochlorperazine has a boxed warning regarding increased mortality in elderly patients with dementia-related psychosis who are treated with antipsychotic drugs. Contraindications include hypersensitivity, comatose states or in the presence of large amounts of CNS depressants, pediatric surgery, in pediatric patients < 2 years or weighing < 20 pounds, or for use in pediatric conditions that the dose has not been determined. Other warnings include tardive dyskinesia, NMS, and falls. Adverse events include drowsiness, dizziness, amenorrhea, blurred vision, skin reactions, and hypotension.
- Transdermal scopolamine is contraindicated in acute closure glaucoma and hypersensitivity. Warnings and precautions include acute angle closure glaucoma, neuropsychiatric adverse reactions, and eclamptic seizures in pregnant women. Scopolamine may cause reduced gastrointestinal motility, urinary retention, and also blurred vision if it comes into contact with eyes. Additionally, patients may experience withdrawal symptoms, and transdermal scopolamine should be removed prior to magnetic resonance imaging. The most common reactions for motion sickness include dry mouth, drowsiness, blurred vision, and pupil dilation, and for PONV include dry mouth, dizziness, somnolence, agitation, visual impairment, confusion, mydriasis, and pharyngitis.
- Trimethobenzamide is contraindicated in hypersensitivity. Warnings and precautions include acute dystonic reactions and other extrapyramidal symptoms, other CNS reactions (eg, coma, depression of mood, disorientation, and seizures), hepatotoxicity, and impairment of mental and/or physical activities. Other adverse events include blurred vision, diarrhea, disorientation, dizziness, drowsiness, headache, jaundice, and muscle cramps.
- Doxylamine/pyridoxine is contraindicated when used with monoamine oxidase inhibitors (MAOIs), as they intensify and prolong the adverse effects of the agent. The most common adverse effect observed with doxylamine/pyridoxine is somnolence. The warning section in the prescribing information states that activities requiring complete mental alertness, such as driving or operating heavy machinery, are not recommended (unless cleared to do so by a health care provider). Doxylamine/pyridoxine is also not recommended when using CNS depressants, such as alcohol. Doxylamine/pyridoxine has anticholinergic properties. It should be used with caution in women with asthma, increased

intraocular pressure, narrow angle glaucoma, stenosis peptic ulcer, pyloroduodenal obstruction, and urinary bladder-neck obstruction. Additionally, false positive urine screening tests for methadone, opiates, and phencyclidine have been reported with doxylamine/pyridoxine use.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
5-HT$_3$ Receptor Antagonists				
Dolasetron	Tablet	Oral	Take within 1 hour before chemotherapy.	Indicated in both pediatric (age 2 to 16 years based on adult PK data) and adults. ECG monitoring recommended in patients with renal impairment and the elderly.
Granisetron	Tablet, injection, injection ER, TD patch	Oral, IV, SC, TD	Take orally within 1 hour before chemotherapy or radiation, or twice daily (with the second dose given 12 hours after the first). Administer patch a minimum of 24 hours before chemotherapy (up to a maximum of 48 hours) and remove a minimum of 24 hours after chemotherapy completion Administer IV or SC within 30 minutes before chemotherapy or administer IV right before induction of anesthesia or immediately before reversal of anesthesia. Do not administer SC injection ER more frequently than once a week.	Injection approved for CINV in children 2 to 16 years. Tablet, injection ER, and TD patch have not studied in pediatrics. Do not use injection ER in severe renal impairment and adjust frequency in moderate renal impairment. Apply patch to upper outer arm. The patch may be worn for up to 7 days depending on the duration of the chemotherapy regimen.
Ondansetron	Tablet, oral solution, ODT, oral soluble film, IV solution, injection	Oral, lingual, IV, IM	Oral administrations vary: (1) Give within 30 minutes before HEC or; (2) given twice daily, with the first dose given 30 minutes before the start of emetogenic chemotherapy and a subsequent dose 8 hours later; then twice daily for 1 to 2 days after the completion of chemotherapy or; (3) give 1 to 2 hours before each fraction of radiotherapy administered each day or; (4) give 1 to 2 hours before radiotherapy, with subsequent doses every 8 hours after the first dose for 1 to 2 days after completion of radiotherapy or; (5) give 1 hour before	Do not exceed 8 mg daily in patients with severe hepatic impairment (Child-Pugh score ≥10). There is no experience beyond first-day administration in these patients. Depending on indication and formulation, drug may be administered in patients aged ≥ 1 month.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			induction of anesthesia or; (6) for pediatric patients, give 3 times daily with the first dose given 30 minutes before the start of emetogenic chemotherapy and subsequent doses 4 and 8 hours later; then 3 times daily (every 8 hours) for 1 to 2 days after completion of chemotherapy. IV administrations vary: (1) administer IV over 15 minutes beginning 30 minutes before chemotherapy and subsequent doses are given 4 and 8 hours after the first dose or; (2) administer IV over 2 to 5 minutes immediately before induction of anesthesia, or postoperatively if the patient did not receive prophylactic antiemetics and experiences nausea and/or vomiting within 2 hours after surgery or; (3) for pediatric patients administer IV over 2 to 5 min immediately prior to or following anesthesia induction, or postoperatively if the patient did not receive prophylactic antiemetics and experiences nausea and/or vomiting occurring shortly after surgery. Administer IM as a single dose.	
Palonosetron	IV solution	IV	IV administrations vary: (1) administer IV over 30 seconds, approximately 30 minutes before the start of chemotherapy or; (2) administer IV over 10 seconds immediately before the induction of anesthesia or; (3) for pediatric patients, administer IV over 15 minutes, beginning approximately 30 minutes before the start of chemotherapy	IV solution approved for prevention o CINV in pediatric patients aged ≥ 1 month.
D2 antagonist				
Amisulpride	IV solution	IV	Prevention of PONV: 5 mg as a single IV injection over 1 to 2 minutes at induction of anesthesia	Use for prevention of PONV may be as monotherapy or in combination with an antiemetic of a different class.

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			Treatment of PONV: 10 mg as a single IV injection over 1 to 2 minutes	Use for treatment of PONV may be in patients who received prophylaxis with an agent of a different class or who have not received prophylaxis. Avoid use in patients with severe renal impairment.
Substance P/NK$_1$ Receptor Antagonists				
Aprepitant	Capsule, combination pack, oral suspension, IV emulsion	Oral, IV	Take orally within 1 hour before chemotherapy and once daily for 2 additional days Administer IV over 2 minutes or 30 minutes completing the administration approximately 30 minutes before chemotherapy (for the 3-day regimen, continue capsules on day 2 and 3).	Given as part of a regimen that includes a corticosteroid and a 5-HT3 antagonist. Oral suspension approved for prevention of CINV in pediatric patients aged 6 months to < 12 years. Give with or without food. Use with caution in severe hepatic impairment.
Fosaprepitant	IV solution	IV	Adults: Administer IV over 20 to 30 minutes before chemotherapy. Administer IV over 30 minutes (12 to 17 years) or 60 minutes (6 months to <12 years) (for the 3-day regimen, continue capsules or oral suspension on days 2 and 3). Complete infusion approximately 30 minutes prior to chemotherapy	Given as part of a regimen that includes a corticosteroid and a 5-HT3 antagonist. Use with caution in severe hepatic impairment.
Rolapitant	Tablet	Oral	Administer orally within 2 hours prior to chemotherapy.	Given as part of a regimen that includes a corticosteroid and a 5-HT3 antagonist. Avoid use in severe hepatic impairment; if use cannot be avoided, monitor for adverse events. Contraindicated in children <2 years of age due to irreversible impaired reproductive development observed in animal studies
THC derivatives				
Dronabinol	Capsule, oral solution	Oral	Take orally 1 to 3 hours before chemotherapy and subsequent	If adverse effects occur and do not resolve in 1 to 3 days with

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			doses every 2 to 4 hours after chemotherapy for a total of 4 to 6 doses/day or; take orally twice daily, one hour prior to lunch and dinner.	continued use, consider dose reductions. In elderly, consider decreasing the initial dose to reduce risk of CNS adverse reactions. Always use calibrated oral dosing syringe for administration; if the prescribed dose is > 5 mg, it must be divided in multiple doses. Take with 6 to 8 ounces of water (oral solution).
Nabilone	Capsule	Oral	Take orally twice daily; initial dose is given 1 to 3 hours before chemotherapy and subsequent doses 2 to 3 times daily.	
Other single-agent products				
Meclizine	Chewable, immediate-release, and ODT	Oral	Take orally 1 hour before travel (may repeat every 24 hours as needed)	Start at the lowest dose for elderly patients due to anticholinergic effects
Promethazine	Tablet, oral syrup, rectal suppository, injectable solution	Oral Rectal IV/IM	Oral administration (motion sickness): Take orally 30 to 60 minutes before departure, then repeated in 8 to 12 hours as needed Oral and rectal administration (PONV): Take orally or rectally every 4 to 6 hours as needed IV and IM (PONV): Administer IV or IM every 4 to 6 hours as needed	Deep IM injection is the preferred parenteral route of administration
Prochlorperazine	Tablet, rectal suppository, injectable solution	Oral Rectal IV/IM	Oral administration: 3 to 4 times per day Rectal administration: Twice daily IV or IM administration: Administer 3 to 4 hours as needed; or administer 1 to 2 hours (IM) or 15 to 30 minutes (IV) before induction of anesthesia and repeat once if necessary	Lower doses are usually sufficient for elderly patients; increase doses gradually
Scopolamine	Transdermal	Trans-dermal	Motion sickness: Apply patch at least 4 hours before antiemetic effects are needed – for use up to	Apply to hairless area of the skin behind the ear

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
			3 days. If therapy for more than 3 days is required, remove the first transdermal system and apply a new one behind the other ear. PONV: Apply patch the evening before scheduled surgery; remove 24 hours after surgery.	
Trimethobenzamide	Capsule, IM solution	Oral IM	Oral: Take orally 3 to 4 times daily IM: Administer 3 to 4 times per day as needed	Reduce daily oral dose in elderly and patients with renal impairment
Combination products				
Palonosetron/ netupitant Palonosteron/ fosnetupitent	Capsule Powder for injection	Oral IV	Oral administration: Take orally within 1 hour before chemotherapy IV administration: Infuse over 30 minutes starting 30 minutes before chemotherapy.	Given as part of a regimen that includes a corticosteroid. Do not use in severe renal or hepatic impairment.
Doxylamine succinate/ pyridoxine HCl	Tablet ER, tablet DR	Oral	Take orally at bedtime. Titrate dose to twice daily (for the 20/20 mg tablet ER) or 3 times daily (for the 10/10 mg tablet DR).	Bonjesta is available in 20/20 mg tablets ER and Diclegis is available in 10/10 mg tablets DR. Should be taken on an empty stomach with a glass of water.

Abbrv: CINV = chemotherapy-induced nausea and vomiting, DR = delayed release, ECG = electrocardiogram, ER = extended release, HEC = highly emetogenic cancer chemotherapy, IM = intramuscular, IV = intravenous, ODT = orally disintegrating tablet, PONV = post-operative nausea and vomiting, PK = pharmacokinetic, SC = subcutaneously, TD = transdermal
See the current prescribing information for full details.

CONCLUSION

- Nausea and vomiting are significant problems, particularly in the treatment of cancer and following surgery. There are several classes of antiemetic drugs that may influence the neurotransmitter receptors involved in the pathway associated with n/v (*Longstreth et al 2021*)
- Choice of agents generally depends upon the relative emetogenic potential of the influencing agent, condition, or procedure, including chemotherapy or radiation therapy. Various formulations may be prescribed based on age of the patient, indication, and persistence of symptoms (*AGA 2001, ACOG 2018, Hesketh et al 2021, Longstreth et al 2021, Longstreth 2020, Roila et al 2010; NCCN 2021*).
- Guideline recommendations vary according to indication. The 2021 ASCO antiemetic guidelines recommend a 4-drug combination of a NK1 receptor antagonist, a 5-HT3 receptor antagonist, dexamethasone, and olanzapine as first-line therapy for the prevention of CINV due to HEC. For MEC, a 2-drug combination of a 5-HT3 receptor antagonist plus dexamethasone is recommended for regimens other than carboplatin area AUC ≥ 4 mg/mL/min or a 3-drug combination of a NK1 receptor antagonist, a 5-HT3 receptor antagonist, and dexamethasone for patients treated with a regimen that includes carboplatin AUC ≥ 4 mg/mL/min (*Hesketh et al 2021*). A 2016 expert opinion statement from ASER states that during the perioperative period, all patients should receive PONV prophylaxis (*Gupta et al 2016*). The clinical consensus guidelines for NVP from the ACOG recommend pyridoxine alone or in combination with doxylamine as first-line pharmacologic therapy (*ACOG 2018 [reaffirmed 2019]*).
- The 5-HT3 antagonists are the cornerstone of therapy for acute emesis with MEC to HEC agents in the management of CINV, in addition to RINV and PONV. These agents include dolasetron, granisetron, ondansetron, and palonosetron. Ondansetron is the most well studied medication; however, trials have not demonstrated a clear treatment leader

between dolasetron, granisetron, and ondansetron. Palonosetron has a longer half-life and a higher receptor binding affinity than the other 5-HT3 receptor antagonists. Single-dose therapy with palonosetron is reported to be more effective than other medications in the class, particularly at preventing delayed emesis. There are very few trials evaluating the prevention of RINV. The 5-HT3 receptor antagonists are the only agents in this class review with demonstrated efficacy and, of these, only ondansetron and granisetron are FDA-approved. Oral formulations appear to have comparable efficacy to IV formulations in CINV. The 5-HT3 receptor antagonists are generally well tolerated, with mild headache the most frequent adverse event. Cardiac abnormalities ranging from ECG interval changes to torsade de pointes or QTc prolongation have been reported with dolasetron, granisetron, and ondansetron. In addition, the development of serotonin syndrome has been reported with 5-HT3 receptor antagonists (*Aapro et al 2005, AGA, 2001, Billio et al 2010, Botrel et al 2011, Dong et al 2011, Eisenberg et al 2003, Gan et al 2020, Gralla et al 2003, Gupta et al 2016, Herrstedt et al 2017, Hesketh et al 2021, Kaushal et al 2010, Kovacs et al 2016, Likun et al 2011, Longstreth 2020, Roila et al 2010, Salvo et al 2012, Simino et al 2016, Spitzer et al 2000, Suzuki et al 2016*).
  - All 5-HT3 antagonist formulations are available generically with the exception of Anzemet (dolasetron) tablets, Sancuso (granisetron) transdermal patch, Sustol (granisetron) extended-release injection, and Zuplenz (ondansetron) oral soluble film.
- The substance P/NK1 receptor antagonists are prescribed for both acute and delayed CINV, which is an advantage over first-generation serotonin antagonists that are generally effective for acute emesis only. These include aprepitant, fosaprepitant, and rolapitant. The substance P/NK1 receptor antagonists are most effective when used in combination with other agents, typically a 5-HT3 antagonist, a glucocorticoid, ± olanzapine, for patients receiving HEC. One MA concluded that aprepitant reduces incidence of PONV and need for rescue medications compared to other 5-HT3 and NK1 antagonists. Aprepitant and fosaprepitant are moderate inhibitors of the CYP3A4 pathway and rolapitant inhibits CYP2D6; therefore, dose reductions may be warranted. Anaphylaxis, anaphylactic shock, and other serious hypersensitivity reactions have also been reported in patients receiving IV formulations, some requiring hospitalization (*AGA 2001, Gralla et al 2005, Grunberg et al 2011, Hesketh et al 2021, Herrington et al 2008, Herrstedt et al 2005, Longstreth 2020, Rapoport et al 2010, Roila et al 2010, Singh et al 2016, Warr et al 2005, Yeo et al 2009)*.
  - The only substance P/NK1 receptor antagonist formulations available generically are aprepitant capsules and combination pack.
- The THC derivatives, also referred to as the cannabinoids, have been prescribed for CINV and also have properties that may contribute to weight gain. The agents include nabilone and dronabinol. Dronabinol is also FDA-approved for anorexia associated with weight loss in adults with AIDS. In terms of CINV, these agents have a modest antiemetic activity and a relatively unfavorable adverse event profile. Side effects include vertigo, xerostomia, hypotension, and dysphoria, particularly in elderly patients. Trials have demonstrated that the cannabinoids are more effective compared to placebo and may be more effective than metoclopramide and prochlorperazine; however, no head-to-head trials have been conducted. The cannabinoids have little clinical utility. Due to the availability of other agents that are more effective and better tolerated, dronabinol and nabilone are recommended for later line therapy *(Hesketh et al 2021, Lane et al 1991, Longstreth 2020, Meiri et al 2007, Machado Rocha et al 2008, Tramer et al 2001)*.
  - Only Marinol (dronabinol) oral capsules are available generically.
- Amisulpride is approved for prevention and treatment of PONV. Supporting evidence includes randomized trials in each indication demonstrating superiority over placebo *(Barhemsys prescribing information 2020)*.
  - Amisulpride is not available generically.
- Combination products include Diclegis and Bonjesta (doxylamine succinate/pyridoxine) and Akynzeo (palonosetron/netupitant and palonosetron/fosnetupitant). Doxylamine succinate/pyridoxine is the only agent in this class FDA-approved for NVP and is guideline-recommended as a first-line pharmacologic therapy. Diclegis and Bonjesta vary by fixed dose strengths; however, each individual component is available over-the-counter (*ACOG 2018 [reaffirmed 2019]*). The fixed-dose combination Akynzeo (palonosetron/netupitant) with dexamethasone has been shown to be significantly superior to each agent administered individually for CINV prevention following MEC (*Aapro et al 2014*); however, results from another study for CINV prevention revealed similar efficacy between the fixed-dose combination and each agent administered individually with dexamethasone (*Gralla et al 2014*). Netupitant is also a moderate inhibitor of the CYP3A4 pathway and clinicians should be aware of potential drug interactions.
- Other agents used for n/v include meclizine, promethazine, prochlorperazine, scopolamine, and trimethobenzamide. Meclizine and scopolamine are generally used for motion sickness. Prochlorperazine may be used in low emetic risk chemotherapy while prochlorperazine, scopolamine, or promethazine may be used for breakthrough treatment *(NCCN 2021)*.

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Publication Date: April 2, 2021

Prior Authorization Guideline

Guideline Name Aduhelm (aducanumab-avwa)

1 . Indications

Drug Name: Aduhelm (aducanumab-avwa)
Alzheimer's Disease Indicated for the treatment of Alzheimer's disease. Treatment with Aduhelm should be initiated in patients with mild cognitive impairment or mild dementia stage of disease, the population in which treatment was initiated in clinical trials. There are no safety or effectiveness data on initiating treatment at earlier or later stages of the disease than were studied.

2 . Criteria

Product Name: Aduhelm	
Diagnosis	Alzheimer's Disease
Approval Length	6 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization, Non-Formulary

Approval Criteria

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

1.1 Based on the National Institute on Aging and the Alzheimer's Association (NIA-AA) criteria, one of the following:

- Diagnosis of mild cognitive impairment due to Alzheimer's disease
- Diagnosis of probable Alzheimer's disease dementia

AND

1.2 All of the following:

- Clinical Dementia Rating-Global (CDR-G) score of 0.5 or Clinical Dementia Rating Sum of Boxes (CDR-SB) score of 0.5-4
- Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score $\leq$ 85
- Mini-Mental State Examination score of 24-30

AND

2 - Documentation of beta-amyloid protein deposition, as evidenced by one of the following:

2.1 Positive amyloid positron emission tomography (PET) scan

OR

2.2 Both of the following:

- Attestation that the patient does not have access to amyloid PET scanning
- Cerebrospinal fluid (CSF) biomarker testing documents abnormalities suggestive of beta-amyloid accumulation (e.g., Aβ42 level, Aβ42:Aβ40 ratio)

AND

3 - Other differential diagnoses (e.g., dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), vascular dementia, pseudodementia due to mood disorder, vitamin B12 deficiency, encephalopathy, etc.) have been ruled out

AND

4 - All of the following:

- Patient is not currently taking an anticoagulant or antiplatelet agent (unless aspirin 325 mg/day or less)
- Patient has no history of transient ischemic attack (TIA) or stroke within previous year prior to initiating treatment
- Patient had no history of relevant brain hemorrhage, bleeding disorder, and cerebrovascular abnormalities in last 6 months

AND

5 - A baseline brain magnetic resonance imaging (MRI) has been completed within 12 months prior to initiating treatment to rule out other causes (e.g. stroke, small vessel disease, tumor)

AND

6 - Counseling has been provided on the risk of amyloid-related imaging abnormalities (ARIA-E and ARIA-H) and patient and/or caregiver are aware to monitor for headache, dizziness, visual disturbances, nausea, and vomiting

AND

7 - Prescribed by a neurologist, geriatrician, or geriatric psychiatrist, or other expert in the disease state

Product Name: Aduhelm	
Diagnosis	Alzheimer's Disease
Approval Length	6 month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization, Non-Formulary

Approval Criteria

1 - Submission of medical records (e.g., chart notes, laboratory values) documenting patient is benefitting from therapy as defined by both of the following:

1.1 Based on the National Institute on Aging and the Alzheimer's Association (NIA-AA) criteria, one of the following:

- Patient continues to have a diagnosis of mild cognitive impairment due to Alzheimer's disease
- Patient continues to have a diagnosis of probable Alzheimer's disease dementia

AND

1.2 All of the following:

- Clinical Dementia Rating-Global (CDR-G) score of 0.5 or Clinical Dementia Rating Sum of Boxes (CDR-SB) score of 0.5-4
- Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) score $\leq$ 85
- Mini-Mental State Examination score of 24-30

AND

2 - Follow-up brain magnetic resonance imaging (MRI) has been completed after the initiation of therapy to show one of the following:

2.1 Both of the following:

- Less than 10 new incident microhemorrhages
- 2 or less focal areas of superficial siderosis

OR

2.2 If 10 or more new incident microhemorrhages or greater than 2 focal areas of superficial siderosis are present then both of the following:

- Patient has been clinically evaluated for ARIA related signs or symptoms (e.g., dizziness, visual disturbances)
- Follow-up MRI demonstrates radiographic stabilization (i.e., no increase in size or number of ARIA-H)

AND

3 - Prescribed by a neurologist, geriatrician, or geriatric psychiatrist

3 . Definitions

Definition	Description
ARIA-E	Amyloid related imaging abnormality due to edema/effusion
ARIA-H	Amyloid related imaging abnormality due to micro hemorrhages and hemosiderin deposits

Nevada Medicaid

Top Ten Therapeutic Classes

Fee for Service

July 1, 2020 - June 30, 2021

Drug Name	Members	Claims	Total Days Supply	Total Quantity
ADUHELM	0	0	0	0

Therapeutic Class Overview
Alzheimer's Disease Agents

INTRODUCTION

- Alzheimer's disease (AD) is a progressive, degenerative neurological disease often presenting in later stages of life. In 2007, it was estimated that 5.1 million Americans are afflicted with AD, of which 4.9 million are aged ≥ 65 years. Before the age of 80 years, AD is more common in men and after the age of 80 years, the disease becomes more common in women (*Alzheimer's Association 2007, Letenneur et al 1999*).
- Patient presentation is diverse and includes a wide range of symptoms that manifest with cognitive and neuropsychiatric effects as a result of brain cell destruction. AD often begins with memory impairment that is followed, after several years, by a variety of other symptoms that affect motor function, planning and reasoning skills, and the ability to recognize objects and people (*American Psychiatric Association [APA] 2007, Bond et al 2012, Jones et al 2004, Wilcock et al 2003*).
- Patients often present with memory loss, aphasia, apraxia, agnosia, and loss of abstract planning skills.
  - Mild disease: Decline in ability to function at work or other usual activities, cognitive impairment, and poor judgment.
  - Moderate disease: Forgetfulness and poor understanding of safety risks that can lead to aimless wandering, mismanagement of finances, and household accidents like kitchen fires for which the individual may not understand how to manage.
  - Severe disease: Rely on others to carry out daily tasks involving grooming, feeding, and general self-care. (*APA 2007, Bond et al 2012, McKann et al 2011).*
- Various criteria have been developed in order to consistently and accurately diagnose AD, the most commonly used tools being the Mini Mental State Examination (MMSE), Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-V), Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), and the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) criteria.
- These clinical diagnostic tools often correlate with pathological diagnosis, which is the only absolute method of diagnosis and can only be completed with an autopsy after death. During this autopsy, the examiner looks for amyloid-beta (Aβ) plaques and neurofibrillary tangles in the cerebral cortex, which confirm the diagnosis of AD (*APA 2007, Bond et al 2012, McKann et al 2011*).
- Typical management of AD includes an acetylcholinesterase (AChE) inhibitor with or without a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist depending on the severity stage diagnosis. These therapies, along with psychosocial treatment methods, have been shown to be effective in managing patient symptoms with some evidence to support their effect on the behavioral symptoms of AD (*APA 2007, Bond et al 2012, Jones et al 2004*).
- The AChE inhibitors include donepezil, rivastigmine, and galantamine. Memantine is a NMDA receptor antagonist.
- AChE inhibitors increase cholinergic function by inhibiting hydrolysis of acetylcholine. NMDA receptor antagonists prevent excess stimulation by blocking glutamate from binding (*Micromedex 2018, Wilcock et al 2003*).
- In the past, Vitamin E, NSAIDs, and estrogen supplements have been recommended for treatment of AD. This is no longer recommended due to a lack of supportive evidence regarding their efficacy as well as potential safety concerns associated with vitamin E (*APA 2007*).
- Tacrine will not be discussed in this overview since it has been withdrawn from the market. Several drug characteristics, the major ones being reversible hepatic toxicity and four times daily administration, made tacrine undesirable compared to the newer AChE inhibitors (*Drugs@FDA 2018*).
- Medispan class: Cholinomimetics – ACHE Inhibitors; Antidementia Agent Combinations; N-Methyl-D-Aspartate (NMDA) Receptor Antagonists

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Aricept (donepezil)	✔
Exelon (rivastigmine)	✔
Namenda (memantine)	✔
Namenda XR (memantine)	✔
Namzaric (donepezil/memantine)	-
Razadyne (galantamine)	✔
Razadyne ER (galantamine)	✔

(*Drugs@FDA 2018, Clinical Pharmacology 2018*)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Aricept (donepezil)	Exelon (rivastigmine)	Namenda, Namenda XR (memantine)	Namzaric* (donepezil/ memantine)	Razadyne, Razadyne ER (galantamine)
Mild dementia of AD	✔	✔			✔
Moderate dementia of AD	✔	✔	✔	✔	✔
Severe dementia of AD	✔		✔	✔	
Mild to moderate dementia of PD		✔			

Abbreviations: XR = extended release; ER = extended release; AD = Alzheimer's disease, PD = Parkinson's disease
*Namzaric is indicated in patients with moderate to severe dementia of AD who are stabilized on certain doses of memantine and donepezil

(*Prescribing information: Aricept 2015, Exelon 2016, Namenda 2013, Namenda XR 2014, Namzaric 2014, Razadyne 2016, Razadyne ER 2016*)

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

CLINICAL EFFICACY SUMMARY

- The following section highlights key studies associated with the treatment of AD, but does not represent the comprehensive body of evidence available.

Aricept

- A double-blind (DB), randomized controlled trial (RCT) (N = 290) in patients with moderate to severe AD evaluated the use of donepezil 5 to 10 mg/day compared with placebo for 24 weeks and was measured using the Clinician's Interview-Based Impression of Change with caregiver input (CIBIC+) as the primary outcome measure. The CIBIC+ least square scores for donepezil were above baseline severity until week 24, while it declined for placebo. A total of 63% of patients in the donepezil group and 42% of patients in the placebo group improved or had no change ($p < 0.0001$). Donepezil was favored over placebo for secondary outcome measures of the standardized Mini-Mental State Examination (sMME), the Severe Impairment Battery (SIB), Disability Assessment for Dementia (DAD), modified Instrumental Activities of Daily Living (IADL+), and the modified Physical Self-Maintenance Scale (PSMS+). Donepezil demonstrated consistent benefit in cognition, global function, behavior, and activities of daily living (ADL) in both primary and secondary outcome measures. Patients who withdrew from treatment due to adverse events represented 8% in the donepezil group and 6% in the placebo group (*Feldman et al 2001*).

Exelon

- An international RCT (N = 725) in patients with mild to moderately severe AD in Europe and North America evaluated the efficacy and safety of higher dose rivastigmine (6 to 12 mg/day) and lower dose rivastigmine (1 to 4 mg/day) vs placebo for an ITT population over 26 weeks. The outcome measures were the ADAS-cog, CIBIC+, and the progressive deterioration scale. On the ADAS-cog, more patients in the higher dose rivastigmine group improved clinically compared with placebo (24 vs 16%, respectively; $p < 0.1$). On the CIBIC+, more patients in both rivastigmine groups received ratings of marked, moderate, or minimal improvement than placebo (37% in higher dose group [$p < 0.001$] and 30% in lower dose group [$p < 0.05$] vs 20% placebo). On the progressive deterioration scale, more patients in the higher dose rivastigmine group significantly improved compared to placebo (29 vs 19%, respectively; $p < 0.01$). Rivastigmine improved cognition, global functioning, and ADL compared with placebo. More patients in the higher dose rivastigmine group (23%) withdrew from treatment due to adverse events compared to the lower dose rivastigmine group (7%) and the placebo group (7%) (*Rosler et al 1999*).
- One DB, RCT (N = 1195) of patients with mild to moderate AD evaluated the safety and efficacy of oral rivastigmine 12 mg daily or 2 doses of transdermal rivastigmine (10 and 20 cm^2) vs placebo for 6 months. The primary efficacy measures were the ADAS-cog and the AD Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC). At week 24, 27.4% of patients in the 10 cm^2 group, 32.8% in the 20 cm^2 group, and 28.5% in the oral rivastigmine group had clinical improvement (4 point improvement in ADAS-Cog) compared with 19.9% in the placebo group ($p < 0.05$). The 20 cm^2 patch had a higher mean improvement on the ADAS-cog vs the 10 cm^2 patch. Both doses of the transdermal rivastigmine were superior to placebo (better cognition, attention, ADL, motor processing speed, and visual tracking) and were non-inferior to oral rivastigmine. The incidence of adverse events was not statistically significantly different between the 10 cm^2 patch (51%) and placebo (46%), but was higher in the 20 cm^2 patch group (66%) and oral capsules (63%) compared to placebo ($p \leq 0.001$ for both) (*Winblad et al 2007*).
- A systematic review of 13 RCTs evaluated the use in patients with mild to moderate AD treated for ≥ 12 weeks. Results demonstrated rivastigmine was beneficial for ADL (standardized mean difference [SMD], 0.20; 95% confidence interval [CI], 0.13 to 0.27; N = 3230; 6 studies); cognitive function on the ADAS-cog (mean difference [MD], -1.79; 95% CI, -2.21 to -1.37, N = 3232, 6 studies) and on the MMSE (MD, 0.74; 95% CI, 0.52 to 0.97; N = 3205; 6 studies), and the clinician's global assessment compared with placebo. No differences were found in behavioral changes and impact on caregivers. In addition, oral rivastigmine was associated with a higher risk of adverse events compared to rivastigmine transdermal patch (odds ratio [OR], 0.68; 95% CI, 0.58 to 0.80) (*Birks et al 2015*).

Namenda

- A pooled analysis of 2 RCTs (Phase 2 dose-finding study [N = 315] and Phase 3 study [N = 432]) in patients with moderate to severe dementia in Japan over 24 weeks found that memantine (10 to 20 mg/day) was superior to placebo based on the Clinician's Interview-based Impression of Change plus Japanese (CIBIC plus-J) assessment. The outcome measures were CIBIC plus-J, Severe Impairment Battery-Japanese version (SIB-J), and the Behavioral Pathology in AD Rating Scale (BEHAVE-AD). At weeks 4, 12, and 24, memantine had statistically significantly better outcomes than placebo on the SIB-J ($p < 0.0001$ for all timepoints). At week 24, memantine had statistically significantly less worsening than placebo on the CIBIC plus-J ($p = 0.047$). At week 24, memantine had statistically significant improvements than placebo on the BEHAVE-AD ($p = 0.0040$). Memantine was associated with less worsening of behavioral symptoms, language ability, language function, attention, visuospatial, and praxis compared with placebo (*Nakamura et al 2014*).
- One meta-analysis of 9 RCTs (N = 2433) in patients with AD for ≥ 24 weeks demonstrated that memantine monotherapy (10 to 20 mg/day) was effective in improving cognitive function, ADL, behavioral disturbances, global function assessment, and stage of dementia compared with placebo. Memantine significantly improved the primary outcome measures of cognitive function (SMD, -0.27; 95% CI, -0.39 to -0.14; $p = 0.0001$) and behavioral disturbances (SMD, -0.12; 95% CI, -0.22 to -0.01; $p = 0.03$). Memantine did not worsen symptoms of AD and potentially reduced agitation vs placebo (RR, 0.68; 95% CI, 0.49 to 0.94; $p = 0.02$) (*Matsunaga et al 2015*).
- One DB, RCT (N = 404) evaluated memantine 20 mg daily and placebo in patients with moderate to severe AD for 24 weeks who were established on stable treatment with donepezil. The primary outcome measures were the SIB and the modified 19-item Alzheimer's Disease Cooperative Study-Activities of Daily Living ($ADCS\text{-}ADL_{19}$). Memantine demonstrated a statistically significant benefit over placebo for the SIB ($p < 0.001$) and $ADCS\text{-}ADL_{19}$ ($p = 0.03$) scales. Memantine had better outcomes in clinical global status, cognition, ADL, and behavior compared with placebo. A total of 12.4% of patients in the placebo group and 7.4% of patients in the memantine group withdrew treatment due to adverse events (*Tariot et al 2004*).

- In another RCT (N = 252) conducted over 28 weeks, patients with moderate to severe AD demonstrated superior outcomes for memantine 20 mg/day vs placebo in CIBIC+, SIB, and the Alzheimer's Disease Cooperative Study Activities of Daily Living modified for more severe dementia (ADCS-ADLsev). There was a high withdrawal rate (28.2%) noted within the trial; therefore, caution should be exercised with applying results. The primary outcome measures were CIBIC+ (MD, 0.3; p = 0.06) and ADCD-ADLsev (MD, 2.1; p = 0.02). The secondary outcome measures were SIB and other measures of cognition, function, and behavior. Patients treated with memantine had less deterioration and less time spent with caregivers. The proportion of patients who discontinued treatment due to adverse events were 17% within the placebo group and 10% within the memantine group (*Reisberg et al 2003*).

Namzaric

- One DB, RCT (N = 677) of patients with moderate to severe AD evaluated the use of memantine extended-release (ER) 28 mg vs placebo over 24 weeks. Patients were concomitantly administered cholinesterase inhibitors with 69% of patients co-administered donepezil. Of note, the donepezil plus memantine is the only combination treatment FDA-approved. For the primary outcome measures, combination treatment with memantine ER plus cholinesterase inhibitor was significantly better in CIBIC+ (p = 0.008), SIB (least square MD, 2.6; 95% CI, 1.0 to 4.2; p = 0.001), Neuropsychiatric Inventory (NPI, p = 0.005), and the Verbal Fluency Test (VFT, p = 0.004) vs placebo plus a cholinesterase inhibitor. No significant differences were found on the ADCS-ADL_{19} (p = 0.177). Approximately, 6% of patients in the placebo group and 10% of patients in the memantine ER group discontinued treatment because of adverse events. The populations that included memantine plus galantamine or rivastigmine were too small to draw any firm conclusions for treatment (*Grossberg et al 2013*). Evidence was consistent with other studies (*Boinpally et al 2015*).
- The DOMINO-AD study was a DB, placebo-controlled (PC), RCT (N = 295) in patients with moderate to severe AD treated with donepezil for at least 3 months. Patients were divided into 4 treatment groups: continuation of donepezil, discontinuation of donepezil, discontinuation of donepezil and initiation of memantine, or continuation of donepezil and initiation of memantine (using the sMMSE and the Bristol Activities of Daily Living Scale [BADLS]). The primary outcome measures were the sMMSE (with higher scores translating to better cognitive function) and BADLS (with higher scores translating to greater impairment). The continuation of donepezil group scored higher on the sMMSE by 1.9 points (95% CI, 1.3 to 2.5; p < 0.001) and lower on the BADLS by 3.0 points (95% CI, 1.8 to 4.3, p < 0.001) compared with the discontinuation of donepezil group. The continuation of memantine group scored higher on the sMMSE by 1.2 points (95% CI, 0.6 to 1.8, p < 0.001) and lower on the BADLS by 1.5 points (95% CI, 0.3 to 2.8, p = 0.02) compared with the discontinuation of memantine group. The combination of donepezil and memantine showed no significant benefit vs donepezil alone (*Howard et al 2012*).

Razadyne

- One DB, RCT (N = 653) evaluated use in patients with mild to moderate AD over the period of 6 months. Results demonstrated that galantamine had improvements in ADL, cognition, global function, and daily function compared to placebo. The primary outcome measures were the CIBIC+ and the ADAS-cog. Galantamine (at lower [24 mg] and higher [32 mg] doses) demonstrated better outcomes for CIBIC+ compared to placebo (p < 0.05). On the ADAS-cog, patients on galantamine had significantly better cognition than patients on placebo at 6 months (lower dose, 3.1; 95% CI, 1.7 to 4.5; p < 0.001 and higher dose, 4.1; 95% CI, 2.7 to 5.6; p < 0.001). Galantamine patients reported more (incidence ≥ 5% vs placebo) nausea, vomiting, diarrhea, dizziness, headache, anorexia, and weight loss. There were a total of 18% of patients on galantamine and 9% of patients on placebo who discontinued treatment due to adverse events (*Wilcock et al 2000*).
- One open label (OL) extension trial of 2 DB and OL studies (N = 491) evaluated the safety and efficacy of galantamine 24 mg in patients with mild to moderate AD for a total treatment period of 24 months (with exposures up to 36 months). Cognitive deterioration occurred slowly in patients treated with galantamine according to the Alzheimer's disease Assessment Scale-cognitive subscale (ADAS-cog), which was a co-primary outcome measure. On the ADAS-cog, 48.8% of patients on galantamine had ≤ 10 point increase, 15.3% maintained cognitive function at or above baseline, and majority of patients on galantamine had ≤ 20 point increase. For the additional co-primary endpoint, total DAD scores decreased significantly throughout the study (p < 0.002 at initial visit and p < 0.001 from baseline). The most common treatment emergent adverse events were agitation (16.1%), insomnia (12.4%), fall (11.2%), and urinary tract infection (10.2%) (*Pirttila et al 2004*).
- The SERAD study was a DB, PC, RCT (N = 407) in patients with severe AD treated with galantamine 24 mg vs placebo for 6 months. The primary outcome measures were the SIB and the minimum data set-activities of daily living (MDS-ADL). Patients who were treated with galantamine improved in the SIB score by week 26 (increased by 1.9 points),

while patients who were treated with placebo declined in the SIB score (decreased by 3.0 points) (least squares mean difference, 4.36; 95% CI, 1.3 to 7.5; p = 0.006). Both treatment groups declined in the MDS-ADL self-performance score at week 26 from baseline with 1.2 points in the galantamine group and 1.6 points in the placebo group; however, differences were not statistically significant (least squares mean difference, -0.41; 95% CI, -1.3 to 0.5; p = 0.38). Galantamine improved SIB domains of memory (p = 0.006), praxis (p = 0.01), and visuospatial ability (p = 0.002) compared with placebo. A total of 88% of patients in the galantamine group and 89% in the placebo group experienced at least 1 adverse event (*Burns at el 2009*).

- One PC, RCT (for 4 months) and OL extension (for an additional 4 months) in patients (N = 130) with mild to moderate AD evaluated galantamine 16 to 24 mg compared to placebo. Galantamine significantly improved the primary outcome measure of the Goal Attainment Scaling (GAS) on the clinician-rate GAS score vs placebo after 4 months (absolute difference, 4.0; p = 0.02; standardized response mean [SRM] = 0.41), but not on the patient-caregiver-rated GAS score (absolute difference between groups, 1.9; p = 0.27; SRM = 0.20). There were significant differences on the ADAS-cog scores and the CIBIC+ that favored galantamine. The most frequently reported adverse events (incidence > 10% vs placebo) were nausea and vomiting (*Rockwood et al 2009*).

Comparative Effectiveness Reviews

- One meta-analysis of 16 RCTs (5169 received AChE inhibitors [donepezil, galantine, and rivastigmine] and 2795 received a placebo) in patients with mild to moderate AD found that AChE inhibitors were effective compared with placebo in AD. AChE inhibitors demonstrated significantly better global improvement response than placebo for minimal improvement or better, marked improvement, and stabilization or better. However, AChE inhibitors also had significantly more adverse events compared with placebo (8%; 95% CI, 5 to 11%). The proportion of patients administered AChE inhibitors who dropped out due to adverse events were 7% (95% CI, 3 to 10%) (*Lanctot et al 2003*).
- One head-to-head RCT (N = 994) evaluated the efficacy, safety, and tolerability of donepezil 5 to 10 mg vs rivastigmine 3 to 12 mg in patients with moderate to moderately severe AD over a 2 year period. For the primary outcome of SIB, results were similar. A total of 34.8% of patients administered donepezil and 36.5% of patients administered rivastigmine had SIB scores equal or better than baseline at 26 months. However, it was not statistically significant. At 104 weeks, rivastigmine demonstrated better efficacy in ADL than donepezil on the ADCS-ADL (24.7 vs 19.4%, p = 0.047) as well as better efficacy in global deterioration than donepezil on the global deterioration scale (GDS; 53.1% vs 45.3%, p = 0.016). Only 57.9% of patients completed the study, mainly due to adverse events (gastrointestinal-related) with more patients in the rivastigmine group experiencing adverse events during the titration Phase. (*Bullock et al 2005*).
- One systemic review evaluated the cognitive decline and the benefits of inventions for clinical Alzheimer's type dementia across 10 studies. Based on results, AChE inhibitors may not reduce the incidence of clinical Alzheimer's type dementia or provide a significant effect on cognitive performance in patients with mild cognitive impairment; however, evidence was of lower quality. A study of patients with normal cognition (N = 28) demonstrated insufficient evidence and no cognitive benefits compared with placebo over 26 weeks. The study of patients with mild cognitive impairment (N = 769) demonstrated low-strength evidence in delaying progression of dementia over 18 months to 2 years and demonstrated no benefit at 3 years compared with placebo (*Kane et al 2017*).

CLINICAL GUIDELINES

Overall

- Several guidelines outline the goals for AD therapy are to delay the progression of symptoms and to preserve functional ability. In general, guidelines do not prefer one agent over another. The choice of treatment is based on tolerability, adverse events and ease of use (*APA 2007, Bond et al 2012, Bullock et al 2005, Hogan et al 2004, Hort et al 2010, Jones et al 2004, Rabins et al 2014, Wilcock et al 2003, Wilkinson et al 2002*).
- All AChE inhibitors are FDA-approved for mild and moderate disease. Donepezil is the only AChE inhibitor that is also approved for severe disease. Memantine is the only NMDA antagonist approved for use in AD and is only indicated for patient with moderate or severe disease. These treatments all show evidence of slowing cognitive decline and improving global outcome, behavior, and activities of daily living (ADL). There is no sufficient evidence to support the use of any medications for the primary prevention of AD (*APA 2007, Bond et al 2012, Hort et al 2010*).
- Medication(s) should be chosen based on the severity of the disease since FDA approval is dependent on disease severity. Guidelines recommend starting patients on one of the approved AChE inhibitors (donepezil, rivastigmine, and galantamine). If symptoms have not improved and the patient has moderate or severe disease, it is recommended to add memantine as adjunct therapy (*APA 2007*). This is due to multiple studies showing that use of an AChE inhibitor in

combination with memantine yields better outcomes than an AChE inhibitor alone (*Bond et al 2012, Bullock et al 2005, Hogan et al 2004, Jones et al 2004, Wilcock et al 2003, Wilkinson et al 2002*).
- AChE inhibitors all show similar efficacy rates with differing tolerability, but none have been shown to be superior (*Bond et al 2012, Bullock et al 2005, Hogan et al 2004, Jones et al 2004, Wilcock et al 2003, Wilkinson et al 2002*).

American Psychiatric Association (APA)
- The American Psychiatric Association (APA) guidelines for AD recommend initiating non-pharmacological management (i.e., occupational therapy, physiotherapy, mental stimulation, social services, speech and language therapy, aromatherapy, education) approaches before prescribing medication due to the modest benefit and varying levels of support for these pharmaceutical treatments. Upon failure of non-pharmacologic treatments, medication should be initiated, but it is recommended that doctors discuss the medication risks and benefits before initiating treatment (*APA 2007, Hort et al 2010*).
  - There is evidence of modest improvement in some patients treated with AChE inhibitors and therapy is appropriate in patients with mild or moderate AD for whom the medication is not contraindicated. Evidence suggests similar efficacy among agents; however, they may differ in tolerability.
  - Memantine should be considered in patients with moderate to severe AD. There is modest evidence that the combination of memantine and donepezil is better than donepezil alone, but there is no evidence that this combination is better than memantine monotherapy.
  - Due to reduced clearance in elderly individuals, medication should be started at low doses and slowly titrated until a reduction in symptoms is seen. This is done to minimize the occurrence of adverse reactions which tend to be mild and predominantly affect the gastrointestinal system but also include confusion, orthostatic hypotension, sedation, and more (*APA 2007*).
  - The APA guidelines discourage the use of NSAIDs, Vitamin E, *Ginko biloba*, and estrogen supplements for the management of AD. No evidence has demonstrated an effect on cognitive decline and some have been shown to be detrimental to cognition and can cause extraneous adverse effects (*APA 2007, Hort et al 2010, Rabins et al 2014*).
- An 2014 update to the APA guidelines stipulate that AD evidence remains modest for certain medications (eg, cholinesterase inhibitors and memantine):
  - No clinically meaningful advantages have been observed with higher doses of donepezil; however, higher doses of the rivastigmine patch may produce efficacy advantages. There is no evidence to support the use for cognitive symptomatic treatment or prevention *(Rabins et al 2014*).
  - New trials for memantine in mild to moderate AD demonstrated no benefit.
  - Caution should be exercised when considering mood stabilizing medications for comorbid conditions due to lack of evidence except for atypical antipsychotics. Upon implementation, these mood stabilizers should be reduced when symptoms have been controlled for 4 to 6 months to assess the need for continued use (*APA 2007, Rabins et al 2014*).

European Federation of Neurological Societies (EFNS)
- The EFNS guidelines are in agreement with the 2007 APA guidelines. Other recommendations include:
  - Recommend AChE inhibitors (donepezil, galantamine, or rivastigmine) be considered at the time of diagnosis for mild to severe disease. Memantine should be considered in patients with moderate to severe AD.
  - Where possible, initial treatment should be non-pharmacological.
  - Evidence does not support the use for any medications for the primary prevention of dementia. Cholinesterase inhibitors, vitamin E, gingko and estrogens should not be used as treatments for those with mild cognitive impairment.
  - Memantine may provide benefits for some non-cognitive symptoms (ie, agitation and delusions) *(Hort et al 2010*).

SAFETY SUMMARY

- Contraindications
  - Patients who have a history of application site reaction with rivastigmine transdermal patch is suggestive of allergic contact dermatitis.

- Warnings/Precautions
  - Namenda, Namenda XR, Namzaric: Increased plasma levels of memantine and decreased urinary elimination of memantine may result if patients have conditions that raise urine pH
  - Razadyne, Razadyne ER: Serious skin reactions (i.e., Stevens-Johnson syndrome) have been reported; patient should discontinue at the first appearance of a skin rash
  - Exelon: May worsen driving or use of machinery in addition to the patient's dementia
  - Cholinesterase inhibitors (donepezil, rivastigmine, galantamine):
    - May exaggerate the neuromuscular blocking effects of succinylcholine-type muscle relaxation during anesthesia
    - May have vagotonic effects on the sinoatrial and atrioventricular nodes, causing heart block or bradycardia in patients with or without underlying cardiac conduction abnormalities
    - May increase gastric acid secretion due to increased cholinergic activity, causing gastrointestinal bleeding or peptic ulcer disease in patients with underlying conditions or on nonsteroidal anti-inflammatory drugs (NSAIDs)
    - May have the potential to cause generalized convulsions, but it may also be a manifestation of Alzheimer's disease
    - Should be prescribed with care to patients with a history of asthma or chronic obstructive pulmonary disease

- The most common adverse events associated with each agent are:
  - Aricept: Nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, anorexia
  - Exelon: Nausea, vomiting, anorexia, dyspepsia, asthenia
  - Exelon patch: Nausea, vomiting, diarrhea
  - Namenda: Dizziness, headache, confusion, constipation
  - Namenda XR: Headache, diarrhea, dizziness
  - Razadyne, Razadyne ER: Nausea, vomiting, diarrhea, dizziness, headache, decreased appetite

- Key Drug Interactions
  - Cholinesterase inhibitors can interfere with the activity of anticholinergic medications
  - Cholinesterase inhibitors have a synergistic effect when given with succinylcholine, cholinergic agonists (ie, bethanechol), other neuromuscular blocking agents, or other cholinesterase inhibitors
  - Exelon and metoclopramide: Increased risk of extrapyramidal adverse effects
  - Exelon and beta blockers: May cause additive bradycardic effects leading to syncope
  - Namenda/Namenda XR and other NMDA antagonists: Approach with caution since it has not been systemically evaluated

- Other safety comments
  - Aricept, Razadyne, Razadyne ER: Pregnancy category C
  - Exelon, Namenda, Namenda XR: Pregnancy category B

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Aricept (donepezil)	Tablet, oral disintegrating tablet	Oral	Once daily in the evening	May be taken with or without food.
Exelon (rivastigmine)	Capsule, TD patch	Oral, TD	Capsule: Twice daily TD patch: Once in a 24 hour period	Capsule: Patients with moderate and severe renal impairment as well as mild and moderate hepatic impairment may only tolerate lower doses. TD patch: Consider dose adjustments in patients with mild to moderate hepatic impairment.
Namenda, Namenda XR (memantine)	Tablet, solution, capsule ER, titration pack	Oral	Once daily	May be taken with or without food. Capsule ER: May be taken whole, or sprinkled on applesauce. Lower doses are recommended in patients with severe renal impairment (CrCL 5 to 29 mL/min). Use with caution in patients with severe hepatic impairment.
Namzaric (donepezil/ memantine)	Capsule ER, therapy pack	Oral	Once daily in the evening	May be taken with or without food, whole, or sprinkled on applesauce.
Razadyne, Razadyne ER (galantamine)	Tablet, capsule ER	Oral	Tablet: Twice daily, Capsule ER: Once daily	Should not exceed 16 mg/day for moderate hepatic impairment (Child Pugh score of 7 to 9) or in patients with CrCL of 9 to 59 mL/min. Do not use for severe hepatic impairment (Child Pugh score of 10 to 15) or in patients with CrCL of < 9 mL/min.

Abbreviations: CrCL = creatinine clearance, ER = extended release, TD = transdermal
See the current prescribing information for full details

CONCLUSION

- AD is a progressive, degenerative neurological disease often presenting in later stages of life. Patients often present with memory loss, aphasia, apraxia, agnosia, and loss of abstract planning skills.
- Non-pharmacological approaches should be initiated before prescribing medication due to the modest benefit and varying levels of support for these pharmaceutical treatments. Upon failure of non-pharmacologic treatments, medication should be initiated, but it is recommended that doctors discuss the medication risks and benefits before initiating treatment.
- Management of AD includes an AChE inhibitor with or without a noncompetitive NMDA receptor antagonist depending on the severity stage diagnosis (mild, moderate, or severe), along with psychosocial treatment methods, have been

shown to be effective in managing patient symptoms with some evidence to support their effect on the behavioral symptoms of AD.

- Common adverse effects for the class include nausea, vomiting, and diarrhea.
- All AChE inhibitors are FDA-approved for mild and moderate disease. Donepezil is the only AChE inhibitor that is also approved for severe disease. Memantine is the only NMDA antagonist approved for use in AD and is only indicated for patient with moderate or severe disease. Evidence has demonstrated that memantine may be combined with a cholinesterase inhibitor. AChE inhibitors all show similar efficacy rates with differing tolerability, but none have been shown to be superior.
- Clinical trials evaluating the efficacy and safety of AD agents include over 40 measurement tools, which measure outcomes related to global function, cognition, behavior, and quality of life. Indirect comparisons between treatments are difficult as there are methodologic limitations including inconsistent results, different tools of measure, inadequately described follow up, and sometimes high dropout rates. None-the-less, current clinical trials, systematic reviews, and meta-analyses support the efficacy of these medications for their FDA-approved indications and have shown to be superior to placebo. There is limited evidence available head-to-head.
- Rivastigmine is available as a transdermal patch and may have less side effects than oral rivastigmine. There may be efficacy advantages with administering higher doses of the rivastigmine patch. Rivastigmine is the only agent in class which has an indication for the symptoms of dementia in PD (*Birks et al 2015, Rabins et al 2014*).
- Several guidelines outline the goals for AD therapy are to delay the progression of symptoms and to preserve functional ability. In general, guidelines do not prefer one agent over another. The choice of treatment is based on tolerability, adverse events and ease of use (*APA 2007, Bond et al 2012, Bullock et al 2005, Hogan et al 2004, Hort et al 2010*, *Jones et al 2004, Rabins et al 2014, Wilcock et al 2003, Wilkinson et al 2002*).
- AD treatments demonstrate evidence of slowing cognitive decline and improving global outcome, behavior, and ADL; however, improvements are modest. Other limitations include inconsistent evidence from large, well-designed trials and in many cases well-designed trials are generally conducted under a duration of 1 year. There is no sufficient evidence to support the use of any medications for the primary prevention of AD.

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Publication Date: May 7, 2018

Prior Authorization Guideline

Guideline Name CGRP Products

1 . Criteria

Product Name: Ajovy, Emgality	
Diagnosis	Episodic Migraine
Approval Length	6 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - The recipient is 18 years of age or older

AND

2 - The recipient has a documented diagnosis of episodic migraines, having 4-14 migraine days per month, but not more than 14 headache days per month

AND

3 - The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist

AND

4 - The recipient must meet TWO of the following:

4.1 One of the following:

- The recipient has a documented history of failure (after at least a two-month trial) or intolerance to Elavil (amitriptyline) or Effexor (venlafaxine)
- The recipient has a contraindication to both Elavil (amitriptyline) and Effexor (venlafaxine)

OR

4.2 One of the following:

- The recipient has documented history of failure (after at least a two-month trial) or intolerance to Depakote/Depakote ER (divalproex) or Topamax (topiramate)
- The recipient has a contraindication to both Depakote/Depakote ER (divalproex) and Topamax (topiramate)

OR

4.3 One of the following:

- The recipient has a history of failure (after at least a two month trial) or intolerance to one of the following beta blockers: atenolol, propranolol, nadolol, timolol or metoprolol
- The recipient has a contraindication to all of the following beta blockers: atenolol, propranolol, nadolol, timolol and metoprolol

Product Name: Nurtec ODT	
Diagnosis	Episodic Migraine
Approval Length	6 Months
Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - The recipient is 18 years of age or older

AND

2 - The recipient has a documented diagnosis of episodic migraines, having 4-18 migraine days per month, but not more than 18 headache days per month

AND

3 - The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist

AND

4 - Two of the following

4.1 One of the following:
- The recipient has a documented history of failure (after at least a two-month trial) or intolerance to Elavil (amitriptyline) or Effexor (venlafaxine)
- The recipient has a contraindication to both Elavil (amitriptyline) and Effexor (venlafaxine)

OR

4.2 One of the following:
- The recipient has documented history of failure (after at least a two-month trial) or intolerance to Depakote/Depakote ER (divalproex) or Topamax (topiramate)
- The recipient has a contraindication to both Depakote/Depakote ER (divalproex) and Topamax (topiramate)

OR

4.3 One of the following:
- The recipient has a history of failure (after at least a two month trial) or intolerance to one of the following beta blockers: atenolol, propranolol, nadolol, timolol or metoprolol
- The recipient has a contraindication to all of the following beta blockers: atenolol, propranolol, nadolol, timolol and metoprolol

AND

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

Product Name: Aimovig	
Diagnosis	Episodic Migraine
Approval Length	6 month(s)

Therapy Stage	Initial Authorization
Guideline Type	Prior Authorization

Approval Criteria

1 - The recipient is 18 years of age or older

AND

2 - The recipient has a documented diagnosis of episodic migraines, having 4-14 migraine days per month, but not more than 14 headache days per month

AND

3 - The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist

AND

4 - The recipient must meet TWO of the following:

4.1 One of the following:

- The recipient has a documented history of failure (after at least a two-month trial) or intolerance to Elavil (amitriptyline) or Effexor (venlafaxine)
- The recipient has a contraindication to both Elavil (amitriptyline) and Effexor (venlafaxine)

OR

4.2 One of the following:

- The recipient has documented history of failure (after at least a two-month trial) or intolerance to Depakote/Depakote ER (divalproex) or Topamax (topiramate)
- The recipient has a contraindication to both Depakote/Depakote ER (divalproex) and Topamax (topiramate)

OR

4.3 One of the following:

- The recipient has a history of failure (after at least a two month trial) or intolerance to one of the following beta blockers: atenolol, propranolol, nadolol, timolol or metoprolol
- The recipient has a contraindication to all of the following beta blockers: atenolol, propranolol, nadolol, timolol and metoprolol

AND

5 - One of the following:

5.1 Patient has experienced therapeutic failure of two preferred medications within the same drug class

OR

5.2 Patient has an allergy, contraindication, drug-to-drug interaction, or a history of unacceptable/toxic side effects with ALL preferred medications within the same drug class

OR

5.3 Non-preferred medication is being requested because it is being used for a unique indication that is supported by peer-reviewed literature or an FDA-approved indication

Product Name: Aimovig, Ajovy, Emgality, Nurtec ODT	
Diagnosis	Episodic Migraine
Approval Length	12 month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

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 medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist

Product Name: Ajovy, Emgality	
Diagnosis	Chronic Migraine
Approval Length	6 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior 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 eight must be migraine days for at least three months

AND

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

AND

5 - The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist

AND

6 - The recipient must meet TWO of the following:

6.1 One of the following:

- The recipient has a documented history of failure (after at least a two-month trial) or intolerance to Elavil (amitriptyline) or Effexor (venlafaxine)
- The recipient has a contraindication to both Elavil (amitriptyline) and Effexor (venlafaxine)

OR

6.2 One of the following:

- The recipient has documented history of failure (after at least a two-month trial) or intolerance to Depakote/Depakote ER (divalproex) or Topamax (topiramate)
- The recipient has a contraindication to both Depakote/Depakote ER (divalproex) and Topamax (topiramate)

OR

6.3 One of the following:

- The recipient has a history of failure (after at least a two month trial) or intolerance to one of the following beta blockers: atenolol, propranolol, nadolol, timolol or metoprolol

- The recipient has a contraindication to all of the following beta blockers: atenolol, propranolol, nadolol, timolol and metoprolol

Product Name: Aimovig	
Diagnosis	Chronic Migraine
Approval Length	6 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior 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 eight must be migraine days for at least three months

AND

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

AND

5 - The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist

AND

6 - The recipient must meet TWO of the following:

6.1 One of the following:

- The recipient has a documented history of failure (after at least a two-month trial) or intolerance to Elavil (amitriptyline) or Effexor (venlafaxine)
- The recipient has a contraindication to both Elavil (amitriptyline) and Effexor (venlafaxine)

OR

6.2 One of the following:

- The recipient has documented history of failure (after at least a two-month trial) or intolerance to Depakote/Depakote ER (divalproex) or Topamax (topiramate)
- The recipient has a contraindication to both Depakote/Depakote ER (divalproex) and Topamax (topiramate)

OR

6.3 One of the following:

- The recipient has a history of failure (after at least a two month trial) or intolerance to one of the following beta blockers: atenolol, propranolol, nadolol, timolol or metoprolol
- The recipient has a contraindication to all of the following beta blockers: atenolol, propranolol, nadolol, timolol and metoprolol

AND

7 - One of the following:

7.1 Patient has experienced therapeutic failure of two preferred medications within the same drug class

OR

7.2 Patient has an allergy, contraindication, drug-to-drug interaction, or a history of unacceptable/toxic side effects with ALL preferred medications within the same drug class

OR

7.3 Non-preferred medication is being requested because it is being used for a unique indication that is supported by peer-reviewed literature or an FDA-approved indication

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

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 medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist

AND

4 - The recipient continues to be monitored for MOH

Product Name: Emgality

Diagnosis	Episodic Cluster Headaches
Approval Length	3 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior 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 - The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist

Product Name: Emgality	
Diagnosis	Episodic Cluster Headaches
Approval Length	12 month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

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

AND

2 - The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist

Product Name: Nurtec ODT, Ubrelvy	
Diagnosis	Acute Migraine
Approval Length	6 month(s)
Therapy Stage	Initial Authorization
Guideline Type	Prior 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 prescribed dose will not exceed two doses per migraine and treating no more than eight migraine episodes per 30 days

AND

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

AND

5 - The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist

Product Name: Nurtec ODT, Ubrelvy	
Diagnosis	Acute Migraine
Approval Length	12 month(s)
Therapy Stage	Reauthorization
Guideline Type	Prior Authorization

Approval Criteria

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

AND

2 - The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist

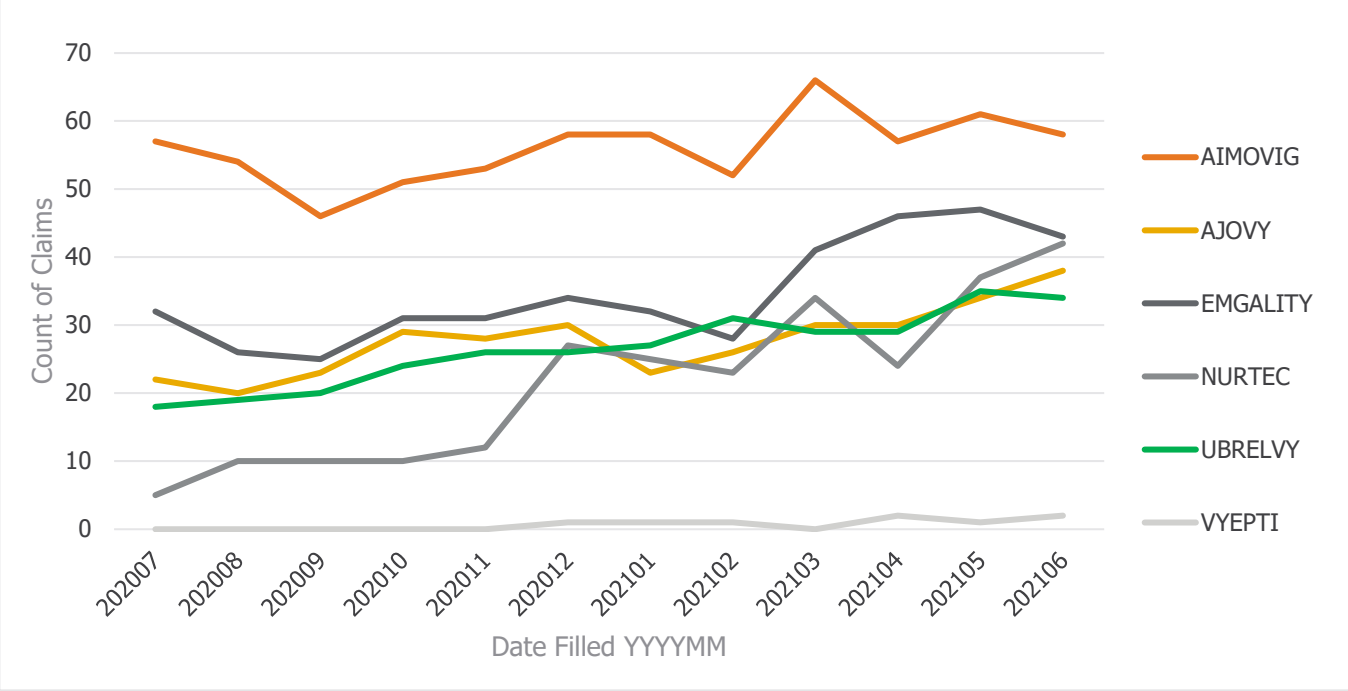
Nevada Medicaid

Top Ten Therapeutic Classes

Fee for Service

July 1, 2020 - June 30, 2021

Drug Name	Members	Claims	Total Days Supply	Total Quantity
AIMOVIG	92	671	21,012	778
VYEPTI	5	8	684	10
NURTEC	76	259	6,581	2,281
EMGALITY	80	416	13,410	485
UBRELVY	74	318	7,817	3,608
AJOVY	66	333	11,715	584



S. Anti-Migraine Medications

Therapeutic Class: Serotonin 5-HT1 receptor agonists (triptans)
Last Reviewed by the DUR Board: July 25, 2019

Therapeutic Class: Calcitonin Gene-Related Peptide (CGRP) Receptor Inhibitor Medications
Last Reviewed by the DUR Board: April 30, 2020

Serotonin 5-HT1 receptor agonists commonly referred to as "triptans" and CGRP Receptor Inhibitor medications or anti-migraine medications are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Serotonin 5-HT1 Receptor Agonists (triptans)

   a. An approved prior authorization is required for any prescription exceeding the quantity limits. Approval for additional medication beyond these limits will be considered only under the following circumstances:

      1. The recipient's current medication history documents the use of prophylactic medications for migraine headache or the medical provider agrees to initiate such therapy which includes beta-blockers, tricyclic antidepressants, anticonvulsants, Selective Serotonin Reuptake Inhibitors (SSRIs) and/or calcium channel blockers; or

      2. The medical provider is aware of and understands the implications of daily use and/or overuse of triptans and agrees to counsel the patient on this issue in an effort to taper the quantity of triptan medication required monthly.

         a. Recipient's current medication history must NOT have Monoamine Oxidase (MAO) Inhibitors present for approval of Imitrex® (sumitriptan), Maxalt® (rizatriptan) or Zomig® (zolmitriptan).

         b. Recipients whose current medication history indicates the use of propranolol will NOT be granted prior authorization of Maxalt® (rizatriptan) 10mg tablet or 10mg orally disintegrating tablet.

         c. Prior authorization will NOT be given to patients with ischemic heart disease.

   b. Prior Authorization Guidelines

      1. Approval for exceeding the quantity limits on triptans will be provided for a two-month time period.

      2. The prior authorization must be initiated by the prescriber. The approved prior authorization must be available if requested.

3. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

2. Calcitonin Gene-Related Peptide (CGRP) Receptor Inhibitor Medications

a. Approval will be given if the following criteria are met and documented:

1. CGRP General Criteria

a. The recipient must have one of the following:

1. Both the following:

a. The recipient has a diagnosis of episodic migraines; and

b. The recipient has four to 14 migraine days per month, but not more than headache days per month; or

2. All the following:

a. The recipient has a diagnosis of chronic migraines; and

b. The recipient has greater than or equal to 15 headache days per month, of which at least eight must be migraine days for at least three months; and

c. The recipient has been considered for medication overuse headache (MOH) and potentially offending medication(s) have been discontinued; and

b. The recipient is 18 years of age or older; and

c. The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist; and

d. The recipient must meet two of the following:

1. One of the following:

a. The recipient has documented history of failure (after at least a two-month trial) or intolerance to Elavil® (amitriptyline) or Effexor® (venlafaxine); or

b. The recipient has a contraindication to Elavil® (amitriptyline) and Effexor® (venlafaxine); or

2. One of the following:

a. The recipient has documented history of failure (after at least a two-month trial) or intolerance to Depakote®/Depakote® ER (divalproex sodium) or Topamax® (topiramate); or

b. The recipient has a contraindication to both Depakote®/Depakote® ER (divalproex sodium) and Topamax® (topiramate); or

3. One of the following:

a. The recipient has documented history of failure (after at least a two-month trial) or intolerance to one of the following beta blockers:

1. Atenolol; or

2. Propranolol; or

3. Nadolol; or

4. Timolol; or

5. Metoprolol; or

b. The recipient has a contraindication to all the following beta blockers:

1. Atenolol; or

2. Propranolol; or

3. Nadolol; or

4. Timolol; or

5. Metoprolol.

2. Recertification Request:

a. The recipient must have a documented positive response to Aimovig® (erenumab-aooe), Ajovy® (fremanezumab-vfrm) or Emgality® (galcanezumab-gnlm) therapy, demonstrated by a reduction in headache frequency and/or intensity; and

b. The recipient has had a decrease in use of acute migraine medications (e.g. NSAIDs, triptans) since the start of CGRP therapy; and

c. The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist; and

d. For chronic migraine only: The recipient continues to be monitored for MOH.

3. Prior Authorization Guidelines:

a. Initial request will be approved for six months.

b. Recertification request will be approved for 12 months.

c. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx.

3. Acute Migraines

a. Ubrelvy® (ubrogepant)

1. Approval will be given if all the following criteria are met and documented:

a. Recipient must have a diagnosis of acute migraine with or without aura; and

b. Recipient is 18 years of age or older; and

c. The prescribed dose will not exceed two doses per migraine and treating no more than eight migraine episodes per 30 days; and

d. The recipient has had at least one trial and failure of triptan agent; and

e. The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist.

2. Recertification Request:

a. The recipient must have a documented positive response to the Ubrelvy® therapy; and

b. The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist.

3. Prior Authorization Guidelines:

a. Initial request will be approved for six months.

b. Recertification request will be approved for 12 months.

c. Prior authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx.

4. Episodic Cluster Headache

a. Emgality® (galcanezumab-gnlm)

1. Approval will be given if all the following criteria are met and documented

a. The recipient has a diagnosis of episodic cluster headache; and

b. 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.

c. The recipient is 18 years of age or older.

d. The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialist.

2. Recertification Request:

a. The recipient has documented positive response to Emgality® therapy, demonstrated by a reduction in headache frequency and/or intensity; and

b. The medication must be prescribed by or in consultation with either a Neurologist or a Pain Specialits.

3. Prior Authorization Guidelines:

a. Initial request will be approved for three months.

b. Recertification request will be approved for 12 months.

c. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx.

Therapeutic Class Overview
Calcitonin gene related peptide (CGRP) inhibitors

INTRODUCTION

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

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

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

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

Table 1. Medications Included Within Class Review

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

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

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

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

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

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

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

CLINICAL EFFICACY SUMMARY

Prevention of episodic migraine

Eptinezumab-jjmr

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

Erenumab-aooe

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

Fremanezumab-vfrm

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

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

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

Galcanezumab-gnlm

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

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

Rimegepant

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

Prevention of chronic migraine

Eptinezumab-jjmr

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

Erenumab-aooe

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

Fremanezumab-vfrm

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

Galcanezumab-gnlm

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

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

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

Treatment of episodic cluster headache

Galcanezumab-gnlm

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

Treatment of acute migraine (with or without aura)

Rimegepant ODT

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

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

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

Ubrogepant

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

Treatment of medication overuse headache

Eptinezumab-jjmr

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

Erenumab-aooe

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

Fremanezumab-vfrm

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

Galcanezumab-gnlm

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

CLINICAL GUIDELINES

Acute treatment of migraine

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

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

Prevention of migraine

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

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

Cluster headache

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

SAFETY SUMMARY

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

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

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

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

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

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

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

CONCLUSION

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

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

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

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

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

APPENDICES

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

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

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

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

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Board Requested Reports

Z. Opioids, Opioid Containing Cough Preparations, Opioids Prescribed to Under Age 18

Therapeutic Class: Opioids, Last reviewed by the DUR Board: July 26, 2018
Opioid Containing Cough Preparations Last reviewed by the DUR Board: July 26, 2018
Opoids Prescribed to Under Age 18: Last Reviewed by the DUR Board: October 18, 2018

Opioids, Opioid Containing Cough Preparations and Opioids Prescribed to Under Age 18 are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

Opioids

1. Coverage and Limitations

   a. Opioids will be covered without prior authorization:

      1. For initial prescriptions of seven days or less; and

      2. For a total of 13 seven-day prescriptions in any rolling 12 month period; and

      3. For prescriptions of 60 mg morphine equivalents or less per day.

   b. Recipients currently on chronic opioid medications will not be subject to the seven-day requirement for an opioid(s) they have been receiving in the past 45 days.

   c. Prior Authorization Criteria: To exceed the number of seven-day prescriptions, or to exceed the seven-day limit, or to exceed the 60 mg morphine equivalents or less per day:

      1. All of the following criteria must be met and documented:

         a. The recipient has chronic pain or requires an extended opioid therapy and is under the supervision of a licensed prescriber; and

         b. Pain cannot be controlled through the use of non-opioid therapy (acetaminophen, NSAIDs, antidepressants, anti-seizure medications, physical therapy, etc.); and

         c. The lowest effective dose is being requested; and

         d. A pain contract is on file.

   d. Exceptions to this policy:

      1. Recipients with cancer/malignancy related pain; or

2. Recipients who are post-surgery with an anticipated prolonged recovery (greater than three months); or

3. Recipients receiving palliative care; or

4. Recipients residing in a long-term care facility; or

5. Recipients receiving treatment for HIV/AIDS; or

6. Prescriptions written by or in consultation with a pain specialist.

2. Prior Authorization Guidelines

a. Prior authorization approval will be for one year.

b. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

3. CDC Guidance:

a. http://www.cdc.gov/drugoverdose/prescribing/guideline.html.

4. Opioid Containing Cough Preparations

a. The recipient must be 18 years of age or older.

b. Prior authorization approval will be for six months.

c. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx.

d. For references purposes, codeine and tramadol for children prior authorization criteria can also be found within this chapter in Section TTT.

5. Opioids Prescribed to Under Age 18

a. Short Acting Opioids will be covered without PA for:

1. Initial prescription of three days or less; and

2. A total of 13 three-day prescriptions in any rolling 12-month period; and

3. Prescriptions of 60 morphine milligram equivalents (MME) or less per day.

b. Recipients currently on chronic opioid medications will not be subject to the three-day requirement for an opioid(s) they have been receiving in the past 45 days.

c. To exceed the number of three-day prescriptions, or to exceed the three-day limit, or to exceed the 60 MME or less per day:

1. All of the following criteria must be met and documented:

   a. The recipient has chronic pain or requires an extended opioid therapy and is under the supervision of a licensed prescriber; and

   b. Pain cannot be controlled through the use of non-opioid therapy (acetaminophen, NSAIDs, antidepressants, anti-seizure medications, physical therapy, chiropractic treatment, etc.); and

   c. The lowest effective dose is being prescribed; and

   d. A pain contract is on file.

d. Exceptions:

   1. Recipients with cancer/malignancy related pain, recipients who are post-surgery with an anticipated prolonged recovery (greater than three months), recipients residing in a long-term care facility, recipients receiving treatment for HIV/AIDS, hospice, palliative care or end-of-life care.

   2. Prescriptions written by or in consultation with a pain specialist.

e. Prior Authorization Guidelines

   1. Prior authorization approval will be for three months.

f. Prescribing Guidance:

   1. CDC Guidance: https://www.cdc.gov/drugoverdose/prescribing/guideline.html

   2. HHS Opioids and Adolescents: https://www.hhs.gov/ash/oah/adolescent-development/substance-use/drugs/opioids/index.html

Q. Long-Acting Narcotics

Therapeutic Class: Analgesics, Narcotic
Last Reviewed by DUR Board: April 28, 2016

Long-Acting Narcotics are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

The current criteria for the use of fentanyl transdermal patches (Appendix A, (F.)) or oxycodone/acetaminophen ER tablets (Appendix A, (XX.)) is to be met.

For all other long-acting narcotics requests that exceed the quantity limit, the following criteria must be met and documented:

a. The recipient has a diagnosis of terminal cancer; or

b. All the the following criteria must be met:

1. The recipient is 18 years of age or older; and

2. The requested agent will be used for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment; and

3. There is documentation in the recipient's medical record that alternative agents (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated or would be otherwise inadequate to provide sufficient management of pain.

2. Prior Authorization Guidelines

a. The prior authorization approval will be for three months.

b. Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

F. Transdermal Fentanyl

Therapeutic Class: Analgesics, Narcotic
Last Reviewed by the DUR Board: April 25, 2019

Transdermal fentanyl, a narcotic agonist analgesic, is indicated in the management of chronic pain in patients requiring continuous opioid analgesia for pain that cannot be managed by lesser means such as acetaminophen-opioid combinations, non-steroidal analgesics or PRN dosing with short-acting opioids. Transdermal fentanyl is subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

Because serious or life-threatening hypoventilation could occur, fentanyl transdermal is contraindicated in management of acute or postoperative pain, mild or intermittent pain responsive to PRN or non-opioid therapy or in doses exceeding 25 mcg/hr at the initiation of opioid therapy. Therefore, patients must meet the following criteria in order to gain prior authorization approval:

a. Patient cannot be managed by lesser means such as acetaminophen-opioid combinations, nonsteriodal analgesics or PRN dosing with short-acting opioid.

b. Patient requires continuous opioid administration.

c. Prescribers are required to check the Nevada State BOPs Prescription Monitoring Program (PMP) prior to prescribing narcotic analgesics. Refer to the PMP website at http://bop.nv.gov/links/PMP/.

d. If transitioning from another opioid, daily morphine equivalent doses are used to calculate the appropriate fentanyl patch dose.

1. Morphine 60-134 mg/day PO; initial Transdermal Fentanyl dose 25 mcg/hr.

2. Morphine 135-224 mg/day PO; initial Transdermal Fentanyl dose 50 mcg/hr.

3. Morphine 225-314 mg/day PO; initial Transdermal Fentanyl dose 75 mcg/hr.

4. Morphine 315-404 mg/day PO; initial Transdermal Fentanyl dose 100 mcg/hr.

5. Morphine 405-494 mg/day PO; initial Transdermal Fentanyl dose 125 mcg/hr.

6. Morphine 495-584 mg/day PO; initial Transdermal Fentanyl dose 150 mcg/hr.

7. Morphine 585-674 mg/day PO; initial Transdermal Fentanyl dose 175 mcg/hr.

8. Morphine 675-764 mg/day PO; initial Transdermal Fentanyl dose 200 mcg/hr.

9. Morphine 765-854 mg/day PO; initial Transdermal Fentanyl dose 225 mcg/hr.

10. Morphine 855-944 mg/day PO; initial Transdermal Fentanyl dose 250 mcg/hr.

11. Morphine 945-1034 mg/day PO; initial Transdermal Fentanyl dose 275 mcg/hr.

12. Morphine 1035-1124 mg/day PO; initial Transdermal Fentanyl dose 300 mcg/hr.

2. Prior Authorization Guidlines

a. Prior authorization approval will be given for 12 months.

b. Prior Authorization forms are available at: http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

G. Immediate-Release Fentanyl Products

Therapeutic Class: Analgesics, Narcotic
Last Reviewed by the DUR Board: July 25, 2013

Immediate-Release Fentanyl Products are subject to prior authorization and quantity limitations based on the Application of Standards in Section 1927 of the SSA and/or approved by the DUR Board. Refer to the Nevada Medicaid and Check Up Pharmacy Manual for specific quantity limits.

1. Coverage and Limitations

Approval will be given if the following criteria are met and documented:

a. Subsys® (fentanyl sublingual spray), Onsolis® (fentanyl citrate buccal film), Fentora® (fentanyl citrate buccal tablet), Lazanda® (fentanyl citrate nasal spray), Abstral® (fentanyl citrate sublingual tablet) and Actiq® (fentanyl citrate transmucosal lozenge):

The recipient must meet all of the following:

1. The recipient is ≥ 18 years of age or ≥ 16 years of age if requesting fentanyl citrate transmucosal lozenge (Actiq®); and

2. The recipient has pain resulting from a malignancy; and

3. The recipient is already receiving and is tolerant to opioid therapy; and

4. The recipient is intolerant of at least two of the following immediate-release opioids: hydrocodone, hydromorphone, morphine or oxycodone.

2. Prior Authorization Guidelines

a. Prior authorization approval will be for six months.

b. Prior Authorization forms are available at:
http://www.medicaid.nv.gov/providers/rx/rxforms.aspx

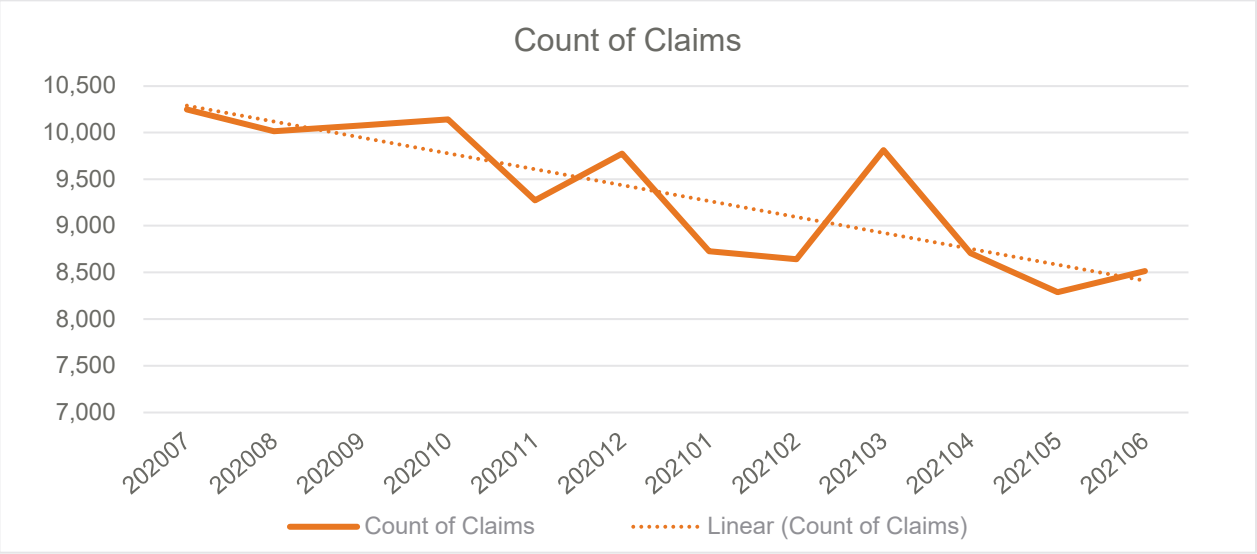
Nevada Medicaid

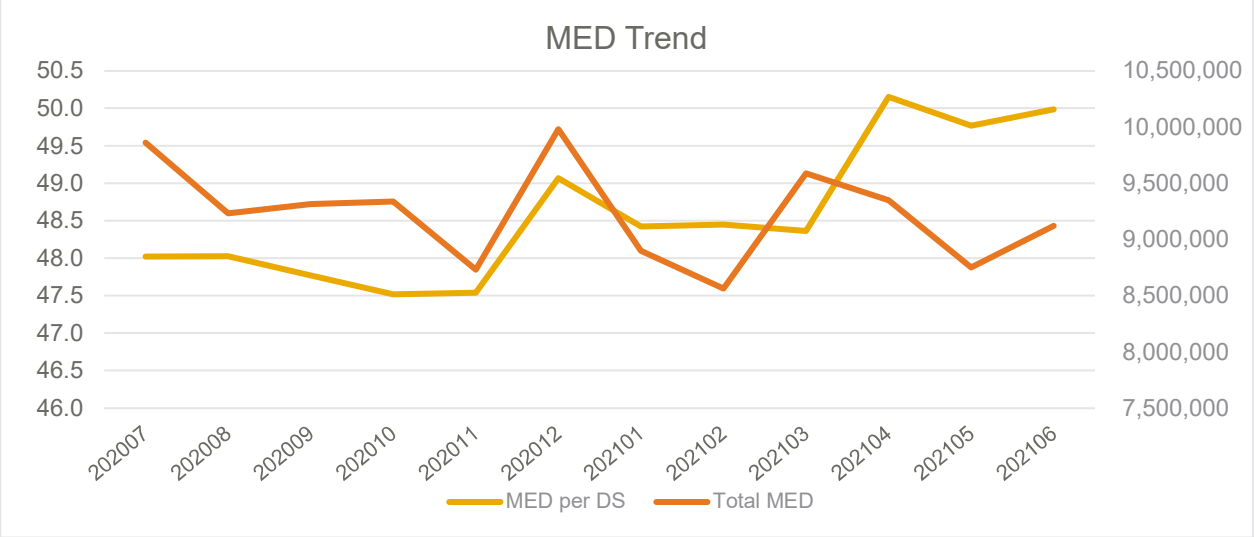
Opioid Trends

Fee for Service

July 1, 2020 - June 30, 2021

Date Filled	Count of Claims	Days Supply	Count of Members	Total Qty	Total MED	MED per DS
202007	10,249	205,347	8,817	691,340	9,860,818	48.0
202008	10,013	192,200	8,814	647,391	9,230,666	48.0
202009	10,076	194,960	8,836	659,402	9,313,441	47.8
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	50.15
202105	8,289	175,838	7,437	593,115	8,750,997	49.77
202106	8,513	182,492	7,505	619,603	9,122,032	49.99





Nevada Medicaid

Top Ten Therapeutic Classes

Fee for Service

July 1, 2020 - June 30, 2021

Member ID Encrypted	Count of Claims	Day Supply	Total Quantity	MED Per DS	Total MED
33330458115	6	180	1,080	320	57,600
44448546720	6	180	1,260	263	47,250
77771952964	6	180	585	315	56,700
11110100737	7	198	840	324	64,200
55550656157	11	156	1,134	422	65,880
22222296971	8	240	840	240	57,600
49044066667	5	150	600	450	67,500
99990949361	6	180	630	240	43,200
44446597311	6	180	990	270	48,600
77771924497	6	180	1,080	225	40,500

Member ID Encrypted	Drug Label Name	Count of Claims	Day Supply	Total Quantity
33330458115 Total		**6**	**180**	**1,080**
33330458115	MORPHINE SUL TAB 100MG ER	3	90	360
	OXYCODONE TAB 20MG	3	90	720
44448546720 Total		**6**	**180**	**1,260**
44448546720	HYDROCO/APAP TAB 10-325MG	3	90	270
	OXYCODONE TAB 30MG	3	90	990
77771952964 Total		**6**	**180**	**585**
77771952964	FENTANYL DIS 100MCG/H	3	90	45
	OXYCODONE TAB 30MG	3	90	540
11110100737 Total		**7**	**198**	**840**
11110100737	MORPHINE SUL TAB 100MG ER	4	112	480
	OXYCODONE TAB 30MG	3	86	360
55550656157 Total		**11**	**156**	**1,134**
55550656157	FENTANYL DIS 100MCG/H	6	81	54
	OXYCODONE TAB 10MG	2	30	720
	OXYCODONE TAB 30MG	3	45	360
22222296971 Total		**8**	**240**	**840**
22222296971	MORPHINE SUL TAB 100MG ER	4	120	360
	OXYCODONE TAB 30MG	4	120	480
49044066667 Total		**5**	**150**	**600**
49044066667	FENTANYL DIS 100MCG/H	2	60	60
	OXYCODONE TAB 30MG	3	90	540
99990949361 Total		**6**	**180**	**630**
99990949361	MORPHINE SUL TAB 100MG ER	3	90	270
	OXYCODONE TAB 30MG	3	90	360
44446597311 Total		**6**	**180**	**990**
44446597311	MORPHINE SUL TAB 60MG ER	3	90	270
	OXYCODONE TAB 30MG	3	90	720
77771924497 Total		**6**	**180**	**1,080**
77771924497	MORPHINE SUL TAB 30MG ER	3	90	540
	OXYCODONE TAB 30MG	3	90	540

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 Q1	Pres 1	LAS VEGAS	NV	- Hospitalist	147	293	8,149	26,675	577,665	70.89	0.48
2021 Q1	Pres 14	SPARKS	NV	- Anesthesiology	89	235	6,670	20,492	531,830	79.73	0.90
2021 Q1	Pres 38	-	-	-	114	261	7,547	25,600	520,738	69.00	0.61
2021 Q1	Pres 36	LAS VEGAS	NV	- Physician Assistant	142	323	9,063	30,482	503,729	55.58	0.39
2021 Q1	Pres 16	SPARKS	NV	Allopathic & Osteopathic Physic	112	291	8,537	34,995	503,418	58.97	0.53
2021 Q1	Pres 17	LAS VEGAS	NV	- Anesthesiology	156	331	8,584	28,449	466,023	54.29	0.35
2021 Q1	Pres 25	LAS VEGAS	NV	- Orthopedic Surgery	162	339	9,633	33,289	463,006	48.06	0.30
2021 Q1	Pres 38	-	-	-	87	170	4,939	16,862	412,230	83.46	0.96
2021 Q1	Pres 2	LAS VEGAS	NV	-	95	186	5,509	19,899	408,026	74.07	0.78
2021 Q1	Pres 11	HENDERSON	NV	- Physician Assistant	41	95	2,796	10,676	403,635	144.36	3.52
2021 Q2	Pres 1	LAS VEGAS	NV	- Hospitalist	183	399	11,117	36,382	875,507	78.75	0.43
2022 Q2	Pres 36	LAS VEGAS	NV	-	157	346	9,630	32,714	577,715	59.99	0.38
2023 Q2	Pres 9	LAS VEGAS	NV	- Physician Assistant	120	266	7,578	25,834	534,835	70.58	0.59
2024 Q2	Pres 25	LAS VEGAS	NV	-	159	342	9,717	34,423	521,985	53.72	0.34
2025 Q2	Pres 14	SPARKS	NV	- Anesthesiology	84	210	6,083	19,713	511,833	84.14	1.00
2026 Q2	Pres 16	SPARKS	NV	Allopathic & Osteopathic Physic	106	273	7,891	31,197	479,133	60.72	0.57
2027 Q2	Pres 3	LAS VEGAS	NV	- Physical Medicine & Rehabilita	115	250	7,306	22,837	472,132	64.62	0.56
2028 Q2	Pres 17	LAS VEGAS	NV	-	158	310	8,023	27,383	416,380	51.90	0.33
2029 Q2	Pres 19	LAS VEGAS	NV	-	135	288	8,356	28,032	374,603	44.83	0.33
2030 Q2	Pres 2	LAS VEGAS	NV	-	89	159	4,731	17,149	373,868	79.03	0.89

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 Q1	Pres 27	HENDERSON	NV	- Hematology/Oncology, Peds	1	2	60	240	10,800	180.00	180.00
2021 Q1	Pres 18	LAS VEGAS	NV	- Nurse Practitioner	1	2	60	240	10,800	180.00	180.00
2021 Q1	Pres 20	HENDERSON	NV	- Internal Medicine	1	1	3	24	540	180.00	180.00
2021 Q1	Pres 31	HENDERSON	NV	- Internal Medicine	1	1	8	30	1,350	168.75	168.75
2021 Q1	Pres 37	LAS VEGAS	NV	- Family Practice	1	1	5	30	675	135.00	135.00
2021 Q1	Pres 34	RENO	NV	- Hematology/Oncology, Peds	1	3	90	540	12,150	135.00	135.00
2021 Q1	Pres 33	LAS VEGAS	NV	Allopathic & Osteopathic Physic	1	3	90	720	10,800	120.00	120.00
2021 Q1	Pres 38	-	-	-	1	1	15	60	1,800	120.00	120.00
2021 Q1	Pres 12	PAHRUMP	NV	- Internal Medicine	1	3	90	360	10,800	120.00	120.00
2021 Q1	Pres 22	LAS VEGAS	NV	- Internal Medicine	1	1	20	80	2,400	120.00	120.00
2021 Q2	Pres 18	LAS VEGAS	NV	-	1	3	90	360	16,200	180.00	180.00
2022 Q2	Pres 38	SALT LAKE CITY	UT	- Student in an Organized Healt	1	1	30	10	5,400	180.00	180.00
2023 Q2	Pres 39	LAS VEGAS	NV	-	1	1	30	120	5,400	180.00	180.00
2024 Q2	Pres 5	LAS VEGAS	NV	- Internal Medicine	1	1	30	90	4,050	135.00	135.00
2025 Q2	Pres 13	LAS VEGAS	NV	- Specialist	2	4	97	577	25,703	264.97	132.49
2026 Q2	Pres 12	PAHRUMP	NV	- Internal Medicine	1	3	90	360	10,800	120.00	120.00
2027 Q2	Pres 4	LAS VEGAS	NV	-	1	1	30	160	3,600	120.00	120.00
2028 Q2	Pres 33	LAS VEGAS	NV	Allopathic & Osteopathic Physic	1	1	30	240	3,600	120.00	120.00
2029 Q2	Pres 6	RENO	NV	- Specialist	1	1	30	60	3,600	120.00	120.00
2030 Q2	Pres 8	RENO	NV	- Physician Assistant	1	1	5	40	600	120.00	120.00

Standard DUR Reports

Nevada Medicaid

Top Ten Therapeutic Classes
Fee for Service
January 1, 2021 - June 30, 2021

Top 10 Classes by Claim Count

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

2020 Q1

Drug Class Name	Count of Claims	Amt Paid
ANTICONVULSANTS - MISC.	27,010	$2,782,581.05
SYMPATHOMIMETICS	17,148	$2,776,809.02
SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIS)	16,582	$210,926.07
OPIOID COMBINATIONS	14,485	$422,549.68
NONSTEROIDAL ANTI-INFLAMMATORY AGENTS (NSAIDS)	13,051	$328,832.95
CENTRAL MUSCLE RELAXANTS	12,928	$213,138.83
HMG COA REDUCTASE INHIBITORS	11,272	$156,104.57
DIBENZAPINES	9,997	$388,235.27
ANTIANXIETY AGENTS - MISC.	9,729	$147,221.71
OPIOID AGONISTS	9,634	$374,384.42

Top 10 Classes by Amount Paid

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

2021 Q1

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

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**

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%***

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***

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.

Nevada Medicaid

RetroDUR

Fee for Service

First Quarter 2021 and Second Quarter 2021

Q1 2021

Initiative	Sent	Responses	Prescribers	Recipients	Response Rate
Montelukast utilizers less than 21 yrs without Asthma dx	27	3	24	27	11.11%
Long term PPI use with duplicate PPIs	69	11	60	69	15.94%
Long Term PPI	139	17	121	139	12.23%

Q2 2021

Initiative	Sent	Responses	Prescribers	Recipients	Response Rate
Gabapentin Utilization without indicated Gabapentin dx	94	12	85	94	12.77%